

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219474Orig1s000

OTHER REVIEW(S)

DIVISION of Dermatology and Dentistry
Associate Director for Labeling Review of the
Prescribing Information

Product Title	ADQUEY (difamilast) ointment, 1%
Applicant	Acrotech Biopharma, Inc.
Application/Supplement Number	NDA 219474
Type of Application/Submission ¹	Original NDA
Is Proposed Labeling in “Old” Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	TRADENAME is indicated for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older.
Approved Indication(s)	ADQUEY is indicated for the topical treatment of adults and pediatric patients 2 years of age and older with mild to moderate atopic dermatitis.
Date FDA Received Application	February 13, 2025
Review Classification (Priority/Standard)	Standard
Action Goal Date	February 13, 2026
Review Date	February 10, 2026
Reviewer	Matthew White

INTRODUCTION

This Associate Director for Labeling (ADL) review is for a 505(b)(1) original NDA for ADQUEY (difamilast) ointment, 1% for the topical treatment of adults and pediatric patients 2 years of age and older with mild to moderate atopic dermatitis. Difamilast is a new molecular entity - topical phosphodiesterase Type 4 (PDE-4) inhibitor. This Application was reviewed under “The Program” that applies to New Molecular Entity New Drug Applications and original Biologics License Applications. The FDA-approved topical phosphodiesterase-4 (PDE-4) inhibitors are EUCRISA and ZORYVE. EUCRISA (crisaborole) ointment, the first-in-class topical PDE-4 inhibitor, was approved in December 2016, for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. In March 2020, the indication was expanded to include children as young as 3 months of age. ZORYVE (roflumilast) cream, initially approved in 2022 for the topical treatment of plaque psoriasis, was approved for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older in July 2024, then expanded to include children 2 to 5 years of age in October 2025. Systemic PDE4 inhibitors include DALIRESP (roflumilast), OTEZLA (apremilast), and JASCAYD (nerandomilast). DALIRESP is an oral PDE4 inhibitor indicated as a treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in

adults with severe COPD associated with chronic bronchitis and a history of exacerbations; DALIRESP is not indicated in pediatric patients. OTEZLA is indicated for the treatment of adult patients with active psoriatic arthritis, plaque psoriasis who are candidates for phototherapy or systemic therapy, or oral ulcers associated with Behcet's Disease. OTEZLA is indicated for the treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with active psoriatic arthritis and moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. JASCAYD (nerandomilast), an oral PDE4 inhibitor, is not labeled with a warning and precaution for weight decrease, but weight decrease is described in "Adverse Reactions." JASCAYD is indicated for the treatment of idiopathic pulmonary fibrosis in adult patients.

LABELING HISTORY

The Applicant submitted the proposed labeling on February 13, 2025. Labeling discussions were initiated via email on January 23, 2026. The Applicant submitted agreed upon labeling on February 9, 2026.

The proposed proprietary name, ADQUEY, was reviewed by DMEPA and is conditionally acceptable. Refer to the DMEPA review in DARRTS (Reference ID: 5578779) for additional details.

DMEPA reviewed the Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling from a medication error perspective. Refer to the DMEPA reviews in DARRTS (Reference IDs: 5639885 and 5741338) for additional details.

The QT-IRT reviewed the Applicant's QTc assessment for difamilast ointment. The Applicant did not propose QTc labeling language. The QT-IRT's labeling recommendation were incorporated into the PI. Refer to the IRT review in DARRTS (Reference ID: 5628165) for additional details.

DPMH/Pediatrics was consulted to assess if difamilast has an effect on weight in pediatric patients 2 years of age and older with mild to moderate atopic dermatitis. Refer to the Pediatrics review in DARRTS (Reference ID: 5728375) for additional details.

The Materna Health team reviewed and revised subsections 8.1, 8.2 and section 17 of labeling for compliance with the PLLR. Refer to the MHT review in DARRTS (Reference ID: 5721968) for additional details.

OPDP reviewed the proposed PI provide by email on January 29, 2026, and February 2, 2026. Refer to the OPDP review in DARRTS (Reference ID: 5739983) for additional details.

PLT reviewed the proposed Patient Package Insert received by DMPP and OPDP on January 30, 2026, and February 2, 2026. Refer to the PLT review in DARRTS (Reference ID: 5740096) for additional details.

REVIEW

This review describes the updates implemented to the PI to help ensure that it:

- Is compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements,²
- Is consistent with labeling guidance recommendations³ and with CDER labeling policies, as appropriate,
- Conveys the essential scientific information needed for safe and effective use of the drug,
- Is clinically meaningful and scientifically accurate,
- Is a useful communication tool for health care practitioners, and
- Is consistent with other PI with the same active moiety, drug class, or similar indication, as appropriate

The following groups provided input to the review of the labeling:

Regulatory Project Manager	Craig Johnson
Nonclinical Reviewer	Renqin Duan
Nonclinical Team Leader	Jianyong Wang
Office of Clinical Pharmacology Reviewer(s)	James Mease Ying-Hong Wang (PBPK)
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla Yuching Yang (PBPK)
Clinical Reviewer	K Dev Verma
Clinical Team Leader	Melinda McCord
Statistical Reviewer	Matthew Guerra
Statistical Team Leader	Matthew Guerra
Cross-Disciplinary Team Leader	Melinda McCord
Division Director (OCP)	Jianmeng Chen
Associate For Therapeutic Review	Gordana Diglisic
Office Director (or designated signatory authority)	Nikolay Nikolov
DPMH Pediatric Team	Karen Fratantoni, Shetarra Walker, John Alexander
DPMH Maternal Health Team	Kerry R. Shaab, Tamara Johnson, Lynne P. Yao
OPQ	Sam Bain, Lawrence Perez, Ghaled Hamad, Baoqing Ma, Satheesh Podaralla, Kshitij Patkar, Marijke Koppenol-Raab, Neal Sweeney
OPDP	Eunice Chung-Davies
OSE/DEPI	Jamie Ridley Klucken, Benjamin Booth
OSE/DMEPA	Kristine Needleman

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(a\) and \(c\)](#) and [201.80](#).

³ See [Prescription Drug Labeling Resources](#) website for PLR labeling guidances. When final, guidances represent the FDA’s current thinking on a topic. Applicants can use an alternative approach if it satisfies statutory and regulatory requirements.

DMPP	Helen Young, Barbara Fuller

The attached PI shows differences between the agreed upon PI, received February 9, 2026, and the Applicant proposed PI received February 13, 2025.

This review includes a high-level summary of the rationale for major changes to the PI proposed by the Agency as compared with the applicant’s draft PI (see the table below).

Full Prescribing Information Sections¹	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)²
1 INDICATIONS AND USAGE	The indication statement was modified to state that ADQUEY is indicated for the topical treatment of adults and pediatric patients 2 years of age and older with mild to moderate atopic dermatitis.
2 DOSAGE AND ADMINISTRATION	The statement, “(b) (4).” was deleted. The following instructions were included • Wash hands after application • Avoid areas of the skin that are infected when applying ADQUEY. The instruction to wash hands after application was included in the PPI, but not the Applicant proposed PI. The instruction to avoid areas of skin that are infected was included in the PPI (b) (4).
4 CONTRAINDICATIONS	No major changes.
5 WARNINGS AND PRECAUTIONS	(b) (4)
6 ADVERSE REACTIONS	Added less common (<1%) adverse reactions in subjects treated in trials -007 and -008 included application site folliculitis, contact dermatitis, application site rash, and molluscum contagiosum.

	Added language that adverse reactions observed in trial 271-12-205, trial 271-15-001, and trial 271-02-00002 were consistent with those observed in the phase 3 trials -007 and -008. Added application site pain and other local tolerability reactions observed in long-term trials. Refer to section 8.2.4 of the unireview for local tolerability analysis. (b) (4) erythema and vesicles/blistering are included under section 6.1.
7 DRUG INTERACTIONS	Not Applicable
8 USE IN SPECIFIC POPULATIONS	Incorporated MHT-recommended pregnancy and lactation labeling with clinical considerations for breastfeeding women per the recommendations of the PLLR Review Tool and the revised draft guidance for industry <i>Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (July 2020). (b) (4) Omitted section 8.3 per MHT recommendation. Refer to the Maternal Health Team review in DARRTS for additional details. Section 8.4 was revised per the recommendations of the guidance for industry <i>Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling</i> (March 2019). The information from 5 vehicle-controlled trials were included in the summary of the basis for approval. The plasma difamilast trough concentration corrected by dose in pediatric patients was removed and included under section 12.3 given that this is a data statement and section 12.3 is a data subsection. Only differences between pediatric and adult responses should be included in subsection 8.4. In section 8.5, the number of subjects 65 years of age and older and 75 years of age and older were included per the recommendations of the draft guidance for industry <i>Geriatric Information in Human Prescription Drug and Biological Product Labeling</i> (September 2020).
9 DRUG ABUSE AND DEPENDENCE	Not Applicable
10 OVERDOSAGE	Not Applicable
12 CLINICAL	Section 12.1 was modified per the recommendations of the

PHARMACOLOGY	Nonclinical review team. Refer to the Nonclinical section of the unireview for additional details. Section 12.2 and 12.3 were modified per the recommendations of the Clinical Pharmacology review team and the guidance for industry <i>Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (December 2016). Refer to the Clinical Pharmacology section of the unireview for additional details. Added statement regarding QTc interval based on interdisciplinary assessment. Refer to the QT-IRT review in DARRTS for additional information.
13 NONCLINICAL TOXICOLOGY	Section 13 was modified per the recommendations of the Nonclinical review team. Refer to the Nonclinical section of the unireview for additional details.
14 CLINICAL STUDIES	Included results from the multinational phase 2 trial (271-12-205) per the recommendations of the Biostatistics review team. Additional baseline demographics of the subjects enrolled in clinical trials were included. This section was also modified per the recommendations of the guidance for industry <i>Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (January 2006).
15 REFERENCES	References were not cited in the text of the labeling and this optional section was removed.
17 PATIENT COUNSELING INFORMATION	Section modified per the recommendations of the guidance for industry <i>Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products –Content and Format</i> (December 2014).
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	No major changes to Section 3. In section 11, a description of the Active Pharmaceutical Ingredient (API) was included, noting it is a crystalline solid or polymorph. The solubility profile was also included per (21 CFR 201.57(c)(12)(ii)). All inactive ingredients except those added to adjust pH or tonicity or water for injection were included per (21 CFR 201.57(c)(12)). In section 16, Included the statement, “Store away from direct sunlight, heat and moisture” for consistency with the PPI.

¹ The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the currently approved PI and the Applicant’s draft PI).

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----
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/

MATTHEW E WHITE
02/11/2026 11:26:12 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	February 10, 2026
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 219474
Product Name, Dosage Form, and Strength:	Adquey (difamilast) ointment, 1%
Applicant Name:	Acrotech Biopharma, Inc.
FDA Received Date:	February 9, 2026
TTT ID #:	2025-13356-2
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

---

1 PURPOSE OF MEMORANDUM

Acrotech Biopharma, Inc. submitted revised container label and carton labeling received on February 9, 2026, for Adquey. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container label and carton labeling for Adquey (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

Acrotech Biopharma, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

^a Needleman, K. Review of Revised Label and Labeling for Adquey (NDA 219474). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2026 FEB 06. TTT ID: 2025-13356-1.

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/

KRISTINE P NEEDLEMAN
02/10/2026 08:25:47 AM

VALERIE S VAUGHAN
02/10/2026 08:34:21 AM

MEMORANDUM
REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	February 6, 2026
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 219474
Product Name, Dosage Form, and Strength:	Adquey (difamilast) ointment, 1%
Applicant Name:	Acrotech Biopharma, Inc.
FDA Received Date:	January 30, 2026
TTT ID #:	2025-13356-1
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

---

1 PURPOSE OF MEMORANDUM

Acrotech Biopharma, Inc. submitted revised Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling received on January 30, 2026, for Adquey. The Division of Dermatology and Dentistry (DDD) requested that we review the revised PI, PPI, container labels, and carton labeling for Adquey (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 Adquey Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling are unacceptable 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 for the Division of Dermatology and Dentistry (DDD) in Section 3 and for Acrotech Biopharma, Inc. in Section 4.

