CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217026Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 1, 2023

To: Brenda Reggettz, Regulatory Project Manager, Division of Neurology 1 (DNI)

Michael Dimyan, Clinical Reviewer, DNI

Tracy Peters, Associate Director for Labeling, DNI

From: Annette Egbonim, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for DAYBUE™ (trofinetide) oral solution

NDA: 217026

Background:
In response to DNI's consult request dated September 2, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for DAYBUE™ (trofinetide) oral solution (Daybue).

PI:
OPDP's review of the proposed PI is based on the draft labeling received by electronic mail from DNI on February 13, 2023, and our comments are provided below.

PPI:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on February 28, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the Sponsor to the electronic document room on January 11, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Annette Egbonim at Annette.egbonim@fda.hhs.gov.

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/s/

ANNETTE O EGBONIM
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 28, 2023
To:	Brenda Reggettz, PharmD Senior Regulatory Project Manager **Division of Neurology I (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Annette Egbonim, PharmD, RPh Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	DAYBUE (trofinetide)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 217026
Applicant:	Acadia Pharmaceuticals, Inc.

1 INTRODUCTION

On July 12, 2022, Acadia Pharmaceuticals, Inc. submitted for the Agency's review a an original New Drug Application (NDA)/New Molecular Entity 217026 for DAYBUE (trofinetide) oral solution. DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients aged 2 years and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on September 2, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DAYBUE (trofinetide) oral solution.

2 MATERIAL REVIEWED

- Draft DAYBUE (trofinetide) PPI received on July 12, 2022, and received by DMPP and OPDP on February 13, 2023.
- Draft DAYBUE (trofinetide) Prescribing Information (PI) received on July 12, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 13, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MARY E CARROLL
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ANNETTE O EGBONIM
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MARCIA B WILLIAMS
02/28/2023 11:46:16 AM

LASHAWN M GRIFFITHS
02/28/2023 11:52:08 AM

Clinical Inspection Summary

Date	01/30/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Brenda Reggettz, Pharm.D., Regulatory Project Manager Michael Dimyan, M.D., Medical Officer Laura Jawidzik, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #	217026
Applicant	Acadia Pharmaceuticals, Inc.
Drug	Trofinetide
NME	Yes
Proposed Indication	Treatment of Rett syndrome
Consultation Request Date	9/8/2022
Summary Goal Date	1/10/2023, extended to 2/3/2023
Priority/Standard Review	Priority
Action Goal Date	3/10/2023
PDUFA Date	3/12/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Skinner, Standridge, Suter, and the contract research organization (CRO), (b) (4) , were inspected in support of this NDA and covered Protocol ACP-2566-003. The study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Trofinetide oral solution is being developed under IND 114319 for the treatment of Rett syndrome in adults and pediatric patients ≥2 years of age. The sponsor has submitted NDA 217026 which includes the results of one Phase 3 study, Protocol ACP-2566-003, in support of the proposed indication.

Protocol ACP-2566-003

Title: "A randomized, double-blind, placebo-controlled, parallel-group study of trofinetide for the treatment of girls and women with Rett syndrome"

Subjects: 187

Sites: 21 sites in the United States

Study Initiation and Completion Dates: 10/29/2019 to 10/28/2021

This was a randomized, double-blind, placebo-controlled study in girls and women 5 to 20 years of age with Rhett syndrome. Main eligibility criteria included classic/typical Rett Syndrome; documented disease-causing mutation in the *MECP2* gene; score of 10 to 36 on the Rett Syndrome Clinical Severity Scale at screening; Clinical Global Impression-Severity (CGI-S) score ≥4 at screening and baseline; post-regression at screening defined as no loss or degradation of ambulation/hand function/speech/nonverbal communicative or social skills within 6 months of screening; body weight ≥12 kg at screening; can swallow the study medication provided as a liquid solution or can take it by gastrostomy tube; and stable pattern of seizures (or no seizures) within 8 weeks of screening.

The study was comprised of three phases: screening, double-blind treatment, and safety follow-up phases.

Screening Phase: up to 3 weeks
Subjects were screened for study eligibility. Assessments included, but were not limited to, labs, ECG, and confirmation of documented Rett diagnosis and *MECP2* mutation.

Double-blind Treatment Phase: 12 weeks
At Baseline (Visit 2), subjects were randomized (1:1) to the following treatment arms:

- Trofinetide oral solution twice daily (morning/evening)
- Placebo oral solution twice daily (morning/evening)

Investigational product (IP) dosing was based on weight at the baseline visit and was to be administered orally or via gastrostomy tube.

Weight	Dose
12-20 kg	30 mL (6 g) twice daily
>20-35 kg	40 mL (8 g) twice daily
>35-50 kg	50 mL (10 g) twice daily
>50 kg	60 mL (12 g) twice daily

IP dose was not to be increased or decreased if the subject's weight at a postbaseline visit put them in a new weight category. IP dose could be decreased due to poor

tolerability any time before the Week 6 visit, but the goal was to return to the originally assigned dose. Caregivers recorded IP dosing, concomitant medications, and meals in a caregiver diary for the two days before scheduled visits and the morning of the scheduled visit. During the study, caregivers also recorded seizures in a "semi-structured" caregiver diary.

IP was shipped directly to the subject and confirmation of any delivery was to be made by a visiting nurse. IP was dispensed at the site during the Baseline visit if the visit was conducted in the clinic. Study visits could be conducted off-site rather than in the clinic with the prior approval of the sponsor or medical monitor; but Screening, Baseline, and End of Study visit were to be completed in the clinic if possible. Study visits occurred at Week 0 (Visit 2, Baseline), Week 2 (Visit 3), Week 6 (Visit 4), and Week 12 (Visit 5).

The primary efficacy measure was the Rett Syndrome Behaviour Questionnaire (RSBQ). Caregivers entered RSBQ data into an electronic device, the (b) (4) tablet, during on-site clinic visits. These tablets were provided to the clinical sites by the vendor, (b) (4). Data were then uploaded into the (b) (4) web portal.

Safety Follow-up Period

A follow-up telephone or telemedicine contact to assess adverse events and concomitant medications occurred 30 days after the End of Study visit for subjects who completed the study and did not continue into the open-label study and for subjects who prematurely discontinued the study.

The co-primary efficacy endpoints were the change from baseline to Week 12 in the RSBQ total score and the Clinical Global Impression-Improvement (CGI-I) score at Week 12. A key secondary efficacy endpoint was the change from baseline to Week 12 in the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist-Social Composite Score (CSBS-DP-IT Social).

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the Clinical Investigator Site Selection Tool (CISST), numbers of enrolled subjects, impact on primary efficacy analyses, and prior inspection history.

III. RESULTS

1. Steve A. Skinner, M.D.
Site #10198
Greenwood Genetic Center
106 Gregor Mendel Circle
Greenwood, SC 29646
Inspection Dates: 10/3/2022 – 10/6/2022

At this site for Protocol ACP-2566-003, 8 subjects were screened, 7 subjects were randomized, and 7 subjects completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist-Social Composite Score (CSBS-DP-IT Social), and co-primary efficacy data (Rett Syndrome Behaviour Questionnaire [RSBQ] total score, Clinical Global Impression-Improvement [CGI-I]) score.

The sponsor had submitted two data line listings for the RSBQ, one for the RSBQ individual item scores and one for derived RSBQ total scores. The RSBQ, CGI-I, and CSBS-DP-IT Social scores were verified against sponsor data line listings. There were no discrepancies in CGI-I or CSBS-DP-IT Social scores. Discrepancies were noted in the RSBQ total scores for four of seven randomized subjects (Table 1) when comparing the RSBQ total scores in source with the derived RSBQ total score data line listing. Specifically, there was a 2-point difference in the RSBQ total score for some timepoints in these four subjects.

During the inspection, the study coordinator contacted the sponsor regarding the RSBQ total score discrepancies. The sponsor explained that the RSBQ includes 45 items that the caregiver rates as 0=not true, 1=somewhat or sometimes true, or 2=true. For all items, except Item 31 (uses eye gaze to convey feelings, needs and wishes), a score of 2 represents a worse rating and a score of 0 represents a better rating. The sponsor noted that they had prespecified in the statistical analysis plan that the score for Item 31 was to be changed in the calculation of the derived RSBQ total score. Specifically, for Item 31, a rating of 2 would be changed to a 0 and a rating of 0 would be changed to a 2; scores of 1 would not be changed.