3 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. Section 2 Dosage and Administration

The applicant is suggesting the following statement be added to the dosage and administration section.

(b) (4)

If the review team determines these instructions will remain in the Prescribing Information, we have the following recommendations:

- a. Consider changing “ (b) (4) ” to “ (b) (4) ” for clarity.
- b. Consider changing “ (b) (4) ” to “ (b) (4) ” to provide clarity to this statement.

---

^a Needleman, K. Label and Labeling Review for Adquey (NDA 219474). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 AUG 08. TTT ID: 2025-13356.

B. Patient Package Insert (PPI)

1. The applicant is suggesting additional administration instructions be included in the *How **should I use ADQUEY?*** section of the PPI. **If the review team determines these instructions will remain in the PPI, we have the following recommendations:**

- a. For clarity, we recommend revising the statement, “ (b) (4)
 (b) (4)
 ” to (b) (4)
 .
- b. For clarity, we recommend revising (b) (4) written instruction from (b) (4)
 to (b) (4)
 ”
- c. Consider changing the statement, “ (b) (4)
 to “ (b) (4)
 ,” to provide clarity to the statement.
- d. The statement, (b) (4)
 ,” is confusing. We defer to the Division of Medical Policy Programs Patient Labeling Team on the final patient-friendly language to use in place of the current statement.

4 RECOMMENDATIONS FOR ACROTECH BIOPHARMA, INC.

A. General Comments (Container Labels and Carton Labeling)

1. All storage statements currently include the abbreviation for Celsius (i.e., C) in place of where Fahrenheit (i.e., F) should be indicated within the parentheses i.e., Store at 20°C to 25°C (68°C to 77°C); excursions permitted to 15°C to 30°C (59°C to 86°C) [see USP Controlled Room Temperature]. Revise the statements to include Fahrenheit (i.e., F) within the parenthesis to read as “Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].”

B. Carton Labeling

1. The 27 g carton labeling includes the statement, “Keep tube tightly closed. Store away from direct sunlight, heat and moisture,” where the word “from” is misspelled. Change the statement to “Keep tube tightly closed. Store away from direct sunlight, heat and moisture.”

APPENDIX A. LABELS AND LABELING RECEIVED ON JANUARY 30, 2026

A.1 List of Labels and Labeling Reviewed

- Prescribing Information available from <\\CDSESUB1\EVSPROD\nda219474\0029\m1\us\114-labeling\114a-draft-label\nda-219474-version-1-pi-20260129-difamilast-uspi-draft-edit.docx>
- Patient Package Insert available from <\\CDSESUB1\EVSPROD\nda219474\0029\m1\us\114-labeling\114a-draft-label\patient-package-insert-30jan2026.docx>
- Professional Sample Container Label
- Professional Sample Carton Labeling
- Container Labels
- Carton Labeling

A.2 Container Labels:



4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

-----
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/

KRISTINE P NEEDLEMAN
02/06/2026 08:48:48 AM

VALERIE S VAUGHAN
02/06/2026 02:01:26 PM

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

Pre-decisional Agency Information

Memorandum

Date: February 4, 2026

To: Craig Johnson Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Kapil Verma, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: Eunice Chung-Davies, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ADQUEY™ (difamilast) ointment, for topical use

NDA: 219474

Background:

In response to DDD's consult request dated January 29, 2026, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for difamilast.

PI/PPI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 29, 2026, and February 2, 2026 and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from DDD's SharePoint folder on February 2, 2026, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Eunice Chung-Davies at 301-796-4006 or Eunice.Chung-Davies@fda.hhs.gov.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/

EUNICE H CHUNG-DAVIES
02/04/2026 11:52:21 AM

**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 4, 2026

To: Craig Johnson, PharmD
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: Barbara Fuller, MSN, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Helen Young, MSN, MPH, CRRN, PHN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Eunice Chung-Davies, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ADQUEY (difamilast)

Dosage Form and Route: ointment, for topical use

Application Type/Number: NDA 219474

Applicant: Acrotech Biopharma Inc.

1 INTRODUCTION

On February 13, 2025, Acrotech Biopharma Inc. submitted for the Agency's review an original New Drug Application (NDA) 219474 for ADQUEY (difamilast) ointment. The proposed indication for ADQUEY (difamilast) is for the treatment of mild to moderate Atopic Dermatitis (AD) in adults and pediatric patients 2 years of age 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 Dermatology and Dentistry (DDD) on January 29, 2026, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ADQUEY (difamilast) ointment.

2 MATERIAL REVIEWED

- Draft ADQUEY (difamilast) ointment PPI received on February 13, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 30, 2026 and February 2, 2026.
- Draft ADQUEY (difamilast) ointment Prescribing Information (PI) received on February 13, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 30, 2026 and February 2, 2026.
- Approved EUCRISA (crisaborole) ointment comparator labeling dated April, 3, 2023.
- Approved ZORYVE (roflumilast) cream comparator labeling dated October 4, 2025.
- Approved VTAMA (tapinarof) cream comparator labeling dated December 12, 2024.

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. In our review of the PPI the target reading level is at or below an 8th grade 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 APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the 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)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

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.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/

HELEN K YOUNG
02/04/2026 01:30:55 PM

EUNICE H CHUNG-DAVIES
02/04/2026 02:18:14 PM

BARBARA A FULLER
02/04/2026 02:20:25 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs, ORPURM
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993

MEMORANDUM TO FILE

From: Karen Fratantoni, MD, MPH, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)

Through: Shetarra Walker, MD, MSCR, Clinical Team Leader, DPMH
John Alexander, MD, MPH, Deputy Division Director, DPMH

Date: January 14, 2026

NDA Number: 219474

Sponsor: Acrotech Biopharma, Inc.

Drug: Difamilast ointment 1%

Proposed Indications: Treatment of mild to moderate atopic dermatitis in adults and pediatric patients 2 years of age and older

Division Consult Request: The Division of Dermatology and Dentistry (DDD) requests DPMH/Pediatrics review pediatric clinical trial growth data and provide an assessment if difamilast has an effect on weight in pediatric patients 2 years of age and older with mild to moderate atopic dermatitis.

BACKGROUND

Difamilast ointment 1% is a topical phosphodiesterase 4 (PDE4) inhibitor proposed for the treatment of mild to moderate atopic dermatitis in adults and pediatric patients 2 years of age and older. NDA 219474 was submitted February 13, 2025, via 505(b)(1) pathway with a PDUFA goal date of February 13, 2026.

DPMH/Pediatrics was consulted to assess if difamilast has an effect on weight in pediatric patients 2 years of age and older with mild to moderate atopic dermatitis. The rationale for the pediatric weight assessment is a labeled warning and precaution for weight decrease for systemic PDE4 inhibitors DALIRESP (roflumilast) and OTEZLA (apremilast). DALIRESP is an oral PDE4 inhibitor indicated as a treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in adults with severe COPD associated with chronic bronchitis and a history of exacerbations; the drug is not indicated in pediatric patients. OTEZLA is indicated for the treatment of adult patients with active psoriatic arthritis, plaque psoriasis who are candidates for phototherapy or systemic therapy, or oral ulcers associated with Behcet's Disease. OTEZLA is indicated for the treatment of

pediatric patients 6 years of age and older and weighing at least 20 kg with active psoriatic arthritis and moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. JASCAYD (nerandomilast), an oral PDE4 inhibitor, is not labeled with a warning and precaution for weight decrease, but weight decrease is described in “Adverse Reactions.” JASCAYD is indicated for the treatment of idiopathic pulmonary fibrosis in adult patients.

The FDA- approved topical PDE4 inhibitors ZORYVE (roflumilast) and EUCRISA (crisaborole) are indicated for use in adults and pediatric patients, and neither includes a warning and precaution for weight decrease nor labeling for growth concerns. ZORYVE, approved as a topical cream (0.3%, 0.15%, and 0.05%) and foam (0.3%), has the following indications:

- ZORYVE 0.3 % cream is indicated for the topical treatment of plaque psoriasis in adult and pediatric patients 6 years of age and older.
- ZORYVE 0.15% cream is indicated for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older.
- ZORYVE 0.05% cream is indicated for the topical treatment of mild to moderate atopic dermatitis in pediatric patients 2 to 5 years of age.
- ZORYVE topical foam, 0.3%, is indicated for the treatment of seborrheic dermatitis in adult and pediatric patients 9 years of age and older and plaque psoriasis of the scalp and body in adult and pediatric patients 12 years of age and older.

EUCRISA is indicated for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older.

REVIEW OF GROWTH DATA

An information request (IR) sent to the Applicant on August 15, 2025, requested baseline and end of trial height, weight, and BMI with corresponding z scores and CDC percentiles for each pediatric patient ≥ 2 years old to < 17 years old who was randomized to a study arm using difamilast ointment 0.3% or 1% in one of the following trials.

Study Title	Study Characteristics
271-102-0007	Phase 3, multicenter, double blind, randomized, vehicle-controlled 4-week study Difamilast 1% ointment Patients aged ≥ 15 years to 70 years old in Japan
271-102-00008	Phase 3, double blind, randomized, vehicle-controlled study in Japan Difamilast 0.3% and 1% ointment Patients aged ≥ 2 years old to < 15 years old
271-102-00002	Phase 2 double blind, randomized, vehicle-controlled study in Japan Difamilast ointment 0.3% and 1% Patients aged 2 years to 14 years old
US-MEDI-MM36-301	Phase 3 double blind, randomized, vehicle-controlled aborted US trial Difamilast ointment 1% Patients aged ≥ 2 years old
271-102-00006	Open label uncontrolled long term safety trial in Japan Difamilast 0.3% and 1% Patients aged ≥ 2 years old
MEDI-MM36-302	Open label uncontrolled long term safety trial in US Difamilast ointment 1% aged > 2 years old

The Applicant provided data for 628 unique patients.¹ Weight was measured at baseline and at approximately 4 weeks and/or 52 weeks, depending on study duration. Weight measurements at the end of study were missing for 38/628 patients.

This reviewer determined that a change in weight z score < 0.5 is unlikely to be clinically significant and used an absolute z score change of ≥ 0.5 to screen for patients who experienced potential significant weight loss or gain during the clinical trial. The group level data did not reveal a clinical signal for weight loss among those receiving treatment; equal numbers of patients met the screening z score threshold for weight loss ($n=17$) and weight gain ($n=17$). Despite no overall signal, this reviewer investigated the data for patients who met or exceeded the z score threshold for weight decrease in the context of the patient's age, sex, and height velocity from baseline to the end of study (at 4 or 52 weeks). Findings are summarized below.

- For 11 of the 17 patients who experienced a decrease in weight z score of ≥ 0.5 , the weight loss was minimal and/or was not concerning based on the other growth parameters.
- The remaining six of the 17 patients warranted further investigation due to the magnitude of the weight loss (3-10 kg over 52 weeks). For five of the six patients, the available data supported plausible clinical rationales for the weight loss. For the remaining one patient, a rationale for the weight loss could not be determined based on the available data.
  - A 15-year-old male patient from the Japanese open label trial 006 was extremely underweight at baseline, weighing 34.1 kg (0.05th weight percentile). This abnormally low baseline weight suggests a pre-existing condition predating difamilast exposure.
  - Each of the remaining five patients (three in the US open label trial and two in the Japanese open label trial 006) had a weight loss of 3-10 kg over 12 months.
    - Three of the five patients were adolescents.
      - Two had baseline weights in the 90th percentile, so the weight loss could represent an attempt to achieve a weight in the healthy range.
      - One had a weight in the 63rd percentile at baseline and at the 40th percentile at trial's end, a loss which is unlikely to be clinically concerning.
    - The remaining two patients with weight loss of 3-10 kg over 12 months were 9.5 years old and 7.9 years old at baseline.
      - The 9.5-year-old had a baseline BMI consistent with a diagnosis of obesity and normalization of BMI during the trial.
      - The 7.9-year-old patient had a weight loss of 5 kg, decreasing from the 82nd percentile weight to the 22nd percentile. The patient exhibited normal height velocity despite the reported weight loss. This reviewer could not find a clinical rationale for this patient's reported weight loss during the trial.