Table 1. RSBQ Total Score Discrepancies

Subject	Study Arm	Visit	RSBQ Total Score	
			Source Data	Sponsor Data Line Listing
(b) (6)	Placebo	Baseline	43	41
		Week 2	41	39
		Week 6	44	42
		Week 12	43	41
(b) (6)	Trofinetide	Baseline	42	44
		Week 2	39	41
		Week 6	32	34
		Week 12	33	35
(b) (6)	Placebo	Week 6	58	60
		Week 12	58	60
(b) (6)	Trofinetide	Week 6	23	21

Paper caregiver diaries were provided to record meals, concomitant medications, investigational product (IP) dosing, and seizures (type, behaviors, and symptoms); no discrepancies were identified. There was no evidence of underreporting of adverse events. Subject # (b) (6), randomized to placebo, had one new seizure type identified during the study which was reported as an adverse event.

Reviewer's comment: The derived RSBQ total score, with reverse scoring for Item 31 (eye gaze), is known to the review division and statistician.

2. Shannon M. Standridge, D.O.
Site #10187
Cincinnati Children's Hospital Medical Center
Department of Neurology
3333 Burnet Avenue
Cincinnati, OH 45229
Inspection Dates: 10/31/2022 – 11/8/2022

At this site for Protocol ACP-2566-003, 15 subjects were screened, 13 subjects were randomized, and 10 subjects completed the study. Three subjects discontinued the study due to noncompliance with investigational product (IP) (n = 1), and adverse events (n = 2). Subject # (b) (6), randomized to trofinetide, discontinued due to the AE of diarrhea. However, this subject also experienced the SAEs of bacteremia and urinary tract infection requiring hospitalization. The onset dates of the SAEs were (b) (6) and the last dose of IP was (b) (6). Subject # (b) (6), randomized to trofinetide, discontinued due to the AE of increased stool frequency. Narratives for these discontinuations due to AEs are included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (CSBS-DP-IT Social), and co-primary efficacy data (RSBQ total score, CGI-I) score.

The RSBQ, CGI-I, and CSBS-DP-IT Social scores were verified against sponsor data line listings; no discrepancies were identified. Although discrepancies for the RSBQ total score, comparing source with the derived RSBQ total scores, were expected (see above), none were identified. It is likely that the RSBQ data verified during the inspection were the individual item scores only and not the RSBQ total score. The RSBQ total scores for this site were verified by this reviewer (*refer to Information Request to Sponsor-RSBQ Source Data at end of this document*).

Paper caregiver diaries were provided to record meals, concomitant medications, investigational product (IP) dosing, and seizures (type, behaviors, and symptoms). There was no evidence of under-reporting of adverse events.

3. Bernhard Suter, M.D
Site #10189
Texas Children's Hospital
Mark Wallace Tower
6701 Fannin St.
Houston, TX 77030
Inspection Dates: 10/18/2022 – 10/21/2022

At this site for Protocol ACP-2566-003, 21 subjects were screened, 18 subjects were randomized, and 16 subjects completed the study. Two subjects discontinued the study due to adverse events (AEs). Subject # (b) (6), randomized to trofinetide, discontinued due to the AE diarrhea and Subject # (b) (6), randomized to placebo, discontinued due to the AE hip pain. Narratives for these discontinuations due to AEs are included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (CSBS-DP-IT Social), and co-primary efficacy data (RSBQ total score, CGI-I) score.

The RSBQ, CGI-I, and CSBS-DP-IT Social scores were verified against sponsor data line listings; no discrepancies were identified. Although discrepancies for the RSBQ total score, comparing source with the derived RSBQ total scores, were expected (see above), none were identified. It is likely that the RSBQ data verified during the inspection were the individual item scores only and not the RSBQ total score. The RSBQ total scores for this site were verified by this reviewer (*refer to Information Request to Sponsor-RSBQ Source Data at end of document*).

There was no evidence of under-reporting of AEs.

4. (b) (4)

Inspection Dates: (b) (4)

This inspection covered responsibilities transferred to the contract research organization (CRO), (b) (4) from the sponsor, Acadia Pharmaceuticals, for Protocol ACP-2566-003. The inspection focused on the three clinical investigator sites chosen for inspection for this protocol.

Study records reviewed included, but were not limited to, transfer of regulatory obligation (TORO); SOPs; organization and personnel; personnel training; monitoring plan; selection of monitors; monitoring procedures and reports; vendor management; quality assurance; data management; safety reporting; investigational product accountability; clinical investigator training and compliance; and financial disclosure.

Responsibilities transferred to (b) (4) included project management; medical monitoring; clinical operations including site initiation, management, and monitoring; and vendor management. Vendor management included (b) (4) (the central IRB), (b) (4) (study recruitment website), and (b) (4) (home health care for home visits).

(b) (4) was responsible for site monitoring. Monitoring visits were conducted according to the monitoring plan and SOPs. (b) (4) also assessed clinical investigator compliance. Most noncompliance issues appeared to be minor (e.g. late entry into electronic data capture [EDC] system, isolated out-of-window visits) and retraining brought clinical investigators back into compliance. At some sites, due to staffing issues related to COVID-19, there was a data entry backlog. The sponsor approved (b) (4) to use a clinical support specialist to assist sites with data entry to address this issue; this assistance was provided to 8 clinical sites. No clinical sites were terminated during the conduct of the study for noncompliance or other issues.

Site monitoring appeared to be adequate for the three clinical sites reviewed with the exception of unreported concomitant medications in one subject. In a review of serious

adverse event (SAE) forms for Subject # (b) (6), randomized to trofinetide, the narrative notes the subject received ondansetron and a "fever reducer" (unspecified) during hospitalization for a urinary tract infection/bacteremia. These concomitant medications were not included in the sponsor data line listings but were included in the narrative submitted in the NDA (fever reducer identified as acetaminophen and ibuprofen). Other concomitant medications administered during this hospitalization (i.e. ceftriazone) were included in the sponsor data line listings. (b) (4) stated that these unreported concomitant medications were not identified during the monitoring visit.

Reviewer comments: It is unlikely that these two unreported concomitant medications would impact the overall efficacy or safety analysis. These unreported concomitant medications were not identified during the inspection of Site #10187.

Information Request to Sponsor – RSBQ Source Data
In order to verify RSBQ total scores for Sites #10187 and #10189, an information request was sent to the sponsor on 1/3/2023 requesting that certified copies of the source data be submitted to the NDA. The sponsor provided these data in responses submitted on 1/19/2023 and 1/20/2023.

The sponsor provided raw HTML files with audit trails for all randomized subjects for all clinical sites. The sponsor noted that most, but not all, RSBQ ratings were entered by caregivers into the (b) (4) electronic tablet. Due to COVID-19, some on-site clinic visits were conducted remotely and the RSBQ was completed by caregivers using either a fillable password-protected PDF created for electronic transmission or paper copies of the RSBQ completed by hand. These alternatives were also used when there were issues with the electronic tablet or (b) (4) portal. Fillable PDFs or paper source were used for a total of 34 of 187 (18.2%) subjects across 11 sites. Specifically, the sponsor submitted certified fillable PDFs for 14 subjects (19 visits) and certified paper source for 22 subjects (24 visits); two subjects had both fillable PDFs and paper source completed by hand.

The raw HTML file RSBQ total scores were verified against the derived RSBQ total score data line listing for the three clinical sites that were inspected. The anticipated discrepancies between the source RSBQ total score and the derived RSBQ total score due to reverse scoring of Item 31 were identified for all subjects who had a score of 0 or 2 for Item 31 (eye gaze).

Reviewer's comment – As noted in the summary for Site #10198, scores of 1 for Item 31 would not be changed in the calculation of the derived RSBQ total score. Therefore, no discrepancies in RSBQ total scores would be identified for those subjects.

In addition, the RSBQ scores recorded on fillable PDF and paper source were verified against the individual RSBQ and derived RSBQ total scores data line listings for baseline and Visit 5 (Week 12/ET) for the 34 subjects with these source documents. Two discrepancies in individual RSBQ scores in one subject were identified that did not impact the RSBQ total score.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

CONCURRENCE:

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Phillip Kronstein, M.D.
Team Leader
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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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cc:

Central Document Room/NDA 217026
Division of Neurology 1/Division Director/Teresa Buracchio
Division of Neurology 1/Deputy Division Director/ Laura Jawidzik
Division of Neurology 1/Medical Team Leader/ Laura Jawidzik
Division of Neurology 1/Medical Officer/ Michael Dimyan
Division of Neurology 1/Project Manager/Brenda Reggettz
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers

OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Clinical Analyst/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague
OSI/GCPAB Program Analyst/Loreto-Corazon Lim

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 18, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217026
Product Name and Strength:	Daybue (trofinetide) oral solution, 200 mg/mL
Applicant/Sponsor Name:	Acadia Pharmaceuticals Inc.
OSE RCM #:	2022-390-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 11, 2023 for Daybue. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Daybue (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Morris, C. Label and Labeling Review for Daybue (NDA 217026). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 NOV 21. RCM No.: 2022-390.