CONCLUSION

A review of the growth data for patients 2 years old to < 17 years old enrolled in the difamilast clinical trials for the treatment of mild to moderate atopic dermatitis did not identify a concern for weight loss.

---

¹ Docubridge NDA 219474 eCTD Sequence 0019

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/

KAREN R FRATANTONI
01/14/2026 05:08:34 PM

SHETARRA E WALKER
01/14/2026 09:13:39 PM

JOHN J ALEXANDER
01/14/2026 10:40:08 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES   Public Health Service

---

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: December 30, 2025   **Date consulted:** April 2, 2025

From: Kerry R. Shaab, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, Division Director
Division of Pediatrics and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: Adquey (difamilast) ointment, 1%

NDA: 219474

Applicant: Acrotech Biopharma, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older

Materials Reviewed:

- DPMH consult request, dated 4/2/2025. DARRTS Reference ID: 5563535.
- Applicant's background package and proposed labeling for NDA 219474, Sequence Number (SN) 0001, dated 2/13/2025.

- Applicant’s response to DPMH Information Request (IR) dated 4/25/2025, SN 0009, submitted 5/20/2025.

Consult Question: PLLR Labeling Review

I. INTRODUCTION AND BACKGROUND

On February 13, 2025, the Applicant, Acrotech Biopharma, Inc. (Acrotech), submitted a 505(b)(1) Original New Drug Application for Adquey (difamilast) ointment 1%, a topical phosphodiesterase-4 (PDE-4) inhibitor, for the topical treatment of mild to moderate atopic dermatitis (AD) in adults and pediatric patients 2 years of age or older. The Division of Dermatology and Dentistry consulted the Division of Pediatrics and Maternal Health (DPMH) on April 2, 2025, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Difamilast was originally developed by Otsuka Pharmaceutical Co., Ltd. (Otsuka) and, in September 2021, it was approved only in Japan, under the brand name Moizerto. In Japan, it is currently approved for the treatment of atopic dermatitis in adults and pediatric patients 2 years of age or older.
- Otsuka initiated product development in the U.S. under IND 112973 which was submitted on October 25, 2011. The IND and U.S. sponsorship were transferred to Medimetriks Pharmaceuticals, Inc. in October 2016, then further transferred to Acrotech on December 21, 2021. Acrotech is responsible for U.S. commercial and regulatory activities. Otsuka is responsible for commercial and regulatory activities in Japan.
- The FDA-approved topical phosphodiesterase-4 (PDE-4) inhibitors are Eucrisa and Zoryve. Eucrisa (crisaborole) ointment, the first-in-class topical PDE-4 inhibitor, was approved in December 2016, for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. In March 2020, the indication was expanded to include children as young as 3 months of age. Zoryve (roflumilast) cream, initially approved in 2022 for the topical treatment of plaque psoriasis, was approved for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older in July 2024, then expanded to include children 2 to 5 years of age in October 2025.¹

---

¹ DPMH did not rely on data in the Eucrisa or Zoryve NDAs or the agency’s finding of safety and effectiveness for Eucrisa or Zoryve to support labeling recommendations provided in this review for NDA 219474.

Atopic Dermatitis and Pregnancy^{2,3,4,5,6}

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease that commonly affects both children and adults. Atopic dermatitis affects approximately 10 percent of adults worldwide with 25 percent of adults with AD reporting adult onset of disease. In the adult population, prevalence has been observed to peak between the ages of 25 and 44 years and to decrease with age. In females, AD is slightly more common after puberty. Therefore, a significant proportion of patients with AD are women of reproductive age.

AD is the most common general skin disease associated with pregnancy, with 75% of women developing manifestations before the third trimester. Of AD cases during pregnancy, 80% are new-onset presentations, while 20% represent recurrences or exacerbations of preexisting disease. Most women with preexisting AD experience a worsening of symptoms or no changes during pregnancy. Just one in five experience an improvement. AD during pregnancy must be differentiated from other pregnancy-related pruritic skin changes, such as idiopathic pruritis (pruritis gravidarum), cholestasis of pregnancy, prurigo of pregnancy, or pruritic folliculitis. The management of atopic dermatitis during pregnancy should emphasize avoidance of triggering factors, maximal use of emollients, and second-generation oral antihistamines as needed to control pruritus. For patients with symptoms despite these measures, mild to medium potency topical corticosteroids may be used until symptoms are controlled. Narrow Band Ultraviolet B phototherapy is recommended when topical therapy is insufficient to control the disease.

II. REVIEW

PREGNANCY

Nonclinical Experience

The nonclinical team reviewed the Applicant's submission and provided the following information:

In the Embryofetal Development (EFD) study conducted in rats, increased post-implantation loss, decreased fetal weight, retarded ossification, and increased visceral abnormalities (membranous ventricular septum defect) were noted when difamilast was administered subcutaneously at the high dose of 100 mg/kg/day. The NOAEL for embryo-fetal development was the mid dose of 10 mg/kg/day (30-times the clinical exposure at the maximum recommended human dose (MRHD) based on AUC comparison). In the EFD study conducted in rabbits, increased skeletal variations (increased supernumerary lumbar vertebra) were observed when difamilast was administered subcutaneously at the high dose of 3 mg/kg/day, resulting in a

---

² Silverberg, JI, and Howe, W. Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis. In:UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed 11/18/2025)

³ Schatz, M. Recognition and management of allergic disease during pregnancy. In:UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed 11/18/2025)

⁴ Balakirski G, Novak N. Atopic dermatitis and pregnancy. J Allergy Clin Immunol. 2022 Apr;149(4):1185-1194. doi: 10.1016/j.jaci.2022.01.010. Epub 2022 Jan 26. PMID: 35090948.

⁵ Munera-Campos M, Carrascosa JM. Atopic Dermatitis: Fertility, Pregnancy, and Treatment Perspectives. Am J Clin Dermatol. 2024 Jan;25(1):55-66. doi: 10.1007/s40257-023-00821-4. Epub 2023 Oct 30. PMID: 37904055.

⁶ Valentini, R, Shahriari, M. Atopic dermatitis in women: special considerations in the childbearing years. International journal of women's dermatology. 2024 Jun;10(2), e151. <https://doi.org/10.1097/JW9.000000000000151>

NOAEL for embryo-fetal development of 1 mg/kg/day (3-times the clinical exposure at the MRHD based on AUC comparison).

In a pre- and postnatal development (PPND) study, difamilast was administered subcutaneously to pregnant rats from implantation through weaning at doses up to 3 mg/kg/day. No adverse effects on reproductive functions of dams, prenatal and postnatal development of F₁ offspring, or implantation and viability of F₂ embryos were observed at any dose tested, resulting in a NOAEL of 3 mg/kg/day (13-times the clinical exposure at the MRHD based on AUC comparison).

The reader is referred to the full nonclinical review by Renqin Duan, Ph.D.

Reviewer Comment:

Although adverse effects, including increased incidence of membranous VSDs, were observed in the rats at the highest dose tested, no adverse effects on embryo-fetal development occurred at the mid-dose, resulting in a safety margin of 30-fold in the rats. No adverse effects were observed with difamilast when administered subcutaneously up to 3-times the exposure at the MRHD in rabbits. Therefore, there were no specific safety signals identified at clinical exposures in the EFD studies.

Review of Pharmacovigilance Database

Difamilast ointment clinical development program^{7,8}:

The Applicant reported 5 pregnancy cases during the clinical development program of difamilast ointment. In one of the five reported cases, the pregnancy was identified at the participant's baseline visit, and did not receive the study drug or participate in the study. The remaining four pregnancy cases are as follows:

- A 22-year-old female participant started on difamilast ointment 1% on [REDACTED]^{(b) (6)}. At her Week 4 study visit, she had a positive pregnancy test which was confirmed by a serum test. Her last menstrual period was on [REDACTED]^{(b) (6)}, two days prior to starting difamilast. Difamilast was discontinued on [REDACTED]^{(b) (6)} and the participant withdrew from the study. The participant was gravida 2, para 1001 with no history of spontaneous or elective abortions, stillbirths, or premature deliveries. The participant delivered via a vaginal birth a full-term, normal infant with no neonatal illness, complications, malformations, or anomalies reported. No further details were provided.
- A 25-year-old female participant received twice daily topical applications of difamilast ointment 1% from [REDACTED]^{(b) (6)}, to [REDACTED]^{(b) (6)}, for a total of 223 applications of difamilast. She discontinued the difamilast on [REDACTED]^{(b) (6)}, due to a positive pregnancy test at Study Visit 6. Her last menstrual period was April 1, 2023. On [REDACTED]^{(b) (6)}, the participant experienced a spontaneous abortion. The participant was also taking phentermine from [REDACTED]^{(b) (6)}, to [REDACTED]^{(b) (6)}. No further details were provided.

Reviewer Comment:

The concomitant phentermine exposure confounds the relationship between difamilast exposure and the adverse pregnancy outcome. In addition, details such

⁷ NDA 219474, Module 2.5, Clinical Overview, p. 41-42 and Module 2.7.4, Summary of Clinical Safety, p. 60-61.

⁸ NDA 219474, SN 0009, Applicant's response to DPMH IR, dated 4/25/2025, p. 4-5.

as the participant's medical and obstetrical history are missing, further contributing to the difficulty in determining a causal relationship.

- A 28-year-old female participant received twice daily topical applications of difamilast ointment 1% from (b) (6), to (b) (6), for a total of 699 applications of difamilast. On (b) (6), she reported a positive pregnancy test and discontinued difamilast. Her last menstrual period was (b) (6), and her urine pregnancy test was negative at her last study visit on (b) (6). The participant was lost to follow-up. No further details were provided.
- A 34-year-old female participant received difamilast ointment 1% from (b) (6), to (b) (6). The participant's last menstrual period was (b) (6). On (b) (6) she had a positive urine pregnancy test with a confirmatory serum pregnancy test, and she discontinued the drug on the same day. On (b) (6), the participant underwent a vaginal ultrasound which indicated an early intrauterine pregnancy with a germ size equivalent to 5 weeks and 6 days gestation. On (b) (6), the participant underwent an elective abortion without any reported complications. No further details were provided.

Difamilast ointment (Moizerto) postmarketing experience in Japan⁹:

According to the Applicant, the commercial supplier of Moizerto (difamilast) Ointment, Otsuka Pharmaceutical Co., Ltd. (Otsuka), conducted a review of their safety database from September 27, 2021 (time of drug approval) to April 25, 2025, and identified fifteen cases involving difamilast-exposure during pregnancy. In one case, a mother was exposed to difamilast when “administering [the ointment] to a 4-year-old child during the preconception and pregnancy periods” and experienced an abortion. This case was reported by the consumer and “no further information about the spontaneous abortion was available”. In the remaining 14 cases, the pregnancy outcomes are unknown.

The Applicant provided their conclusions with respect to the cases from the Moizerto safety database. Given detailed information on the timing of administration of the drug product, the timing of the adverse event in relation to drug exposure, and the exposed woman's medical history including obstetrical history and concurrent medications, were not available, the Applicant concluded that it was not possible to evaluate whether the spontaneous abortion case from the Moizerto safety database was caused by exposure to difamilast. Additionally, given the outcomes of the remaining cases were unknown, the effects of difamilast-exposure on the mothers and infants could not be evaluated.

Reviewer Comment:

With respect to the spontaneous abortion case from the Moizerto safety database, DPMH agrees with the Applicant's conclusion. With respect to the pregnancy cases from the Applicant's drug development program, difamilast exposure during early pregnancy occurred in all four cases. None of the individual pregnancy outcomes raise specific safety concerns. There is limited clinical data on difamilast exposure during pregnancy

---

⁹ NDA 219474, SN 0009, Applicant's response to DPMH IR, dated 4/25/2025, p. 5-8.

and the limited clinical data are insufficient to draw meaningful safety conclusions about the effects of difamilast during pregnancy.

Review of Literature

Applicant's Review:

The Applicant performed a cumulative literature search with the following strategy:

- Databases: Medline and Embase
- Search terms: difamilast (or Moizerto or moizerto or difamilast or "OPA-15406" or "OPA 15406" or "OPA15406" or "MM36" or "OPC-271" or "OPC 271" or "OPC271")
- Limits: From September 27, 2021 (Japanese PMDA approval date) to March 31, 2025

The Applicant did not identify any published clinical literature related to difamilast use during pregnancy.¹⁰

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "difamilast" and "pregnancy", "pregnancy outcomes", "pregnant", "major birth defects", "birth defects", "congenital malformations", "congenital anomalies", "teratogenicity", "miscarriage", "spontaneous abortion", "elective abortion", "pregnancy loss", "stillbirth", "fetal loss", "fetal demise", "fetotoxicity", "adverse pregnancy outcomes", "prematurity" and "low birth weight". No relevant publications were found.

In addition, DPMH conducted a search for difamilast in Micromedex¹¹, Reprotox¹², TERIS¹³, Shepard's¹⁴, and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*¹⁵. No information was found.

Reviewer comment:

The Applicant's review is adequate.

LACTATION

Nonclinical Experience

Difamilast was excreted in the milk of lactating rats following a subcutaneous injection of 3 mg/kg ¹⁴C-difamilast administered on lactation day 15 to 16. The concentration of radioactivity in milk was higher than that in blood (with milk/blood ratios at C_{max} and AUC_∞ of 13.7 and 5.4, respectively).

The reader is referred to the full nonclinical review by Renqin Duan, Ph.D.

---

¹⁰ NDA 219474, SN 0009, Applicant' response to DPMH IR, dated 4/25/2025.

¹¹ Truven Health Analytics information, <http://www.micromedexsolutions.com> Accessed 8/21/2025.

¹² Reprotox Website: www.Reprotox.org. Accessed 8/21/2025.

¹³ TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/21/2025.

¹⁴ Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 8/21/2025.

¹⁵ Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021.

Reviewer Comment:

The presence of difamilast in rat milk was demonstrated following a single subcutaneous dose of difamilast given to lactating rats. In the PPND study, no adverse developmental effects were observed in the nursing pups.

Review of Pharmacovigilance Database

Difamilast ointment clinical development program¹⁰:

According to the Applicant, there were no reported cases of difamilast exposure in lactating women during the clinical development program.

Difamilast ointment (Moizerto) postmarketing experience in Japan¹⁰:

According to the Applicant, the commercial supplier of Moizerto (difamilast) Ointment, Otsuka, conducted a review of their safety database for reports of difamilast exposure in lactating women from September 27, 2021 (time of drug approval) to April 25, 2025, identifying nine cases of “exposure via breast milk”. The Applicant noted that, “in each case, information on the measures taken against the drug and the outcome is not known” and “none of the cases reported adverse events”. No further details were provided.

Reviewer Comment:

There are limited clinical data on difamilast exposure in lactating women. No exposures were reported during the clinical drug development program. No safety concerns have been identified from reports of exposure in lactating women in the postmarketing setting in Japan. The limited clinical data are insufficient to draw meaningful safety conclusions about difamilast use in lactating women.

Review of Literature

Applicant’s review:

Refer to the Pregnancy section of this review for the Applicant’s literature search parameters. The Applicant did not identify any published clinical literature related to difamilast use in lactating women¹⁰.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms “difamilast” and “lactating”, “lactation”, “human milk”, “breastfeeding”, “breastfed”, “neonates”, and “infants”. No relevant publications were found.

In addition, DPMH conducted a search for difamilast in Micromedex, Reprotox, Hale’s *Medications and Mothers’ Milk*¹⁶, the Drugs and Lactation Database (LactMed), and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. No information was found.

Reviewer comment:

The Applicant’s review is adequate.

---

¹⁶ Hale, Thomas W. *Hale’s Medications and Mother’s Milk 2021: A Manual of Lactational Pharmacology*. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com. Accessed 1/8/2025.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In a fertility and early embryonic development (FEED) study conducted in female and male rats, irregular estrus cycles, sperm abnormalities, increased preimplantation loss rate, decreased copulation and fertility indexes were observed at the high dose of 100 mg/kg/day. The NOAEL for reproductive functions and early embryonic development was the mid dose of 10 mg/kg/day in males and females (20 times the MRHD for males and 30 times the MRHD for females, respectively, based on AUC comparison).

The reader is referred to the full nonclinical review by Renqin Duan, Ph.D.

Reviewer Comment:

Although effects on fertility were seen in the female and male rats, these effects occurred at dose exposures greater than 20 times the clinical exposure at the MRHD. Based on this safety margin, difamilast ointment is not expected to affect human fertility at clinical exposures.

Review of Pharmacovigilance Database

*Difamilast ointment clinical development program*¹⁰:

According to the Applicant, there were no reported cases related to effects of difamilast on female or male fertility during the clinical development program.

*Difamilast ointment (Moizerto) postmarketing experience in Japan*¹⁰:

According to the Applicant, the commercial supplier of Moizerto (difamilast) Ointment, Otsuka, conducted a review of their safety database for reports of difamilast effects on female or male fertility from September 27, 2021 (time of drug approval) to April 25, 2025, identifying one case. “Decreased sperm concentration” was reported in a 30-year-old male who received the drug transdermally in the pubic region. According to the report, the drug was withdrawn. No further details, including the outcome after drug discontinuation, were available.

The Applicant concluded that “it is difficult to evaluate whether the decrease in sperm [concentration] was caused by difamilast because information on the duration of administration and outcome is not available”.

Reviewer Comment:

DPMH agrees with the Applicant’s conclusion. The identified case is missing pertinent information, including frequency and duration of use of Moizerto, timing of use in relation to the onset of the adverse event, reversibility of the adverse event, and use of concomitant medications. In addition, the clinical impact of the decreased sperm concentration is unknown.

Review of Literature

Applicant’s review:

Refer to the Pregnancy section of this review for the Applicant’s literature search parameters. The Applicant did not identify any published clinical literature with relevant safety information related to males and females of reproductive potential.

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms “difamilast” and “fertility”, “infertility”, “decreased sperm count”, “contraception”, “oral contraceptives”, “effects on fertility”, and “reproduction”.

In addition, DPMH conducted a search for difamilast in Micromedex, Reprotox, and TERIS. No relevant publications or additional information on the effects of difamilast on human fertility were found in the literature search.

Reviewer comment:

The applicant’s review is adequate.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

The animal reproduction studies did not identify a specific safety signal indicating an increased risk for embryo-fetal toxicity at clinical exposures. Animal reproduction data do not suggest a serious risk of developmental toxicity during pregnancy.

Although no safety concerns have been raised by the pregnancy exposure cases reported in either the clinical drug development program or the postmarketing experience with difamilast ointment, there are insufficient data on difamilast use in pregnancy to allow assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Atopic dermatitis is the most common skin disease associated with pregnancy. However, since emollients, moisturizers, low to medium potency topical corticosteroids, and phototherapy are the preferred treatments for mild to moderate atopic dermatitis during pregnancy, difamilast ointment would not be used as first-line treatment in pregnant women. Topical PDE-4 inhibitors have been on the market for almost a decade and specific pregnancy safety concerns have not been identified. In addition, topical difamilast systemic exposure is generally comparable to the most recently approved topical PDE-4 inhibitor. Given animal reproduction data do not suggest a serious risk of developmental toxicity during pregnancy and the lack of safety concerns for the topical PDE-4 inhibitor class in general, DPMH does not recommend a postmarketing pregnancy safety study at this time. Routine drug pharmacovigilance and published literature reviews would be reasonable to monitor pregnancy and infant outcomes.

Lactation

Lactation data for difamilast are not currently available for humans. In nonclinical studies, after subcutaneous administration, difamilast was present in the milk of lactating rats. Although there were no lactational exposures reported during the clinical drug development program for difamilast ointment, no safety concerns have been identified from the limited reports of lactational exposures in the difamilast ointment postmarketing setting in Japan. Based on the lack of safety concerns for the PDE-4 inhibitor class in general, as well as the amount expected to transfer into breastmilk given the low systemic exposure of this topical difamilast product, DPMH does not recommend a clinical lactation study at this time. Routine drug pharmacovigilance and published literature reviews would be reasonable.

Females and Males of Reproductive Potential

There are no available human data to suggest difamilast adversely effects female or male fertility. Animal fertility studies did not indicate any adverse effects at clinical exposures. In addition, there is no evidence of fetal harm at clinical exposures that would require pregnancy testing or contraceptive use during treatment with difamilast. Therefore, DPMH recommends omitting labeling subsection 8.3 Females and Males of Reproductive Potential.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2 and section 17 of labeling for compliance with the PLLR. DPMH discussed our labeling recommendations with the Division of Dermatology and Dentistry on 12/11/2025. DPMH recommendations are below and reflect the discussions with DDD. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS



1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A –

Drug Characteristics¹⁷

Drug Class	Phosphodiesterase-4 (PDE-4) inhibitor
Proposed Mechanism of Action	Difamilast is an inhibitor of phosphodiesterase-4 (PDE-4). Difamilast inhibition of PDE-4 (a major cyclic 3',5'-adenosine monophosphate [cyclic AMP] metabolizing enzyme) activity leads to accumulation of intracellular cyclic AMP. The specific mechanism(s) by which difamilast exerts its effects for the treatment of mild-to-moderate atopic dermatitis is not well-defined.
Proposed Dosage form and administration	1% ointment: 10 mg of difamilast per gram of ointment Apply a thin layer twice daily to affected areas (b) (4) (b) (4) and rub in completely. (b) (4)
Molecular weight	446.44 g/mol
Half-life	Not specified in labeling.
% protein bound	99.7%
Bioavailability	Unknown

¹⁷ NDA 219474, draft Annotated Labeling with DDD review team edits, review ongoing.

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/

KERRY R SHAAB
01/05/2026 08:34:38 AM

TAMARA N JOHNSON
01/05/2026 09:26:07 AM

LYNNE P YAO
01/05/2026 10:00:19 AM

Clinical Inspection Summary

Date	11/13/2025
From	Stephanie Coquia, MD, Reviewer Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Kapil (Dev) Verma, MD, Clinical Reviewer Melinda McCord, MD, Clinical Team Leader Craig Johnson, Regulatory Project Manager Division of Dermatology and Dentistry (DDD)
NDA #	219474
Applicant	Acrotech Biopharma Inc.
Drug	Difamilast
NME (Yes/No)	Yes
Therapeutic Classification	Phosphodiesterase 4 inhibitor
Proposed Indication	For the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older
Consultation Request Date	6/17/2025
Summary Goal Date	12/12/2025
Action Goal Date	2/13/2026
PDUFA Date	2/13/2026

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Acrotech Biopharma Inc., submitted clinical data from Studies 271-102-00007 (NCT03908970) and 271-102-00008 (NCT03911401) to support a New Drug Application (NDA 219474) for difamilast. The proposed indication is for the topical treatment of mild to moderate atopic dermatitis (AD) in adult and pediatric patients 2 years of age and older.

Three clinical investigators (Drs. Toyofuku, Kume, and Tsujino) were inspected.

The inspections did not find significant concerns regarding the conduct of the clinical trials or GCP or regulatory compliance. Overall, the data generated by the clinical sites and submitted by the Applicant appear acceptable in support of the proposed indication.

Inspections by The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan

Note: The information below from PMDA must be redacted should this CIS be made public as it was received from PMDA under the terms of the confidentiality agreement between the

two agencies.

(b) (4)

II. BACKGROUND

Acrotech Biopharma Inc. seeks approval of an NDA for difamilast for the above proposed indication. In 2021, difamilast was approved in Japan for adults and children with atopic dermatitis. In support of the NDA, the Applicant submitted clinical data from Studies 271-102-00007 and 271-102-00008. The following is a summary of the study protocols and key study information relevant to the clinical inspections.