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/s/

JOHN C MORRIS
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STEPHANIE L DEGRAW
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M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 4, 2023

To: Teresa Buracchio, MD, Director
Division of Neurology 1

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Jovita Randall-Thompson, PhD, Pharmacologist
Controlled Substance Staff

Subject: NDA 217026 (IND 114319), Trofinetide/Daybue (ACP-2566, and NNZ-2566)
Indication: Treatment of Rett syndrome in adults and pediatric patients 2 years of age and older
Dosages: administered based on weight at 5 g (25 mL) to 12 g (60 mL) BID
Formulation: 200 mg/mL oral solution
Sponsor: Acadia Pharmaceuticals Inc.
PDUFA Goal Date: March 12, 2023

Materials Reviewed:

- NDA 217026, 2.7.4 Summary of Clinical Safety, July 12, 2022 and 120-day Safety Update, November 8, 2022 (Sequence# 0001/Supporting Doc.# 1, and Sequence# 0019/Supporting Doc.# 19, respectively)
- NDA 217026, 5.3.5.3 Trofinetide-Integrated Summary of Safety (ISS), July 7, 2022 (Sequence# 0001/Supporting Doc.# 1)
- IND 114319, CSS Reviews, Edward G. Hawkins, DARRTS, February 14, 2022, and July 28, 1915

I. Background

This memorandum is in response to a consult request dated August 3, 2022, from the Division of Neurology 1 (DN1) pertaining to trofinetide oral solution (Daybue). In accordance with Section 505(b)(l) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314, Acadia Pharmaceuticals Inc. (Sponsor) submitted NDA 217026 for trofinetide oral solution for the treatment of Rett syndrome. DN1 requested CSS to review the submitted NDA for filing and abuse potential.

Trofinetide is a central nervous system (CNS) active drug. However, the underlying mechanism of action of trofinetide is not fully understood. The blockade of metabotropic glutamate receptors was considered the primary mechanism of action, but when investigating the affinity of trofinetide for G-protein-coupled glutamate receptors (metabotropic glutamate receptor 1 to 8 [mGluR1 to mGluR8]), binding of trofinetide was shown only at micromolar contrations, a finding inconsistent with the low-mid nanomolar concentrations at which the neuroprotective effects of trofinetide were hypothesized to occur (Study 2566-003).

Trofinetide was also shown to bind significantly to N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at micromolar concentrations (Study 100056763). The modulation of NMDA and AMPA receptors are known to induce central nervous system (CNS) -mediated adverse events (AEs) which may be drug abuse-related. Under IND (140184), the Sponsor was asked to provide additional information to support their assertion that trofinetide did not show a signal of abuse and that abuse-related studies were are not needed. In response, the Sponsor submitted in vitro, in vivo, and phase 1 and 2 clinical studies adverse event assessments. CSS reviewed this information and concluded that inconsistent preclinical behavioral symptoms were reported (Irwin data), abuse-related AEs were not observed, and that there were no AEs related to a withdrawal syndrome upon discontinuation of the drug. Based on the data provided, CSS conveyed to the Sponsor that nonclinical and clinical abuse-related studies were not necessary and agreed with the Sponsor's proposed plan to assess abuse-related adverse event data (IND 114319, CSS review, August 20, 2021 by Dr. Edward Hawkins).

In their NDA, the Sponsor has included a drug abuse potential assessment (Module 2.7.4 Summary of Clinical Safety), which includes an assessment of abuse-related adverse events (AEs) and withdrawal-related AEs, and functional assays evaluating the effects of trofinetide on NMDA receptors (Study 21NSAPR121).

II. Conclusions

There is no need to further evaluate the abuse potential of trofinetide. This is based on our review of the drug abuse potential assessment (Module 2.7.4 Summary of Clinical Safety,

Section 2.7.4.5.6, July 12, 2022, pages 201 to 212; and Section 2.7.4.5.6, 120-day Safety Update, November 2022, pages 130 to 140), the functional assay data from Study 21NSAPR121, and the finding that centrally-mediated adverse events (AEs) following trofinetide administration did not present a signal of abuse potential or dependence.

In Study 21NSAPR121 using patch-clamp electrophysiology, trofinetide (up to 30 μM) did not demonstrate significant agonist or antagonist activity on NMDA receptor currents. Trofinetide (10 μM) also did not block NMDA currents in comparison to the blockage by MK-801 (dizocilpine,10 μM), an NMDA receptor pore blocker (Study 21NSAPR121).

For drug abuse-related AEs, when administered to healthy subjects and to subjects with Rett syndrome (RTT) and other neurological conditions (fragile X syndrome (FXS) and traumatic brain injury (TBI)), centrally-mediated AEs potentially related to trofinetide included: somnolence, headache, dizziness, anxiety, lethargy, fatigue, syncope vasovagal, decreased appetite, irritability, seizure, insomnia, bruxism and paranesthesia. These symptoms are not specific abuse-related effects that are linked to euphoric like properties and reported with abusable drugs. The discontinuation AEs potentially related to trofinetide use were limited and included vomiting. All other centrally-mediated and discontinuation AEs were reported by less than 2% of subjects. These conclusions draw on data from the following locations in the NDA submission:

- Trofinetide -Treatment emergent adverse events (TEAEs) by treatment, MedDRA system organ class and preferred term from Phase 1 Clinical Study Reports: *Study ACP-2566-006*, Table 14.3.1.3, pages 102 to 104; *Study ACP-2566-007*, Table 14.3.1.2, page 95; *Study Neu-2566-HV-005*, Table 14.3.2, pages 84 to 85; *Study Neu-2566-HV-001*, Table 14.3.5, pages 113 to 116; *Study Neu-2566-HV-002*, Table 6a, page 49; *Study Neu-2566-HV-003*, Table 6f, page 67.; *Study Neu-2566-HV-004*, Table 14.3.2, page 89 to 91; and *Study ACP-2566-008*, Table 14.3.1.3, pages 279 to 288; and from Phase 3 Clinical Study Report: *Study ACP-2566-009*, Table 14.3.1.3, pages 69 to 71

- Trofinetide -ISS: TEAEs Related to Physical Dependence Potential by System Organ Class and Preferred Term Safety Analysis Set Trofinetide-Treated Subjects with Rett Syndrome in Phase 3 Double-Blind and Open-Label Long-Term Extension (*Studies ACP-2566-003, ACP-2566-004, ACP-2566-005*), Table RTTLT.6.15, pages 2924 to 2933

- Trofinetide -ISS: TEAEs by System Organ Class, Preferred Term Safety Analysis by Dose or Trofinetide Group: Table RTTDB.6.7, pages 1859 to 1863 (*Studies Neu-2566-RETT-001, Neu-2566-RETT-002, ACP-2566-003*); Table ALLDB.6.2 (*Studies Neu-2566-TBI-003, Neu-2566-FXS-001, Neu-2566-RETT-001, Neu-2566-RETT-002, ACP-2566-003*), pages 1115 to 1134; Table RTTLT.6.7 (*Studies ACP-2566-003,*

ACP-2566-004, ACP-2566-005), pages 2870 to 2883; and Table RTTOL.6.2 (*Studies ACP-2566-004, ACP-2566 -005*), pages 3167 to 3198

- Trofinetide- Module 2.7.4 Summary of Clinical Safety, TEAEs by Preferred Term Considered Related to Study Drug Experienced by ≥2% of Subjects in the All Trofinetide Group: RTTDB Pool Table 2.7.4-38; page 92, ALLDB Pool Table 2.7.4-41, page 96; RTTLT Pool Table 2.7.4-44, page 102; and RTTOL Pool Table 2.7.4-47, page 106

III. Recommendations (to the Division)

- Trofinetide does not appear to present a potential for abuse and does not warrant scheduling under the Controlled Substances Act.
- Section 9 (Drug Abuse and Dependence) should not be included in the labeling for trofinetide.
- CSS will not need to review this NDA further. However, we recommend that the Division contact CSS if they identify any abuse-related concerns associated with the product during the course of their review of this NDA.

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/

JOVITA F RANDALL-THOMPSON
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 21, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217026
Product Name and Strength:	Daybue (trofinetide) oral solution, 200 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Acadia Pharmaceuticals Inc.
FDA Received Date:	July 12, 2022
TTT ID #:	2022-390
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Daybue (trofinetide) oral solution, the Division of Neurology 1 (DN 1) requested that we review the proposed Daybue Prescribing Information (PI), Patient Prescribing Information (PPI), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Example Dosing Table	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, PPI, carton labeling, and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Acadia Pharmaceuticals Inc.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The dosing table does not contain the recommended dose of trofinetide in mg.	Incomplete dosing information may increase the risk for wrong dose medication errors.	We recommend adding the dose in mg as a separate column in the dosing table in HPI and Section 2. See

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Appendix E for an example dosing table.
2.	The dosing tables contain symbols.	Symbols can be error prone and may increase the risk for wrong dose medication errors.	We recommend replacing symbols with their intended meaning and deleting unnecessary symbols. See Appendix E for an example dosing table.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Sections 2.1 and 2.2 contain instances of passive voice.	Passive voice is less direct and concise than active voice.	We recommend revising the statements (b) (4) " in Section 2.1 and " (b) (4) " in Section 2.2 to read "Administer Daybue orally"
2.	In Section 2.2, the statement "A calibrated measuring device" is unclear.	Selecting an unacceptable measuring device may increase the risk for wrong dose medication errors.	We propose specifying acceptable types of measuring devices. For example, "A calibrated measuring device, such as an oral syringe or oral dosing cup, should be obtained from the pharmacy to measure and deliver the prescribed dose accurately. A household measuring cup, (b) (4) are not adequate measuring devices."
3.	Storage information is presented in Section 2.2 which describes administration information.	The presentation of unnecessary information may detract from the prominence of the beyond use statement.	We recommend deleting the statements (b) (4)
4.	In Section 2.2, the statement (b) (4) " can be improved for clarity	Unclear discard instructions may increase the risk for deteriorated drug medication errors.	For clarity, we recommend the language "Discard any unused oral solution after 14 days of first opening the bottle" or similar because we will

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	and align with recommendations for the carton labeling and container label.		recommend the Sponsor adds a similar "(b) (4)" statement on the carton labeling and container label.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	In Section 16.1, the statement "(b) (4) is inconsistent with the strength presentation throughout the rest of the labeling.	Inconsistent strength presentation may increase the risk for wrong dose medication errors.	We recommend presenting the strength as 200 mg/mL.
2.	In Section 16.2, the statement "(b) (4) can be improved for clarity and to align with recommendations for Section 2.2 and carton labeling and the container label.	Unclear discard instructions may increase the risk for deteriorated drug medication errors.	We recommend clarifying the beyond use statement and aligning with language recommended for Section 2.2 and the carton labeling and the container label.
Full Prescribing Information – Section 17 Patient Counseling			
1.	The section "Daybue Administration" contains language of concern that was identified in other areas of the labeling (i.e., calibrated measuring devices, storage information, and beyond use information).	This may increase the risk for wrong dose or deteriorated drug medication errors.	We recommend revising the language to align with finalized language recommended for Sections 2.1, 2.2 and 16.2.
Patient Prescribing Information			
1.	The sections "How should I take Daybue"	Unclear patient instructions may increase the risk for	We recommend revising the language to align with finalized

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	and "How should I store Daybue" contain language of concern we identified in other areas of the labeling. Specifically, (b) (4) and (b) (4)	wrong dose or deteriorated drug medication errors.	language recommended for Sections 2.1, 2.2, 16.2, and 17 of the PI, including the addition of the statement that specifies appropriate measuring devices and revised beyond use statement.

5 RECOMMENDATIONS FOR ACADIA PHARMACEUTICALS INC.

Table 3. Identified Issues and Recommendations for Acadia Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The proposed format for the expiration date reads "(b) (4)	We are unable to assess the expiration date from a medication error perspective.	Please specify whether the month will be represented with numerical or alphabetical characters. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month,

Table 3. Identified Issues and Recommendations for Acadia Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The dosage form statement is presented with the strength statement, and not immediately following the established name.	This is not in alignment with our Guidance document Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors available from: https://www.fda.gov/media/158522/download	We recommend moving the dosage form statement to appear either on the same line as the established name or directly below the established name.
3.	The [redacted] (b) (4) " statement does not align with language used in the prescribing information (PI).	This can be improved for consistency with the PI.	We recommend revising the " [redacted] (b) (4) " statement to read: "Recommended Dosage: see prescribing information."
4.	The statement [redacted] (b) (4) ." can be improved for clarity.	Unclear discard instructions may increase the risk for deteriorated drug medication errors.	Please revise [redacted] (b) (4) ." to read "Discard unused portion 14 days after first opening" and relocate immediately below the "Date of first opening" statement. Note, we recommend adding a "Date of first opening" statement to the carton labeling below.
5.	The storage statement can be improved for clarity and directness.	As currently presented, this may increase the risk for deteriorated drug medication errors.	We recommend revising the storage statement to read "Must be refrigerated. Store at 2°C to 8°C (36°F to 46°F). Also,

Table 3. Identified Issues and Recommendations for Acadia Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			please present in bold font to ensure this information is not overlooked.
Carton Labeling			
1.	Some users may store the container within the carton. The date of first opening is an important component of the use process but a space to write this information is not present on the carton.	Absence of this information may increase the risk for deteriorated drug medication errors.	Since there appears to be space on the side and back panels, we recommend adding the "Date of first opening _ _ /_ _ /_ _" statement to the carton labeling in alignment with the container label.
2.	The net quantity statement is located in close proximity to the strength statement.	This may increase the risk for numerical confusion.	We recommend relocating the net quantity statement to an area not in close proximity to the strength statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Daybue that Acadia Pharmaceuticals Inc. submitted on July 12, 2022.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Daybue</th></tr>
<tr><td>Initial Approval Date</td><td>n/a</td></tr>
<tr><td>Active Ingredient</td><td>trofinetide</td></tr>
<tr><td>Indication</td><td>treatment of Rett syndrome in adults and pediatric patients 2 years of age and older</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>Oral solution</td></tr>
<tr><td>Strength</td><td>200 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td><table><tr><th>Patient Weight</th><th>DAYBUE Dose</th></tr><tr><td>9 kg to <12 kg</td><td>25 mL twice daily</td></tr><tr><td>≥12 kg to <20 kg</td><td>30 mL twice daily</td></tr><tr><td>≥20 kg to <35 kg</td><td>40 mL twice daily</td></tr><tr><td>≥35 kg to <50 kg</td><td>50 mL twice daily</td></tr><tr><td>≥50 kg</td><td>60 mL twice daily</td></tr></table></td></tr>
<tr><td>How Supplied</td><td>Carton containing one bottle (450 mL fill)</td></tr>
<tr><td>Storage</td><td>Store in an upright position refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze.</td></tr>
<tr><td>Container Closure[a]</td><td>500 mL high-density polyethylene (HDPE) bottles, closed with a (b) (4) child resistant closure (CRC).</td></tr>
</table>

[a] Container closure specifications available from: \\CDSESUB1\EVSPROD\nda217026\0001\m3\32-body-data\32p-drug-prod\trofinetide-oral-solution-all\32p7-cont-closure-sys\32p7-container-closure-system-trof-oral-solution.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 28, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, trofinetide, Daybue, and NDA 217026. We did not identify any previous reviews.

APPENDIX E. EXAMPLE DOSING TABLE

Table 1. Recommended Dosage

Patient Weight	DAYBUE Dosage (mg)	DAYBUE Dosage Volume (mL)
9 kg to less than 12 kg	5,000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6,000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or more	12,000 mg twice daily	60 mL twice daily

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Daybue labels and labeling submitted by Acadia Pharmaceuticals Inc. on July 12, 2022.

- Container label
- Carton labeling
- Prescribing Information and Patient Prescribing Information (Images not shown), available from \\CDSESUB1\EVSPROD\nda217026\0001\m1\us\draft-labeling-text-word.docx

F.2 Label and Labeling Images

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JOHN C MORRIS
11/21/2022 01:33:43 PM

STEPHANIE L DEGRAW
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217026
Submission Number	001
Submission Date	7/12/2022
Date Consult Received	7/26/2022
Drug Name	Trofinetide (ACP-2566)
Indication	Treatment of Rett syndrome in adults and pediatric patients 2 years of age and older
Therapeutic Dose	12g BID (>= 50 kg)
Clinical Division	DN1
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 7/26/2022 regarding the sponsor's QTc evaluation. We reviewed the following materials:

- TQT study ECG analysis report (NDA 217026, eCTD 0001; link);
- Study report Neu-2566-RTT-002 (NDA 217026, eCTD 0001; link);
- Study report ACP-556-003 (NDA 217026, eCTD 0001; link);
- Study report ACP-556-004 (NDA 217026, eCTD 0001; link);
- TQT study PK report (NDA 217026, eCTD 0001; link);
- Previous IRT for IND 114319 review dated 01/10/2019; 04/09/2020; 09/14/2020 in DARRTS;
- Investigator's brochure (IND 114319 / eCTD 0182; link);
- PBPK Renal Impairment Brief Report (NDA 217026, eCTD 0001; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 217026 / eCTD 0003; link).