Study Designs

The studies were similar in design, these were phase 3, multicenter, randomized, double-blind, vehicle-controlled parallel-group comparison trials designed to evaluate the efficacy and safety of difamilast ointment in adult (271-102-00007) and pediatric (271-102-00008) AD subjects.

Objectives and Endpoints

The primary objective of 271-102-00007 was to demonstrate the superiority of 1% difamilast ointment to the vehicle. The primary objective of 271-102-00008 was to demonstrate the superiority of 0.3% and 1% difamilast ointment to the vehicle.

The primary endpoint for both studies was the success rate in the Investigator's Global Assessment (IGA) at Week 4, defined as the percentage of subjects with an IGA score of 0 or 1 with improvement by at least 2 grades compared to baseline.

Secondary endpoints of interest were the improvements in the Eczema Area and Severity Index (EASI) at Week 4 compared to baseline. For the EASI score, four individual body regions (head, trunk, upper limbs, and lower limbs) are assessed for extent of eczema (% body surface area (BSA) involvement) and severity (graded 0-3) based on four signs (erythema, infiltration, excoriation, and lichenification). The sum of the scores for each body region yields the total score, with higher values indicating more severe and/or extensive disease.

Key Eligibility Criteria

- 271-102-00007 only:
  - Age between 15 to 70 years, inclusive
  - History of AD for at least 3 years
- 271-102-00008 only:
  - Age between 2 to 14 years, inclusive

- Diagnosis of AD based on the Japanese Dermatological Association's criteria
- At screening and baseline:
  - AD affecting $\geq 5\%$ to $\leq 40\%$ of BSA, excluding scalp
  - IGA score of 2 (mild) or 3 (moderate)
- None of the following (list not exhaustive):
  - AD or contact dermatitis flare-up within 28 days of baseline examination
  - Concurrent or history of skin disease other than AD and who were judged inappropriate for the assessment of AD
  - Never been treated with a prescription medication for AD or were satisfied with their current AD treatment regimen
  - Subjects who did not respond at all to treatment with existing topical drugs for AD
  - Unable to stop or unable to continue in the trial without changing the dosage and administration of certain medications

Study Conduct

Thirty sites in Japan enrolled at least one subject for 271-102-00007. The trial was conducted between March 25, 2019, and December 28, 2019, and enrolled 364 subjects.

Thirty sites in Japan enrolled at least one subject for 271-102-00008. The trial was conducted between May 7, 2019, and December 13, 2019, and enrolled 251 subjects.

III. RESULTS

1. Dr. Akihiro Kume (Site 313, Study 271-102-00007)

1-65-2, Otorihigashimachi, Nishi-Ku
Sakai-Shi, Osaka 593-8324 Japan

Inspection Dates: September 1-4, 2025

This investigator was inspected as a BIMO Review-based inspection for Study 271-102-00007. This investigator was previously inspected in 2004. Observations from that inspection included failure to establish administered dose criteria, inadequate source documentation, late adverse event reporting, and protocol deviations related to eligibility and study procedures.

The site screened, enrolled and randomized 17 subjects. The subject records of all 17 subjects were reviewed, and included: informed consent forms (ICFs), electronic case report forms (eCRFs), medical records, laboratory test results, and documentation of eligibility, concomitant medications, physical examinations, rating scale assessments, adverse events (AEs), and investigational product (IP) assignment and administration.

Study- and site-related documents and records reviewed included: the protocol, subject visit log, IP handling log, signature and delegation of authority log, financial disclosures, documentation of training, qualifications, site monitoring, protocol deviations, and institutional review board (IRB) and foreign regulatory approvals.

The source data for IGA, EASI, and BSA at screening, baseline, and Week 4 were reviewed and compared against the submitted data in the NDA. No discrepancies were identified, and all subjects met eligibility criteria according to IGA and BSA. There was a single rater for each subject. No unreported AEs or protocol deviations were identified.

Based on the results of the inspection, the data generated at Dr. Kume's site appear acceptable in support of the proposed indication in the NDA.

2. Dr. Kazutomo Toyofuku (Site 307, Study 271-102-00007)

2-17-15 Takadanobaba, Karahashi Building 6F
Shinjuku-ku, Tokyo 169-0075 Japan

Inspection Dates: September 16-19, 2025

This investigator was inspected as a BIMO Review-based inspection for Study 271-102-00007. This was the investigator's first FDA inspection.

The site screened 45 subjects and enrolled and randomized 41 subjects. The subject records of all 45 screened subjects were reviewed. Records reviewed included: ICFs, eCRFs, medical records, laboratory test results, documentation of eligibility, concomitant medications, physical examinations, rating scale assessments, AEs, and IP assignment and administration.

Study- and site-related documents and records reviewed included the protocol, subject visit log, IP handling log, signature and delegation of authority log, financial disclosures, documentation of training, qualifications, site monitoring, protocol deviations, and IRB and foreign regulatory approvals.

The source data for IGA, EASI, and BSA at screening, baseline, and Week 4 were reviewed and compared against the submitted data in the NDA. There was a single rater for each subject.

Although no discrepancies were noted when efficacy source data were compared to the data submitted in the NDA, it was noted that some subjects' source data had revisions weeks after their original assessment (with the revised scores were submitted to FDA) without an adequate justification recorded:

USUBJID	Arm	Assessment Timepoint	Initial Score	Initial Date	Revised Score	Revised Date	Comment
(b) (6)	Difamilast	IGA Week 4	3	(b) (6)	2	(b) (6)	No change in IGA responder status, still a non-responder
(b) (6)	Placebo	EASI Lower Limb Area Week 4	3	(b) (6)	4	(b) (6)	Still a non-responder according to

							EASI, no reduction in EASI observed
(b) (6)	Placebo	EASI Head Erythema, Area Week 4	1, 2	(b) (6)	0, 0	(b) (6)	Still not an EASI75 or EASI90 responder, subject did not achieve a 75% or 90% reduction in total EASI score*

* Subject achieved an EASI50 response (50% reduction in EASI compared to baseline) only when the revised scores were used.

Similarly, IGA and BSA scores were observed to have been revised for several subjects at screening and baseline, but all revised scores matched the data listings, and all subjects met eligibility according to IGA and BSA regardless of whether the original scores or revised scores were used to make the determination.

Reviewer's comments: While the documentation of revisions to the above scores was inadequate, the revisions did match the submitted data listings and did not significantly alter overall efficacy findings or eligibility for the affected subjects.

In his October 9, 2025, response to the inspectional findings, Dr. Toyofuku stated that the scores were corrected and revised after discussion with the study monitor when considering all the disease severity scores (IGA, EASI, and BSA) for the timepoint of interest.

No unreported AEs or protocol deviations were identified. Based on the results of the inspection, the data generated at Dr. Toyofuku's site appear acceptable in support of the proposed indication in the NDA.

3. Dr. Yoshiaki Tsujino (Site 429, Study 271-102-00008)

5-9-86, Uozaki-kitamachi, Higadshinada-ku
Kobe-Shi, Hyogo 658-0082 Japan

Inspection Dates: September 8-12, 2025

This investigator was inspected as a BIMO Review-based inspection for Study 271-102-00008. This was the investigator's first FDA inspection.

The site screened and randomized 15 subjects. The subject records of all 15 subjects were reviewed, and included: ICFs, eCRFs, laboratory test results, subject diaries, and documentation of eligibility, concomitant medications, medical histories, physical examinations, rating scale assessments, AEs, and IP assignment and administration.

Study- and site-related documents and records reviewed included: the protocol, subject visit log, IP handling log, signature and delegation of authority log, financial disclosures, documentation of qualifications, training, site monitoring, protocol deviations, and IRB approvals.

The source data for IGA, EASI, and BSA at screening, baseline, and Week 4 were reviewed and compared against the submitted data in the NDA. For efficacy, only the source data for IGA and EASI at baseline and Week 4 for subjects in the 1% difamilast (the proposed strength) and placebo arms were reviewed. No discrepancies were identified, and all subjects met eligibility criteria according to IGA and BSA. There was a single rater for each subject. No unreported AEs or protocol deviations were identified.

Based on the results of the inspection, the data generated at Dr. Tsujino's site appear acceptable in support of the proposed indication in the NDA.

{ See appended electronic signature page }

Stephanie Coquia, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division/Division Director/Jill Lindstrom
Review Division/Project Manager/Craig Johnson
Review Division/Cross Discipline Team Lead/Melinda McCord

Review Division/Clinical Reviewer/Kapil (Dev) Verma
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

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/

STEPHANIE F COQUIA
11/13/2025 09:33:45 AM

MICHELE B FEDOWITZ
11/13/2025 09:35:01 AM

JENN W SELLERS
11/13/2025 09:42:48 AM

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA CONSULT

Consultant Reviewer: Roberta Rasetti, MD, PhD, Clinical Reviewer, Division of Psychiatry (DP)
Jean Kim, MD, Clinical Team Leader, DP

Consultation Requestor: Craig Johnson, RPM, Division of Dermatology and Dentistry (DDD)
Kapil Verma, Clinical Review, DDD
Melinda McCord, Clinical TL, DDD

Subject of Request: NDA 219474; Adquey (difamilast) ointment

Date of Request: 07/22/2025

Date Received: 07/22/2025

Desired Completion Date: 08/26/2025 (Mid-Cycle Meeting)

Specific Consultative Request

The Division of Dermatology and Dentistry (DDD) submitted a consult to the Division of Psychiatry (DP) on July 22, 2025, with the following request:

The Applicant submitted NDA 219474 on February 13, 2025, for difamilast ointment 1% for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older. Difamilast is a phosphodiesterase 4 (PDE4) inhibitor and labeling for oral PDE4 inhibitors (e.g., DALIRESP [roflumilast] tablets) include a Warning and Precaution for psychiatric events including suicidality. DP provided prior input on psychiatric monitoring and scales in a consult dated April 7, 2022 (Shamir Kalaria, PharmD, PhD) under IND 112973. Please review adverse event data related to psychiatric adverse events (e.g., depression, SIB) and data related to changes in psychiatric monitoring instrument scores. Please provide comments, labeling recommendations and attend relevant meeting.

Executive Summary

This review focused specifically on the completed phase 3 studies within the difamilast clinical development program. As requested, our analysis was aimed at evaluating the potential signal of suicidal ideation or behavior (SI/B) based on treatment emergent adverse events (TEAEs) and psychiatric scale results. The review process included a thorough analysis of all death cases and TEAEs, focusing on those related to psychiatric disorders, suicidal ideation, or behavior.

Clinical trial data from the Placebo-Controlled Studies Pool, Long-Term Uncontrolled Studies, and CSR review of the 8-week dose-finding studies are insufficient to support a causal link between difamilast and adverse events (AEs) related to SI/B or psychiatric disorders. However, this conclusion requires caution due to limited psychiatric assessments in most studies and early termination of the only placebo-controlled study using validated psychiatric instruments.

The Division does not recommend including information about increased psychiatric disorder risks in Section 5 of the prescribing information. While dedicated SI/B studies are usually impractical due to design and interpretation challenges, in order to more accurately monitor for psychiatric signals in any future postmarketing studies, they should incorporate validated depression rating scales and prospective SI/B score assessment at all visits, including telehealth encounters, with third-party information gathering for completed suicides when feasible. These measures would help quantify risk, identify potential risk factors, and develop appropriate risk mitigation strategies for patients receiving difamilast. At this time though, based on the results to date, no dedicated SI/B study is recommended for difamilast.

Background

Difamilast (also known as MM-36), a selective phosphodiesterase 4 (PDE4) inhibitor, is under review for topical treatment of atopic dermatitis (AD) in patients 2 years of age and older. The proposed dosing regimen is difamilast ointment 1% applied topically twice daily to affected areas. Difamilast received approval in Japan in 2021 for adults and children with AD based on demonstrated safety and effectiveness in clinical studies.