1 SUMMARY

The totality of evidence from the TQT study suggests an absence of QTc prolongation at the clinical exposure; however, the data does not permit excluding QTc prolongation at the high clinical exposure scenario (renal impairment).

The effect of trofinetide was evaluated in a thorough QT study (ACP-2566-008). The highest dose that was evaluated was a single 24g dose, which is expected to cover the clinical exposure, but not the high clinical exposure scenario (renal impairment). Based on PBPK modeling, (b) (4), the increase in Cmax with ESRD is 1.7-fold (section 3.1.2). Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that trofinetide is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results. Findings of

this analysis are further supported by lack of QTc interval prolongation using by-time analysis (section 4.3) and categorical analysis (section 4.4). The negative findings of the thorough QT study are further supported by the lack of concerning outliers or cardiac safety findings in the phase 3 study (double-blind and open-label extension).

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration	ΔΔ	90% CI
QTc	Trofinetide 24g	195.6	-3.1	-5.4, -0.9

For further details of the FDA analysis, please see section 4.

While the maximum lower bound for moxifloxacin exceeded 5 msec, it is not possible to conclude that the study has demonstrated assay sensitivity because of the limited post-dose time-points (section 3.2.1.1). To address this limitation, we conducted QT bias analysis. This analysis showed significant negative QTc bias when comparing provided QT measurements and automatic QT measurements (section 4.2.2). Sensitivity analysis to QT measurement algorithm was therefore conducted, which confirmed the results of the primary analysis (section 4.5.1).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN eCTD 0001 (link) from the CSS-IRT

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At (b) (4) the maximum (b) (4) recommended dose in healthy adult subjects, trofinetide does not prolong the QT interval to any clinically relevant extent.

(b) (4)

(b) (4)

3 SPONSOR'S SUBMISSION

3.1 BACKGROUND

3.1.1 Overview

Trofinetide is a synthetic analog of tripeptide glycine-proline-glutamate with a proposed indication of treatment of Rett syndrome in adults and pediatric patients 2 years and older. The recommended dose is twice daily, without regard to food, according to patient weight. Table 2 shows the proposed weight-band based dosing for trofinetide.

Table 2: Labeled dosing (Trofinetide Oral solution, 1 g/5 mL)

Patient Weight	DAYBUE Dose
9 kg to <12 kg	25 mL twice daily
≥12 kg to <20 kg	30 mL twice daily
≥20 kg to <35 kg	40 mL twice daily
≥35 kg to <50 kg	50 mL twice daily
≥50 kg	60 mL twice daily

(b) (4)

(b) (4)

A thorough QT study protocol (ACP-2566-008) was submitted for review in 2020. (b) (4)

We disagreed with this design (b) (4) (DARRTS 04/09/2020). We recommended that the sponsor considers a nested cross-over study for moxifloxacin and placebo administered through periods 1-3 to establish assay sensitivity or consider a two-part TQT study. The revised study protocol included two cohorts. Subjects in cohort 1 received ascending doses of trofinetide in periods 2 through 4 (12g, 18g, and 24g) and subjects in cohort 2 received placebo in periods 2 through 4. In periods 1 and 5 subjects received placebo or moxifloxacin as a crossover for assay sensitivity analysis with ECGs collected up to 4 h post-dose. The study included collection of a baseline during the screening period, used by the sponsor as the primary baseline calculation, as well as a predose baseline within each period and dose group. We recommended sex as a factor is not necessarily to be included in the by-time and concentration-QTc model (DARRTS 09/14/2020).

3.1.2 Clinical Pharmacology

Trofinetide is formulated as solution (1 g / 5 mL trofinetide) for oral administration. It exhibits dose-proportional increase in exposure up to 12g and has minimal to no accumulation following twice daily dosing ($T_{1/2,\alpha}$ = 1.5 h, $T_{1/2,\beta}$ = 30 h). The population

predicted mean steady state blood Cmax following 5g BID, 6g BID, 8g BID, 10g BID, and 12 g BID were 203 µg/mL, 174 µg/mL, 156 µg/mL, 146 µg/mL, and 143 µg/mL, respectively, with median Tmax of 2 hours. Based on the sponsor's assessments, age, sex, race, and hepatic impairment have no clinically relevant impact on PK of trofinetide. Renal route accounts for up to ~80% of trofinetide excretion. Based on the sponsor's PBPK modeling, mean plasma Cmax was predicted to be 1.07-fold, 1.3-fold, 1.5-fold, and 1.7-fold higher in renal impairment severity of mild, moderate, severe, and ESRD, respectively, compared with normal renal function (PBPK report, page 9 of 51). The sponsor states that trofinetide is not recommended in subjects with moderate or severe renal impairment until results from a dedicated renal impairment study becomes available. Since trofinetide is not hepatically metabolized and is eliminated unchanged in urine, drug-drug interactions are not expected. See the table of highlights of clinical pharmacology and cardiac safety for additional summary on trofinetide clinical pharmacokinetics.

Based on the presented information, the anticipated high clinical exposure scenario is when trofinetide is administered to subjects 9 to < 12 kg at 5g BID. Therefore, the observed mean blood Cmax of 196 µg/mL at the maximum tested dose of 24g in the TQT study provides adequate coverage of the clinical exposure of 203 µg/mL.

3.1.3 Nonclinical Safety Pharmacology Assessments

Refer to sponsor's highlights of clinical pharmacology and clinical safety.

Trofinetide was tested at concentrations of 3, 36, and 6300 µg/mL (approximately 11, 115, and 20,000 µM) for its effect on hERG channel-mediated potassium current in HEK293 cells stably transfected with hERG channels (Study 050627.OQM; Study 061211.OQM). Trofinetide inhibited hERG currents by 1.4% at both 3 and 36 µg/mL (not statistically significant) and by 6% at 6300 µg/mL (statistically significant). An IC50 could not be established. At the highest concentration tested (based on free levels of the compound), there is a margin of >75-fold the human Cmax of 83.7 µg/mL at a dose of 200 mg.

In a single-dose CV safety pharmacology study in telemetered dogs (Study GBH5000), a 2-hour IV infusion of 60, 120, 200, or 400 mg/kg/h (total doses of 120, 240, 400, and 800 mg/kg) was without effect on arterial blood pressure, heart rate, RR interval, PR interval, QRS duration and QT interval. The corrected QT intervals were considered unaffected by the administration of trofinetide at 60 or 120 mg/kg/h (end of infusion concentrations of 158 and 335 µg/mL respectively). Corrected QT intervals were slightly (<10%) prolonged at doses of 200 mg/kg/h and 400 mg/kg/h. QTc prolongations did not exceed 30 ms, and no arrhythmias or AEs accompanied the QTc prolongations. There was a statistically significant increase in QTc from vehicle of 18.2 ms at 200 mg/kg/h and 13.6 ms at 400 mg/kg/h (maximum increase was ~8%). The increases in QTc were associated with mean peak plasma levels of 568 and 933 µg/mL for doses of 200 and 400 mg/kg/h, respectively.

Reviewer's comment: *The hERG assay showed deviations (uncertainty in sample collection method for drug concentration verification; lack of reference drugs; lack of multiple concentrations of positive control drug) of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1. The estimated hERG safety*

margin was greater than ~ 32x (6% inhibition at 20 mM), which does not preclude excluding a potential risk for QT prolongation by direct inhibition of the hERG current at therapeutic exposure. The results of the in vivo dog study show a potential for QTc prolongation with increases in the QTc interval observed near Tmax, however, the findings were not dose-proportional.

3.2 SPONSOR'S RESULTS

Sponsor used time-matched baseline collected during the screening visit for all analysis.

3.2.1 By-Time Analysis

The primary analysis for trofinetide was based on exposure-response analysis, please see section 3.2.3 for additional details.

Sponsor presented by-time analysis for all intervals (QTcF, HR, PR and QRS).

Trofinetide demonstrated no clinically meaningful effects on QTcF, HR, PR and QRS interval duration, or cardiac morphology in healthy adult subjects in this study.

Reviewer's comment: *Reviewer's by-time analysis results are similar to the sponsor's analysis results. For additional details, please see section 4.3.*

3.2.1.1 Assay Sensitivity

Sponsor's report shows that the maximum lower bound for moxifloxacin was 5.5 for hour 4 (i.e., 8.9 msec [90% CI: 5.5,12.3]).

Reviewer's comment: *Reviewer's analysis also shows that the maximum lower bound for moxifloxacin exceeded 5 msec (i.e., 8.7 msec [97.5% CI: 5.0, 12.4]). However, since the study only collected ECGs up to 4 h post-dose in the moxifloxacin periods it is not possible to assess if the time-course of moxifloxacin supports demonstrating assay sensitivity. QT bias analysis was therefore conducted, which showed negative QT bias, which did not influence the concentration-QTc relationship.*

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

Reviewer's comment: *Reviewer's independent analysis shows negative QTc bias. Please see section 4.2.2 for additional details.*

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *Reviewer's categorical analysis also shows similar results. For additional details, please see section 4.4.*

3.2.3 Exposure-Response Analysis

The primary endpoint is ΔQTcF and the relationship between ΔQTcF and trofinetide blood concentration is investigated by linear mixed-effects modeling. The model includes

the ΔQTcF values as the dependent variable with time, treatment, and period as fixed effects, and the corresponding time-matched blood concentrations (values lower than the quantification limit or if assigned to placebo will be set to zero) and predose QTcF as covariates, with subject and subject-by-period interaction as random effects.

A slightly positive slope (0.0121; 90% CI: 0.003, 0.0239) was observed using this model. The predicted QTcF increase at the highest dose in the study (24 g) using this model was -0.31 (90% CI: -3.989, 6.010).

Reviewer's comment: *The sponsor's concentration-QTc model deviates from the model recommended in the white paper, e.g., it includes treatment group (i.e., 12, 18, 24 g trofinetide or placebo) and period and no model diagnostic plots could be located. The reviewer analyzed the concentration-QTc relationship using the white paper recommended model (section 4.5.1), which like the sponsor's analysis excluded 10 msec QTc prolongation at the 24 g dose.*

3.2.4 Cardiac Safety Analysis

There were no deaths or discontinuations due to treatment-emergent adverse event (TEAE). One subject experience a serous AE (hospitalization due to COVID-19). No subject had a TEAE in the 'Cardiac Disorders' SOC or the PT of "QTc interval prolongation."

Reviewer's comment*: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

Pre-dose baseline within each period was used as baseline instead of the time-matched baseline collected during the screening visit in all analysis.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

We conducted QT bias assessment by evaluating the relationship between the difference in the sponsor-provided QT measurements and those from the automated algorithm used by the ECG Warehouse, and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (active/placebo/overall) is presented for QTcF (Table 3). This analysis suggests the presence of significant negative treatment bias and sensitivity analysis to ECG measurement methodology was therefore performed (Figure 7), which did not show an impact on the concentration-QTcF relationship.

Table 3: QTcF Bias Assessment by Treatment

Treatment	# of ECGs	Mean (SD)	Slope [95% CI], msec per 100 msec
Overall	5476	10.29 (23.96)	-27.61 [-29.22 to -25.99]
Trofinetide	1565	14.13 (24.78)	-17.02 [-20.28 to -13.75]
Placebo	2173	7.59 (23.08)	-27.78 [-30.01 to -25.55]
Moxifloxacin	584	10.08 (22.51)	-28.57 [-33.56 to -23.59]

4.3 By-Time Analysis

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The by-period model included treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. Placebos were not pooled across periods. The model also included an unstructured covariance matrix to explain the associations among repeated measures within the treatment.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 4.

Figure 1: Mean/Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

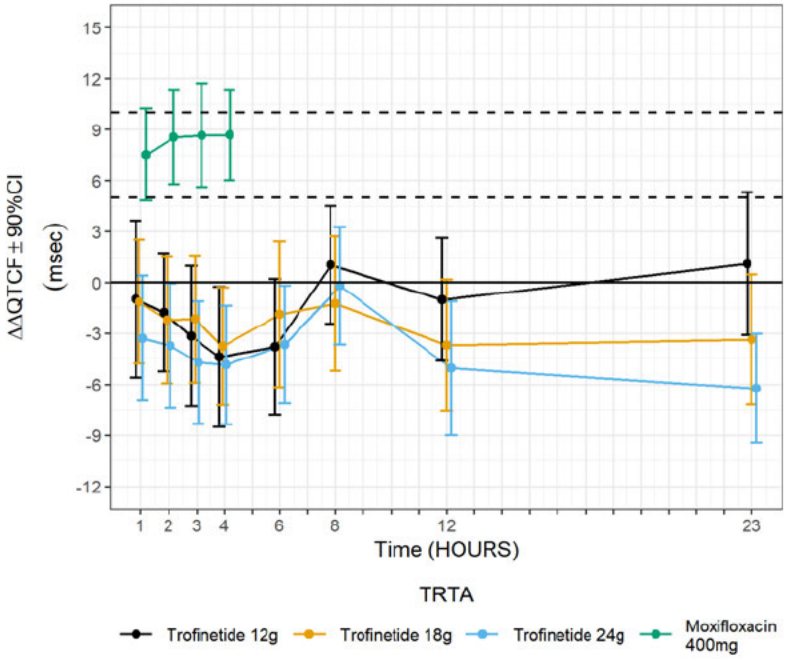


Table 4: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Treatment	Period (C)	Nact / Npbo	Time (HOURS)	ΔΔQTCF (msec)	90.0% CI (msec)
Trofinetide 12g	Period 2	20 / 20	23.0	1.1	(-3.1 to 5.3)
Trofinetide 18g	Period 3	20 / 20	8.0	-1.2	(-5.2 to 2.7)
Trofinetide 24g	Period 4	18 / 20	8.0	-0.2	(-3.6 to 3.2)

4.3.1.1 Assay Sensitivity

The primary method for assay sensitivity is by-time analysis. The statistical reviewer used a linear mixed model to analyze the moxifloxacin effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

The time-course of changes in ΔΔQTcF is shown in Figure 1 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 4).

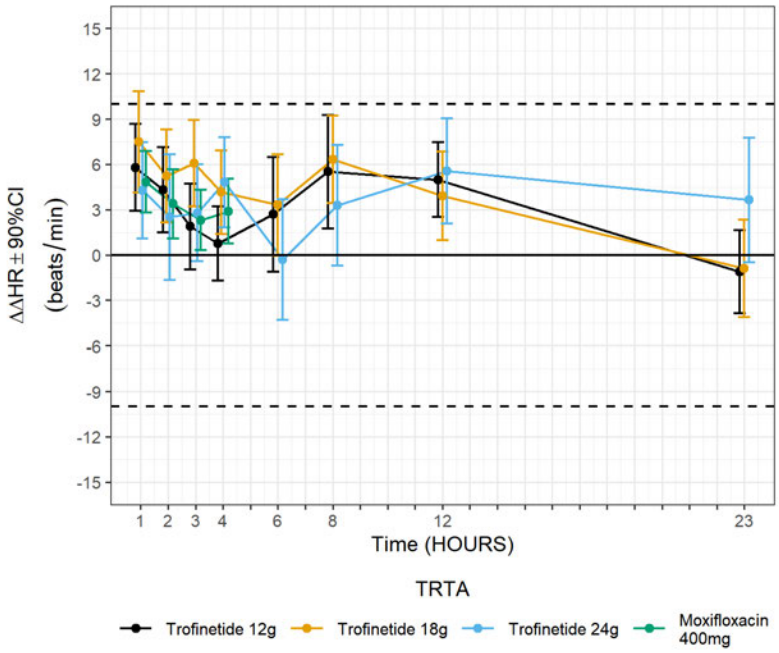
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Time (HOURS)	Moxifloxacin 400 mg				
	ΔQTCF		ΔΔQTCF		
	LSmean (msec)	LSmean placebo (msec)	Diff LS Mean (msec)	90.0% CI (msec)	97.5% CI (msec)
4.0	9.2	0.5	8.7	6.0, 11.4	5.0, 12.4

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

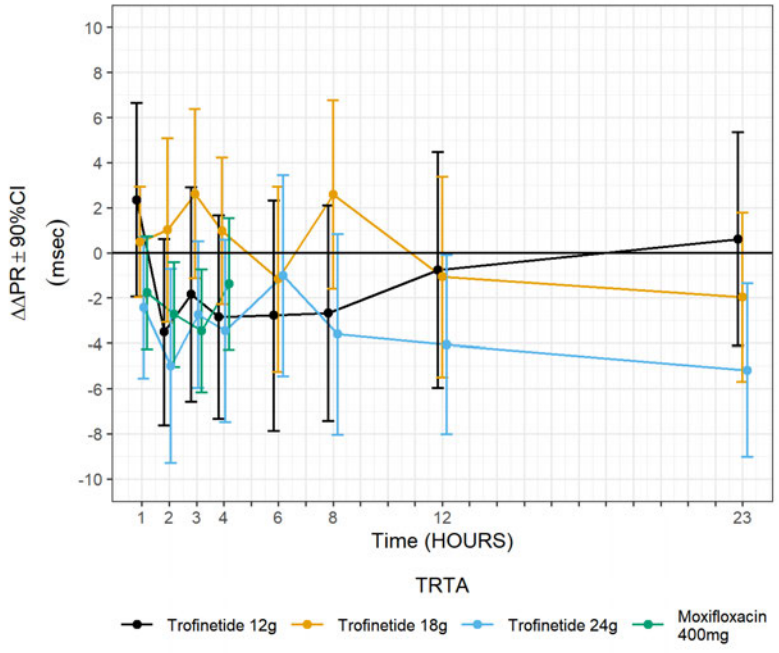
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