AD is a chronic inflammatory skin disorder characterized by pruritic, eczematous lesions including erythema, papules, scales, crusts, and recurrent exacerbations. As the most common skin disease in children, AD affects approximately 15% to 20% of children and 1% to 3% of adults worldwide. In the United States, approximately 7.3% of adults have AD, with around 40% experiencing moderate to severe symptoms, while the prevalence among children is higher at approximately 10.7%. Most AD cases begin before age 5, commonly between 3 and 6 months of age during infancy or early childhood.

Multiple topical anti-inflammatory agents are currently available for AD treatment, primarily targeting acute inflammatory activity. Topical corticosteroids (TCS) remain the first-line treatment but present concerns including steroid phobia, rebound effects, and adverse reactions such as skin atrophy, particularly in sensitive areas. Topical calcineurin inhibitors (TCIs) provide nonsteroidal alternatives but carry limitations due to boxed warnings for potential cancer risks.

Recently approved topical therapies include PDE4 inhibitors (crisaborole and roflumilast), Janus kinase (JAK) inhibitors (ruxolitinib), and aryl hydrocarbon receptor agonists (tapinarof). Despite these advances, adherence remains challenging due to adverse drug reactions and complex

regimens, highlighting the continued need for additional treatment options with different mechanisms of action and improved tolerability profiles.

AD has complex pathogenesis involving genetic, immunologic, and environmental factors that lead to skin barrier dysfunction and immune dysregulation. Patients with AD experience skin barrier dysfunction, resulting in increased cutaneous irritability and heightened susceptibility to antigen sensitization and inflammation. Various hyperactive immune cells (Th1, Th2, Th17, and Th22 cells) produce cytokines that serve as causative factors for skin inflammation. These cytokines disrupt skin barrier function and trigger itch, contributing largely to AD pathology. An unmet need exists for topical treatments that can address both inflammatory processes and barrier dysfunction while providing long-term management with minimal local tolerability issues.

PDE4-mediated pathways are considered critical for inflammatory activation of immune cells including macrophages, lymphocytes, and neutrophils, both peripherally and locally in the skin. According to the Applicant, difamilast, as a selective PDE4 inhibitor with the strongest inhibitory effect against PDE4B among PDE4 subtypes, has potential to inhibit inflammatory processes driving AD symptoms and progression by increasing intracellular cAMP concentrations and suppressing cytokine production.

PDE4 plays a crucial role in the central nervous system and may be involved in various neurological and psychiatric disorders, from cognitive decline in Alzheimer's disease to mood disturbances in depression, making PDE4 a promising therapeutic target for these conditions.¹ However, two approved oral PDE4 inhibitors, Otezla (apremilast tablets) and Daliresp (roflumilast tablets), are associated with psychiatric symptoms. Both drugs carry labeling statements under Warnings and Precautions regarding depressive symptoms, with Daliresp also including warnings for suicidal thoughts and behaviors, insomnia, and anxiety.

Notably, topical ointment formulations of approved PDE4 inhibitors, including Eucrisa (crisaborole ointment) for atopic dermatitis and Zoryve (roflumilast ointment) for atopic dermatitis and plaque psoriasis, do not carry warnings and precautions for psychiatric disorders. Given that these drugs are topical, they have a lower likelihood of systemic effects and therefore have a lower likelihood of psychiatric ones as well. Safety analyses of these drugs have been consistent with this hypothesis and have shown no significant psychiatric safety signals thus far.

Additionally, there is an increased baseline risk of suicide and psychiatric concerns in the AD treatment population that warrants consideration.²

---

¹ Nahid S, Saeedi S, Hopkins CR. Phosphodiesterase 4 (PDE4) and neurological disorders: A promising frontier in neuropharmacology. *Adv Pharmacol.* 2025;102:159-209.

² Rønnstad, Amalie Thorsti Møller et al. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*, Volume 79, Issue 3, 448 - 456.e30.

Regulatory History: Division of Psychiatry Interactions

DDD has consulted with DP on four occasions regarding the assessment of psychiatric safety for the development program of difamilast ointment for mild to moderate AD in patients ≥ 2 years of age under IND 112973. These consultations were necessary due to the increased baseline risk of suicide in this treatment population and known psychiatric safety concerns with other approved PDE4 inhibitors (apremilast and roflumilast), which carry warnings for depression, suicidal ideation/behavior, and other psychiatric symptoms.

- October 31, 2018 - DP provided advice during a Type B End-of-Phase 2 (EOP2) meeting on October 31, 2018. The meeting minutes advise the Applicant that depression and SI/B should be assessed in a systematic and prospective manner using validated instruments, such as the 9-item Patient Health Questionnaire (PHQ-9) for depression and the Columbia-Suicide Severity Rating Scale (C-SSRS) for SI/B (see the response to Question 21 in the meeting minutes).
- October 5, 2020 - Dr. Joseph Callicott (DP reviewer) completed a consultative review addressing the assessment of potential psychiatric adverse events in the planned long-term difamilast safety trial and the applicability of psychiatric safety data from Japanese trials to the U.S. population. DP recommended that the lack of prospective, standardized assessment of depression and suicidal ideation/behavior (SI/B) in Japanese trials limited their usefulness and provided specific recommendations for Study MEDI-MM36-301 including the use of PHQ-9 and C-SSRS instruments, involvement of mental health professionals, specific exclusion criteria, and comprehensive safety monitoring protocols.
- August 20, 2021 - Dr. Gregory Dubitsky provided a consultative review for the Special Protocol Assessment of Study MEDI-MM36-301, specifically addressing the appropriateness of the Children's Depression Rating Scale-Revised (CDRS-R) for assessing depressive symptoms in children and adolescents ages 6 to 17 years. DP confirmed the CDRS-R was appropriate but noted that the C-SSRS version in the protocol was not acceptable, recommending use of the Baseline/Screening and Since Last Visit versions instead.
- April 26, 2022 - Dr. Shamir Kalaria completed a review of the revised Study MEDI-MM36-301 and Study MEDI-MM36-302 protocols, evaluating the Applicant's proposed clinical outcomes assessments for monitoring depression and SI/B. DP found the revised protocol generally reasonable, acknowledging the use of the Child Behavior Checklist (CBCL) 1½ to 5 for children ages 2 to 5 years and the Center for Epidemiologic Studies Depression Scale for Children (CES-DC) for ages 6 to 17 years, while recommending more frequent administration of the CBCL and clarification regarding instrument selection.

Review of Clinical Data

Selection of Relevant Clinical Trials

This marketing application includes multiple difamilast efficacy and safety studies across different phases, encompassing both placebo-controlled and open-label long-term studies:

Phase 2 Studies:

- 271-12-205: A completed phase 2, dose-finding, randomized, double-blind, placebo-controlled, parallel group, multicenter study evaluating the efficacy and safety of difamilast ointments 0.3% and 1% versus placebo in adult and pediatric subjects (2 years of age and older) with atopic dermatitis, conducted in the United States, Australia, and Poland. Treatment duration was 8 weeks.
- 271-15-001: A completed phase 2, dose-finding, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of difamilast ointments 0.3% and 1% versus placebo in adult subjects with atopic dermatitis, conducted in Japan. Treatment duration was 8 weeks.
- 271-102-00002: A completed phase 2, dose-finding, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of difamilast ointments 0.3% and 1% versus placebo in pediatric subjects with atopic dermatitis, conducted in Japan. Treatment duration was 4 weeks.

Phase 3 Pivotal Studies:

- 271-102-00007: A completed phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter confirmatory study evaluating the efficacy and safety of difamilast ointment 1% versus placebo in adult subjects (15 to 70 years of age) with mild to moderate atopic dermatitis, conducted in Japan. Treatment duration was 4 weeks.
- 271-102-00008: A completed phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter confirmatory study evaluating the efficacy and safety of difamilast ointments 0.3% and 1% versus placebo in pediatric subjects (2 to 14 years of age) with mild to moderate atopic dermatitis, conducted in Japan. Treatment duration was 4 weeks.
- MEDI-MM36-301: A phase 3, randomized, double-blind, placebo-controlled study in adult and pediatric subjects (2 years of age and older) with mild to moderate atopic dermatitis, conducted in the United States. This study was terminated early by the Applicant for business reasons and not for safety-related reasons after enrolling 153 of the target 336 subjects. Treatment duration was 4 weeks.

Long-Term Extension Open-Label Phase 3 Studies:

- 271-102-00006: An ongoing phase 3, open-label, uncontrolled, long-term treatment study investigating the safety and efficacy of difamilast ointment (1% for adults ≥ 15 years; 0.3% or 1% for children 2-14 years) for up to 52 weeks in subjects with atopic dermatitis, conducted in Japan.
- MEDI-MM36-302: A phase 3, open-label, uncontrolled, long-term treatment study investigating the safety and efficacy of difamilast ointment 1% for up to 52 weeks in adult and pediatric subjects with atopic dermatitis, including both de novo subjects and rollover subjects from Study MEDI-MM36-301, conducted in the United States.

The clinical development program also included specialized pharmacokinetic and dermal safety studies, including a maximal use study (MEDI-MM36-206) in pediatric subjects and various dermal safety assessments for phototoxicity, photoallergy, and irritation potential.

Based on the DDD consult request, we focused on the following defined pooling strategies in the psychiatric safety analyses:

1. Placebo-Controlled Studies Pool

- Studies included: 271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301
- Design: All randomized, double-blind, placebo-controlled studies
- Duration: 4-week treatment period across studies
- Population: 734 subjects total (386 Difamilast 1%, 348 Placebo)
- Purpose: Broader safety assessment across all controlled studies with placebo comparator

2. Long-Term Uncontrolled Studies Pool

- Studies included: 271-102-00006 and MEDI-MM36-302
- Design: Open-label, uncontrolled, long-term studies
- Duration: Up to 52 weeks of treatment
- Population: 857 subjects treated with Difamilast 1%
- Purpose: Long-term safety evaluation and assessment of safety over extended treatment periods

3. Single study assessment

- Study 271-15-001 and Study 217-12-205
- Design: Double blind dose finding studies
- Duration: 8 weeks of treatment
- No database available, only clinical study report reviewed
- Purpose: Further exploring safety assessment in double-blind studies

Review Strategy

The safety review strategy was focused on treatment-emergent adverse events (TEAEs) in the categories of psychiatric disorders and SI/B events, and on depression and SI/B assessments with psychiatric scales when available. The approach to the safety review encompassed several key areas:

- Each individual case of death was analyzed, regardless of cause, and their narratives were reviewed. However, only deaths related to psychiatric disorders, suicidal ideation, or behavior are reported and discussed in this review.
- The ADAE.xpt dataset (i.e., the dataset with listed TEAEs) was queried for psychiatric disorders and their subcategories, with particular attention to SI/B, overdose, depressive and anxiety disorders (except for Study 271-15-001 and Study 217-12-205, where only clinical study reports – CSR - were available)
- Shift tables for psychiatric scales (HPQ-9, C-SSRS, CES-DC, and CBCL) were carefully analyzed, where available (studies MEDI-MM36-301 and MEDI-MM36-302 only).

Placebo-Controlled Studies Pool

Study Design

Studies 271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301 were included. Study designs are described in Table 1.

Table 1. Placebo-Controlled Studies Pool

Phase	Study Number	Subjects Enrolled	Description
2	271-102-00002	73 1% Difamilast = 25 0.3% Difamilast = 24 Placebo = 24	Double-blind, placebo-controlled, efficacy, safety, and pharmacokinetic (PK) study with 4-week treatment duration in subjects 2-14 years of age
3	271-102-00007	364 1% Difamilast = 182 Placebo = 182	Pivotal Study 1: double-blind, placebo-controlled, efficacy and safety study with 4-week treatment duration in subjects 15-70 years of age
3	271-102-00008	251 1% Difamilast = 85 0.3% Difamilast = 83 Placebo = 83	Pivotal Study 2: double-blind, placebo-controlled, efficacy and safety study with 4-week treatment duration in subjects 2-14 years of age
3	MEDI-MM36-301	153 1% Difamilast = 94 Placebo = 59	Double-blind, placebo-controlled, efficacy and safety study with 4-week treatment duration in subjects 2 years of age and older; terminated early*

Source: clinical reviewer, modified from Applicant's Integrated Summary of Safety Document - Table 1.