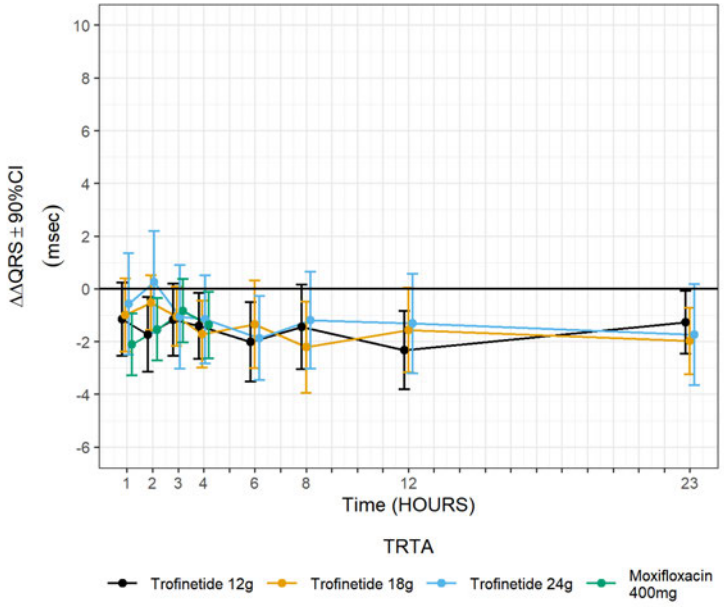
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF >480 msec and/or ΔQTcF >60 msec for any of the dose levels of trofinetide.

4.4.2 HR

None of the subjects experienced HR >100 beats/min for any of the dose levels of trofinetide.

4.4.3 PR

None of the subjects experienced PR >220 msec with 25% increase over baseline for any of the dose levels of trofinetide.

4.4.4 QRS

None of the subjects experienced QRS >120 msec; with and without 25% increase over baseline for any of the dose levels of trofinetide.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]

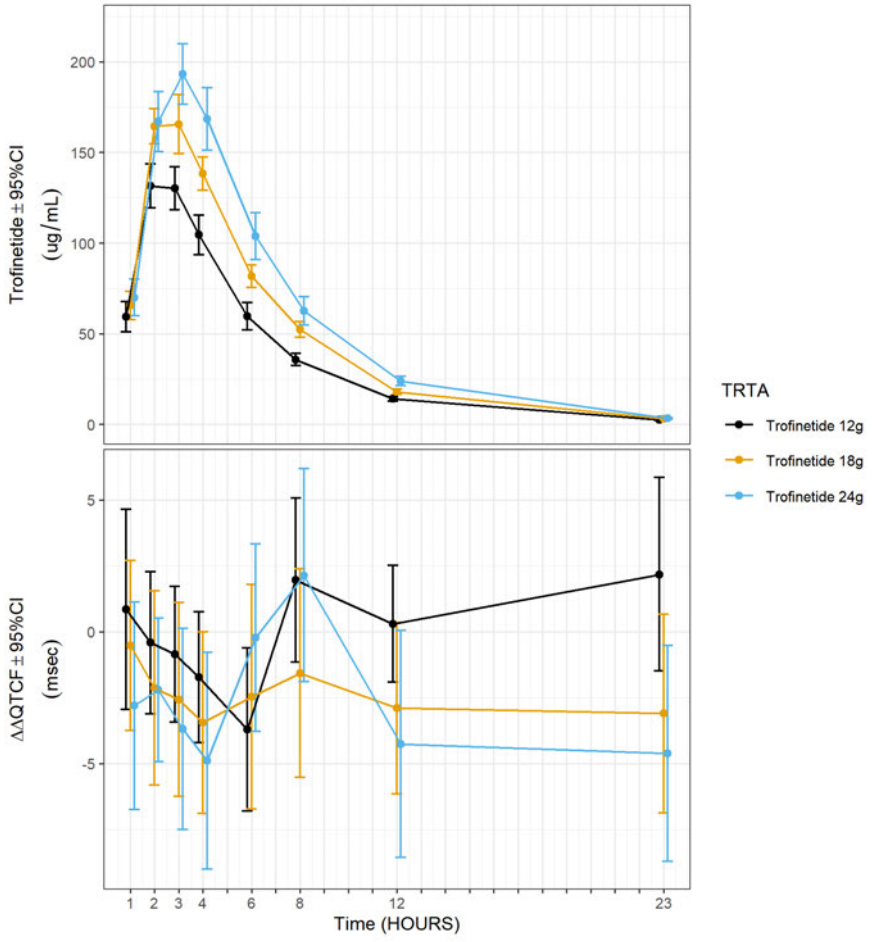
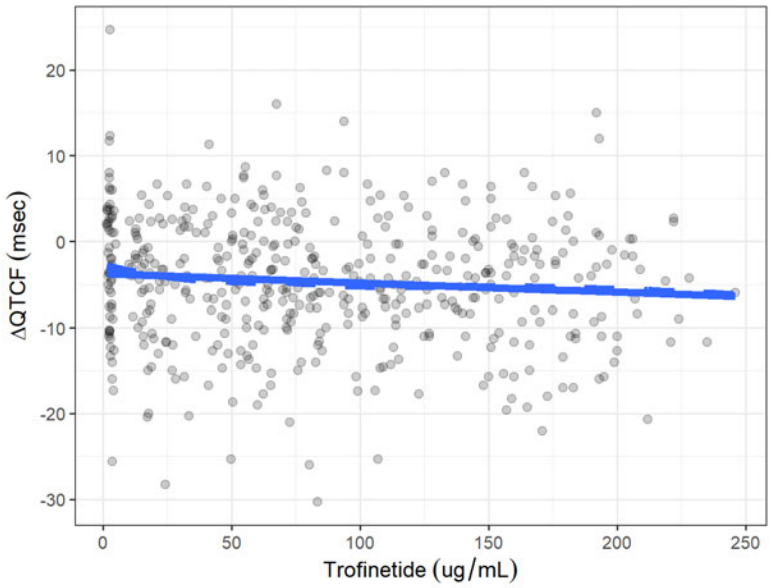


Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows

[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

the relationship between drug concentration and ΔQTcF, and supports the use of a linear model.

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data. Because of observed negative QTc bias (Table 2), the concentration-QTc analysis was performed using both semi-automatic measurements and fully-automatic measurements and included in the goodness-of-fit plot showing no differences (Figure 7). Predictions from the concentration-QTcF model are provided in Table 14 using the semi-automatic measurements.

Figure 7: Goodness-of-fit Plot for QTcF

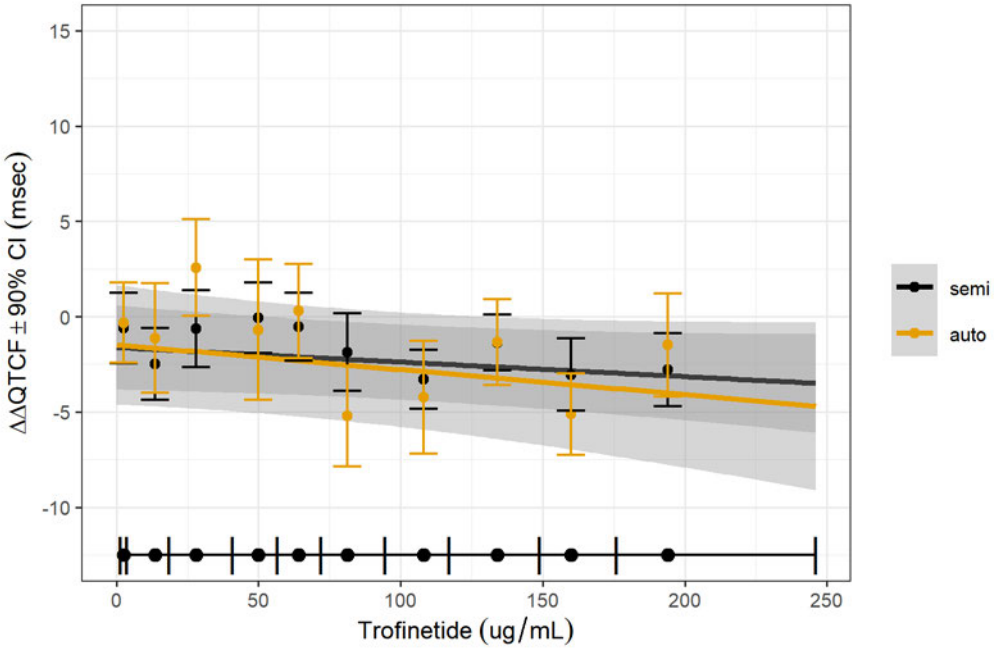


Table 6: Predictions from Concentration-QTcF Model

Actual Treatment	Trofinetide (ug/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Trofinetide 12g	141.4	-2.7	(-4.7 to -0.7)
Trofinetide 18g	175.0	-3.0	(-5.1 to -0.8)
Trofinetide 24g	195.6	-3.1	(-5.4 to -0.9)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