*This study was early terminated for business decision.

All four studies utilized the same study design (i.e., double-blind, placebo-controlled studies) and treatment duration (4 weeks) and had similar eligibility criteria (mild or moderate AD affecting 5 to 40% of body surface area - BSA).

These studies evaluated Difamilast Ointment 1% and this review will focus on findings in subjects receiving Difamilast Ointment 1% only, given that the Applicant is seeking marketing authorization for only Difamilast Ointment 1%. Studies 271-102-00002, and 271-102-00008 also included a Difamilast Ointment 0.3% arm for pediatric subjects <15 years of age, but these subjects were not included in this review. Per the Applicant, a review of safety data from subjects who received Difamilast Ointment 0.3% did not identify any unique or additional safety findings that were not observed in subjects who received Difamilast Ointment 1%.

All trials consisted of a 2 to 30-day screening period, a 4-week assessment period, and a 2-week post-treatment observation period. Subjects received topically the 1% formulation or the placebo of difamilast ointment. These investigational medicinal products (IMPs) were administered twice daily (approximately 12 hours apart between morning and night administration) for 4 weeks. The age range differed across studies, as described in Table 1.

Table 2 reports the extent of exposure in the Placebo-Controlled Studies Pool.

Table 2. Extent of Exposure – Placebo-Controlled Studies (Safety Population)

Category	Difamilast 1% N = 386	Placebo N = 348
Duration of Treatment ¹ (days)		
n	386	348
Mean (SD)	27.4 (5.36)	24.4 (8.23)
Median	29.0	28.0
Minimum, Maximum	1, 39	1, 38
Total Amount of Test Article Used ² (g)		
n	384	345
Mean (SD)	138.89 (93.455)	133.16 (98.265)
Median	115.55	106.60
Minimum, Maximum	2.8, 553.6	3.1, 652.8
Mean Daily Amount of Test Article Used ³ (g/day)		
n	384	345
Mean (SD)	5.1005 (3.26818)	5.6395 (3.67355)
Median	4.3517	4.6276
Minimum, Maximum	0.330, 19.090	0.110, 25.108

Source: Table 4, Integrate Summary of Safety Document.

SD=Standard Deviation.

Placebo-controlled studies include 271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301.

Percentages are based on the number of subjects with available data in each treatment group (n) for the safety population.

¹Duration of treatment = (date of final application) – (date of first application) + 1.

²The total amount of test article used for a subject was calculated as the difference between the weight of the test article(s) dispensed and weight of test article(s) returned. For the calculation of total amount of test article used, if test article was not returned at a given collection period, the amount of test article used for that period was unknown and treated as missing.

³The mean daily amount of test article applied for a subject was calculated as the total amount of test article applied divided by the duration of treatment.

Reviewer’s comments: The study design of these studies and the sample size of participants that were exposed to difamilast appear adequate to assess TEAEs differences in psychiatric disorders and SI/B between placebo and difamilast. However, the actual utility of the study to evaluate differences depends on additional factors such as the type of psychiatric assessment to detect TEAEs, its frequency, and observed frequency of TEAEs.

Psychiatric Inclusion/Exclusion Criteria

The studies recruited male and female participants over 2 years of age (with age ranges varying by study) who had a diagnosis of AD affecting $\geq 5\%$ to $\leq 40\%$ BSA.

The studies had the following exclusion criteria related to psychiatric issues:

1. Study MEDI-MM36-301 (conducted in the United States)

Exclusion criteria

- Subjects with greater than minimal/mild depression at Screening (Visit 1) or Baseline (Visit 2) defined as:
  - PHQ-9 total score ≥ 7
  - CES-DC total ≥ 15
  - CBCL 1½ - 5 total syndrome scale II Anxious/Depressed score ≥ 9
  - Subjects with suicidal ideation (a “Yes” response to Question 3, 4, or 5 of the C-SSRS or a response of 1, 2, or 3 to Question 9 on the PHQ-9) within the past month, suicidal behavior within the previous 6 months, or psychiatric hospitalization within the 12 months prior to Screening or between Screening and Baseline (Visit 2).
- Subjects who had a known history of alcohol abuse or use of illicit drugs within 6 months prior to Screening (Visit 1) or, in the opinion of the Investigator, known or suspected use of illicit drugs prior to Baseline (Visit 2)
- Subjects who had any other medical or psychiatric conditions, which, in the opinion of the Investigator, would place the subject at increased risk, preclude obtaining voluntary consent/assent, or confound the primary or secondary objectives of the study

2. All other double-blind studies (conducted ex-U.S.)

Exclusion criteria

- Subjects with a clinically significant complication or history of any of the following disorders that the investigator or subinvestigator judged would prevent safe conduct of the trial or impact efficacy assessments:
  - Psychiatric disease

Reviewer's comments: The exclusion criteria for psychiatric disorders in Study MEDI-MM36-301 align with recommendations provided by DP in previous consultations regarding this development program. However, all other studies conducted outside the United States used very broad criteria for excluding psychiatric disorders, which may have biased the selected population and potentially underestimated the frequency of SI/B.

Psychiatric Assessment and Safety Monitoring

1. Study MEDI-MM36-301

- **Columbia Suicide Severity Rating Scales**
The C-SSRS was completed by subjects ≥ 6 years of age. This is a standard questionnaire (Screening/Baseline and Since Last Visit) used to assess treatment-emergent suicidal ideation and behavior in clinical studies.^{3,4} A “Yes” answer at any time to any one of the 5 suicidal ideation and associated behavioral questions on the C-SSRS Since Last Visit, was indicative of possible suicidal risk. The subject was referred for immediate assessment by a mental health professional via referral to psychiatric emergency services. The event was recorded as an AE. In addition, if the subject answered “yes” to question 3, 4, or 5, the study drug should have been discontinued. If the subject answered “yes” to question 1 or 2, the mental health professional should have determined whether the study drug should have been discontinued or not.
- **Patient Health Questionnaire-9 (PHQ-9)**
The PHQ-9 was completed by subjects ≥ 18 years of age.^{5,6} The instrument only takes a few minutes to complete. A score of 1 to 4 indicated minimal depression, score of 5 to 9 indicated mild depression, score of 10 to 14 indicated moderate depression, a score of 15 to 19 indicated moderately severe depression and 20 to 27 severe depression. A subject was permitted entry in the study with a score of ≤ 6 and a score of 0 for Question 9. A shift of symptoms at a subsequent visit, as quantified by the questionnaire, defined as a score of ≥ 7 with a change from Baseline of >2 points, warranted prompt referral for psychiatric evaluation. The event was recorded as an AE, and the Investigator determined whether study drug should have been discontinued depending on severity of symptoms.

Additionally, if at a subsequent visit, the subject indicated score of ≥ 1 for Question 9 (Thoughts that you would be better off dead, or of hurting yourself), the subject should have been discontinued from study drug and referred for immediate assessment by a

---

[3 Guidance for Industry – Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. Draft Guidance, 2012.](#)

⁴ <https://cssrs.columbia.edu/pharmaceutical-funded-research/>

⁵ Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine.* 2001;16:606-13.

⁶ Kroenke K, Spitzer RL. The PHQ-9: A New Depression Diagnostic and Severity Measure. *Psychiatric Annals.* 2002;32:509-15

mental health professional via referral to psychiatric emergency services. The event was recorded as an AE.

- **Center for Epidemiologic Studies Depression Scale for Children (CES-DC)**
The CES-DC is a 20-item self-report depression inventory with possible scores ranging from 0 to 60. The CES-DC was completed by subjects ≥ 6 years to ≤ 17 years of age. The developers of the CES-DC have used the cutoff score of 15 as being suggestive of depressive symptoms in children and adolescents. A score of 0 to 14 indicated no depression to mild depression. Higher CES-DC scores indicated increasing levels of depression. A subject was permitted entry in the study with a score of ≤ 14 . A shift of symptoms at a subsequent visit, as quantified by the questionnaire, defined as a score of ≥ 15 with a change from Baseline of >5 points, warranted prompt referral for psychiatric evaluation. The event was recorded as an AE, and the Investigator determined whether study drug should have been discontinued depending on severity of symptoms.
- **Child Behavior Checklist for Ages 1½ - 5 (CBCL 1½ - 5)**
The CBCL 1½ - 5 was completed by parent/caregiver for a child ≥ 2 to ≤ 5 years of age. The recommended interval for this scale should not have been less than 4 weeks in order to allow time for behavioral changes to stabilize and become clearly evident. Low frequency behaviors may also have been missed if the rating interval was too short. It was recommended that the evaluation period at baseline be the same as the follow-up interval. Therefore, the parent/caregiver considered the 4-week interval prior to the Screening and Baseline assessments. The assessment took about 10 to 15 minutes to complete.

The parent/caregiver completed the entire checklist, but assessment for the potential for depression was placed on the syndrome scale II, Anxious/Depressed. This syndrome scale comprised 8 responses; clings, feelings hurt, upset by separation, looks unhappy, nervous, self-conscious, fearful, and sad. An Anxious/Depressed syndrome scale score of 0 to 6 was in the normal range and a score of 7 to 8 was borderline. A score to ≥ 9 was considered in the clinical range. A subject was permitted entry in the study with a syndrome scale II, Anxious/Depressed score of ≤ 8 . A shift of symptoms at a subsequent visit, as quantified by the questionnaire, defined as a score of ≥ 9 with an increase of >2 points on the syndrome scale II Anxious/Depressed, warranted prompt referral for psychiatric evaluation. The event was recorded as an AE, and the Investigator determined whether study drug should have been discontinued depending on severity of symptoms.

2. All other studies:

No specific psychiatric scales were administered in the studies conducted outside the United States. Those studies included only the following subject-stopping criteria:

- If withdrawal was necessitated by problems with safety, such as the occurrence of an AE

or aggravation of an underlying disease, the investigator or subinvestigator was promptly to take appropriate measures and perform follow-up if necessary

Reviewer's comments: The C-SSRS, PHQ-9, CES-DC, and CBCL 1½-5 are acceptable instruments for assessing SI/B in this development program and are consistent with recommendations provided by DP in previous consultations regarding this development program. However, psychiatric assessment scales were used only in Study MEDI-MM36-301. All other studies conducted outside the United States employed very broad criteria for treatment discontinuation at the subject level, which may have underestimated the frequency of SI/B events.

The safeguards implemented in the event of SI/B were adequate for Study MEDI-MM36-301. However, safeguards for managing SI/B events were not described for any of the studies conducted outside the United States that were included in the Placebo-Controlled Studies Pool, representing a significant limitation in the safety monitoring approach for these trials.

Results

Coding of SI/B Adverse Events

The Applicant's coding of investigator adverse event terms to MedDRA preferred terms (MedDRA version 25.0) was evaluated by examining adverse event datasets for the Placebo-Controlled Studies Pool analysis. All events classified under the Preferred Term and under the Reported Term that included the word stems "Suici" and "Depr" were assessed. All events classified under the System Organ Classes (SOCs) of Psychiatric Disorders and Investigations (Psychiatric) were examined, as changes in psychiatric scales were recorded under SOC Investigations. Overall, the coding of reported terms to preferred terms was acceptable.

Review of Deaths Related to SI/B

No deaths were reported.

Review of TEAEs Related to SI/B

No TEAEs related to SI/B were reported.