The phase 3 study (ACP-2566-003) was a randomized, double-blind, placebo-controlled, parallel-group study which included 187 patients randomized 1:1 to trofinetide (labeled dosing) or placebo. ECGs were collected in this study at screening, baseline, 2 to 3 h after first dose (corresponds to Tmax) and end of study in triplicates. Single ECGs were also collected at weeks 2 and 6 (timing not specified). Due to the lack of significant accumulation (see section 3.1.1), the ECG at Tmax on day 1 represents Cmax,ss. The change from baseline at this time-point was 0.5 msec (SE: 1.52) and 3.1 msec (1.41) for trofinetide and placebo respectively. There was no post-dose maximum QTcF > 500 msec or > Δ60 msec in the trofinetide treated patients. The sponsor did not report any AEs related to significant ventricular arrhythmias or sudden cardiac death. However, a slight numerical imbalance in seizures were observed (trofinetide: 8 [8.6%] vs placebo: 5 [5.3%]).

ECGs were also collected in the 40-week open-label extension study to the phase 3 study (ACP-5566-004, ongoing) at baseline, 2-3 h post the first dose and at weeks 2, 12, 26 and 40/EOT. For patients that completed the week 12/EOT visit in ACP-2566-003, that was used as the baseline ECGs. ECGs at baseline, post-dose first dose and at week 40/EOT were collected in triplicate. There were no QTcF > 500 msec in this study and two patients experienced a QTcF > Δ60 msec compared to the double-blind baseline at a single time-point. Both patients received placebo during the DB phase. Using the OL baseline, there were no measurements > Δ60 msec. Like the DB phase, there were no reported AEs related to significant ventricular arrhythmias or sudden cardiac death, but 11 patients (7.1%) reported seizures.

Twelve-lead ECGs were also collected in Neu-2566-Rett-002, a randomized, double-blind, placebo-controlled, dose-ranging study, at screening, pre- and post-placebo run-in, days 21, 28, 42 and 54 (before dose down titration) and at day 66/follow-up. Timing of ECG collection relative to dosing is not clear. Patients in the study were randomized to 50, 100, 200 mg/kg trofinetide (titrated over up to 54 days) and placebo. The Cmax for the highest dose group was 83.7 ug/mL, which is below the clinical exposure scenario (see section 3.1.1). There were three subjects with post-baseline QTcF > 450 msec (no QTcF > 480 msec), no reported AEs related to significant ventricular arrhythmias or sudden cardiac death, and one subject experienced a seizure.

4.7 NONCLINCIAL ASSAY ASSESSMENT

The sponsor evaluated the effects of trofinetide (NNZ-2566) on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The hERG study report (061211-OPM;link) describes the potential effects of trofinetide on the hERG current in HEK293 cells. The hERG current was assessed at near-physiological temperature (33 - 37 °C), using a voltage protocol that is similar to the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology. A full blocker (E-4031 at 0.5 µM) was added to the end of the experiment to assess the non-hERG currents evoked by the voltage protocol. The positive control (60 nM terfenadine) inhibited hERG potassium current by 82.9%. Samples of the test article solutions collected from the solution reservoir (before the perfusion line) were analyzed for concentration verification. The results from the sample analysis indicated that measured concentrations was 22 mM (108% of the target concentration 20 mM). Since the measured concentration was within ±10% acceptance range, the nominal concentration was used to describe drug effects. Trofinetide inhibited the hERG currents by 6.0 ± 0.8% at 20 mM

The sponsor also evaluated the effects of trofinetide on hERG current at lower concentrations in another hERG study. The in vitro hERG assay (050267.OQM) was conducted under the same conditions (temperature, voltage protocols, positive control and drug verification method, etc.) by the same CRO ([redacted](b) (4)). The positive control (60 nM terfenadine) inhibited hERG potassium current by 86.9%. Trofinetide inhibited the hERG current by 1.4% and 1.4% at 10 and 100 µM, respectively.

Taken together, trofinetide inhibited the hERG currents by 1.4%, 1.4% and 6.0% at 10 µM, 100 µM and 20,000 µM. The estimated IC50 for the inhibitory effect of trofinetide on hERG current was expected to be greater than 20 mM.

The hERG safety margins of trofinetide on hERG current are summarized below:

Table 7 Safety Margin of trofinetide on hERG Current

	Cmax (µg/mL)	*Protein Binding*	*Free Cmax (µg/mL)*	*hERG IC50 (µM)*	*Mol Weight (g/mol)*	*Safety Margin (Ratio)*
trofinetide	*203*	*4%*	*195*	*>20,000 (6%)*	*315.3*	*>32x*

Cmax,ss: 203 µg/mL (see section 3.1.1).

The assessment of the hERG assay is summarized below:

Table 8 Evaluation of In Vitro hERG Assays

Best Practice Element	***Deviation/Issue***	***Impact of Deviation/Issue***
Temperature (35-37°C)	*None*	
Voltage Protocol	*Lack of steps in the voltage protocol to enable cell*	*Cannot determine the input resistance and monitor cell's health*

	health monitoring throughout the experiment	
Recording Quality	*None*	
IC50 Calculation	*None*	
Concentration Verification	*Solution sample was collected in the solution reservoir*	*May slightly underestimate the drug loss but is not likely to impact the safety margin as the non-specific binding or absorption by the perfusion system is minimum at such high concentration (20 mM).*
Positive Control	*Only one concentration of positive control was tested*	*The potency (i.e., IC50 value) of the positive control drug cannot be determined*
Negative Control	*None*	

The in vivo dog study (GBH5000) assessed the potential effects of trofinetide on ECG parameters following a single dose (120, 240, 400 and 800 mg/kg, respectively) of trofinetide administered as a an intravenous infusion over 2 h in conscious dogs. For each dose, ECG data collection commenced at least 30 min before dosing and ended approximately 22 h after dosing. Venous blood samples (approximately 2 mL) for determination of test substance in plasma were taken at -5, + 10, 30, 60, 90, 120 (pre-end of infusion sample), 150, 180, 210 and 240 min after the start of dose administration (including the vehicle). Mean plasma Cmax following 120, 240, 400 and 800 mg/kg were 158 µg/mL, 335 µg/mL, 568 µg/mL and 933 µg/mL, respectively. Protein binding in dogs is not available and comparisons of exposures in the in vivo QT study to the high clinical exposure scenario is based on total concentration. The exposure at 120 mg/kg didn't exceed (~0.7x) the expected high clinical exposure (203 µg/mL). The exposures at, 240, 400 and 800 mg/kg doses exceeded (1.7x~4.6x) the anticipated therapeutic clinical Cmax in humans (203 µg/mL). There were no trofinetide -related QTc, PR, QRS changes at tested doses of 120 mg/kg (~ 0.7x the clinical exposure) and 240 mg/kg (~1.7x the clinical exposure). However, QTc interval was prolonged at 90 to 120 min (Tmax was ~ 120 min at 400 mg/kg) and 60 to 90 min (Tmax was ~90 min at 800 mg/kg) after the administration of 400 and 800 mg/kg, respectively. QTc intervals were increased by 16 ms and ~18 ms (7%~8% of the vehicle control) at 400 mg/kg (~2.8x high clinical exposure) and 800 mg/kg (~4.6x clinical exposure), respectively. There were no trofinetide -related PR and QRS changes at doses of 400 and 800 mg/kg. No positive control drugs were used in the study.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

See prior reviews under IND 114319 dated 04/09/2020 and 09/14/2020

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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