TEAE dataset

Table 3. Psychiatric TEAEs in Difamilast Studies (Safety Populations)

<i>System Organ Class</i> Preferred Term	Placebo-Controlled Studies		Uncontrolled Studies
	Difamilast 1% N = 386 n (%)	Vehicle N = 348 n (%)	Difamilast 1% N = 857 n (%)
<i>Psychiatric Disorders</i>	1 (0.26)	0	19 (2.22)
Depression	1 (0.26)	0	8 (0.93)
Anxiety	0	0	3 (0.35)
Insomnia	0	0	3 (0.35)
Sleep disorder	0	0	2 (0.23)
Adjustment disorder with depressed mood	0	0	1 (0.12)
Attention deficit hyperactivity disorder	0	0	1 (0.12)
Generalised anxiety disorder	0	0	1 (0.12)
Irritability	0	0	1 (0.12)
Major depression	0	0	1 (0.12)
<i>Investigations (Psychiatric)</i>	0	0	6 (0.70)
Depression rating scale score increased	0	0	6 (0.70)

Source: Modified from Applicant's Integrate Summary of Safety, Table 18.

Placebo-controlled studies include 271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301.

Long-Term Uncontrolled Studies include 271-102-00006 and MEDI-MM36-302. Crude percentages are based on Safety Population.

Adverse events were coded using MedDRA version 25.0.

One participant reported a TEAE of worsening depression in Study MEDI-MM36-301 (Subject ID MEDI-MM36-301- (b) (6)) (Table 3, Placebo-Controlled Studies column). This was a 37-year-old White female who started treatment with difamilast 1% on (b) (6), and developed a TEAE of worsening depression on (b) (6), which she attributed to the death of a close family member. The subject was referred for psychiatric evaluation, and the event resolved 24 days after onset.

Given that the event occurred concomitantly with the acute stressor of the loss of a close family member, a causal relationship with the study drug is unlikely.

No other TEAEs related to psychiatric disorders and SI/B were reported in the Placebo-Controlled Studies Pool analysis (Table 3, Placebo-Controlled Studies column).

Psychiatric Scale Assessment

C-SSRS, PHQ-9, CES-DC, and CBCL 1½-5 assessments and shifts in these scales confirmed the results observed in the TEAE dataset. Only one participant (Subject ID MEDI-MM36-301- (b) (6)) had a shift in the PHQ-9 and was referred for psychiatric evaluation. This case has been described above.

Reviewer’s comment: Our comprehensive analysis examined the frequency of TEAEs categorized as “psychiatric disorders” within the SOC across both study populations. The analysis revealed no significant difference in psychiatric disorder occurrence between the difamilast and placebo groups. Psychiatric scale shift analyses yielded consistent findings. However, psychiatric scales were evaluated in only one study (Study MEDI-MM36-301), which substantially limits the generalizability of these conclusions due to insufficient psychiatric assessment across the broader study program. Additionally, Study MEDI-MM36-301 was terminated early, further decreasing the size of its database.

Long-Term Uncontrolled Studies Pool

Study Design

Studies 271-102-00006 and MEDI-MM36-302 were both open-label, uncontrolled, long-term studies and are therefore described together. The study designs are described in **Table 4**.

Table 4. Long-Term Uncontrolled Studies Pool

Phase	Study Number	Subjects Enrolled	Description
3	271-102-00006	366 1% Difamilast = 222 0.3% Difamilast = 144 (started at 0.3% and escalated to 1% during study = 98)	Open-label, long-term safety and efficacy study with up to 52-week treatment duration in subjects 2 years of age and older
3	MEDI-MM36-302	542 1% Difamilast = 542 (De Novo subjects = 437) (Difamilast → Difamilast = 69) (Placebo → Difamilast = 36)	Open-label, long-term safety and efficacy study with up to 52-week treatment duration in subjects 2 years of age and older

Source: clinical reviewer, modified from Applicant’s Integrated Summary of Safety Document - Table 1.

Both studies used the same study design (open-label long-term extension studies) and treatment duration (up to 52 weeks) and had similar eligibility criteria: subjects 2 years of age and older with atopic dermatitis affecting $\geq 5\%$ of BSA (excluding scalp).

Table 5 reports the extent of exposure in the Long-Term Uncontrolled Studies Pool.

Table 5. Extent of Exposure – Long-Term Uncontrolled Studies (Safety Population)

Category	Difamilast 1% N = 857
Duration of Treatment ¹ (days) n ²	856
Mean (SD)	225.5 (125.65)
Median	230.0

Minimum, Maximum	1, 397
Total Amount of Test Article Used ² (g)	
n ²	704
Mean (SD)	967.75 (1311.095)
Median	506.25
Minimum, Maximum	0.0, 11277.7
Mean Daily Amount of Test Article Used ³ (g/day)	
n ²	703
Mean (SD)	3.9642 (3.99442)
Median	2.5187
Minimum, Maximum	0.000, 31.150
Number of 4-Week Exposure Periods ⁴ n (%)	
0-1	81 (9.5%)
2	73 (8.5%)
3	43 (5.0%)
4	36 (4.2%)
5	52 (6.1%)
6	49 (5.7%)
7	53 (6.2%)
8	51 (6.0%)
9	41 (4.8%)
10	31 (3.6%)
11	34 (4.0%)
12	55 (6.4%)
13	239 (27.9%)
14	18 (2.1%)
Any Exposure ⁵	856 (99.9%)

Source: Applicant's Integrated Summary of Safety document, Table 14.3.1.3. SD=Standard Deviation.

Long-Term studies include 271-102-00006 and MEDI-MM36-302.

There were 98 subjects in study 271-102-00006 assigned to the 0.3% dose level who escalated to the 1% dose. Safety data for these subjects are analyzed for their exposure to the 1% dose.

¹Duration of treatment = total number of days on all on-treatment periods.

²The total amount of test article used for a subject was calculated as the difference between the weight of the test article(s) dispensed and weight of test article(s) returned. For the calculation of total amount of test article used, if test article was not returned at a given collection period, the amount of test article used for that period was unknown and treated as missing.

³The mean daily amount of test article applied for a subject was calculated as the total amount of test article applied divided by the duration of treatment.

⁴Number of 4-week periods of exposure are calculated as treatment duration divided by 28. Exposure periods were rounded to the nearest integer value. Percentage is based on number of subjects in treatment group. The duration of exposure for rollover subjects who received Difamilast 1% in study MEDI-M36-301 was derived as the days from treatment start date in MEDI-M36-301 to treatment end date in the MEDI-MM36-302 study.

⁵Subject MEDI-MM36-302- (b) (6) was enrolled in an off-treatment phase and never met protocol criteria to start treatment before discontinuing the study, thus the subject's exposure is 0.

Reviewer's comments: Although the time of exposure appears adequate to detect psychiatric disorders, the absence of placebo control groups prevents direct comparison of psychiatric disorders and SI/B between treatment groups. Without a placebo-controlled comparator, any observations of psychiatric TEAEs cannot be clearly attributed to difamilast treatment. Therefore, results from these open-label studies must be interpreted with caution.

Psychiatric Inclusion/Exclusion Criteria

The studies recruited male and female participants >2 years of age with a diagnosis of AD affecting ≥ 3 of BSA for Study MEDI-MM36-302 or $\geq 5\%$ of BSA for Study 271-102-00006.

The studies had the following exclusion criteria related to psychiatric issues:

1. Study MEDI-MM36-302 (conducted in the United States)
Same exclusion criteria as the placebo-controlled study MEDI-MM36-301. Refer to Study MEDI-MM36-301 exclusion criteria described previously for more details.
2. Study 271-102-00006 (conducted outside the United States)
Same exclusion criteria as the placebo-controlled studies conducted outside the United States. Refer to placebo-controlled studies conducted outside the United States.

Reviewer's comments: As we commented for the placebo-controlled studies, the exclusion criteria for psychiatric disorders in Study MEDI-MM36-302 align with recommendations provided by DP in previous consultations regarding this development program. However, as discussed for the studies conducted outside the United States, Study 271-102-00006 used very broad criteria for excluding psychiatric disorders and may have biased the selected population and potentially underestimated the frequency of SI/B.

Psychiatric Assessment and Safety Monitoring

1. Study MEDI-MM36-302
Same as for MEDI-MM36-301. Refer to Study MEDI-MM36-301 safety monitoring described previously for more details.
2. Study 271-102-00006 (conducted outside the United States)
Same as for placebo-controlled studies conducted outside the United States. Refer to psychiatric safety monitoring for placebo-controlled studies conducted outside the United States described previously for more details.

Reviewer's comments: As we commented for the placebo-controlled studies, while the C-SSRS, PHQ-9, CES-DC, and CBCL 1½-5 are acceptable instruments for assessing SI/B and are consistent with recommendations provided by DP in previous consultations regarding this development program, these scales were used only in Study MEDI-MM36-302 among the open-label studies. Additionally, the safeguards implemented in the event of SI/B were adequate for Study MEDI-MM36-302; however, psychiatric safeguards were not described for the open-label study conducted outside the United States, representing a significant limitation in the safety monitoring approach for these trials.

Results

Coding of SI/B Adverse Events

Same as for Placebo-Controlled Studies Pool.

Review of Deaths Related to SI/B

No deaths were reported in the long-term extension studies.

Review of TEAEs Related to SI/B

No TEAE related to SI/B were reported.

Review of TEAEs Related to Psychiatric Disorders

TEAE dataset

A total of 25 TEAEs occurred within the SOC of Psychiatric Disorders and Investigations (Psychiatric) in the TEAE dataset from the long-term extension studies. Of these, two TEAEs led to treatment discontinuation: one case of sleep disorder (subject 27110200006-^{(b) (6)}) and one case of depression rating scale increased (coded under Investigations, subject MEDI-MM36-302-^{(b) (6)}) (**Table 3**, Uncontrolled Studies column).

None of the psychiatric TEAEs were SI/B, as shown in **Table 3** (Uncontrolled Studies column).

Psychiatric scale assessment

Fifteen participants in Study MEDI-MM36-302 reported elevated scores in the psychiatric scales. The narratives for each case were available and reviewed. Six of these changes were recorded as "Depression rating scale score increased," while the others were recorded as TEAEs (depression, generalized anxiety disorder, attention deficit hyperactivity disorder). With the exception of four subjects (Subjects ^{(b) (6)}), all other eleven subjects had a psychiatric condition documented in their medical history at baseline.

Reviewer's comment: No cases of SI/B were reported in the open-label studies. While psychiatric disorders, including depression, were observed in the open-label studies, the absence of a placebo-controlled comparator arm precludes meaningful interpretation of these events and limits the ability to establish a causal relationship with the investigational product. Generally, the rates appear low, at 2% for all psychiatric AEs, and 1% or lower for each separate type.

Single Study Assessment

For completeness, the CSRs for Study 271-15-001 and Study 271-12-205 were reviewed and searched for TEAEs related to psychiatric disorders and SI/B. These studies were phase 2,

double-blind, dose-finding studies, each with a duration of 8 weeks. One case of depression was reported among participants receiving difamilast 1% compared to no cases in the placebo group in Study 271-12-205: subject (b) (6) a 16-year-old, experienced a serious TEAE of depression. The subject had worsening of depression that resulted in hospitalization for evaluation and treatment. The investigator assessed the event as CTCAE Grade 4 and not related to the investigational medicinal product. Of note, the participant had a relevant medical history that included attention deficit/hyperactivity disorder and depression. Given the participant's past psychiatric history of depression, a causal link with difamilast is very unlikely. The worsening of a pre-existing psychiatric condition in this case is more consistent with disease progression rather than a drug-related adverse event.

No other psychiatric disorders or SI/B events were reported in that study or in Study 271-15-001.

Reviewer's comment: The review of CSRs for these two studies did not identify any signal for psychiatric disorders or SI/B, which is consistent with the results from the other phase 3 studies and long-term extension studies in the development program.

Recommendations

Signal for Psychiatric AEs or Suicidal Ideation and Behavior:

The clinical trial data are insufficient to support a causal link between difamilast and adverse events related to suicidal ideation and behavior (SI/B) or depression or other psychiatric disorders. Only one psychiatric AE (for depression) occurred on drug, and none on placebo for the placebo-controlled trials. Rates of psychiatric AEs in open-label trials were generally low (under 1% for each type of AE, and 2% total). No SI/B events were reported.

However, this conclusion must be interpreted with caution for several reasons.

First, two of the three double-blind placebo-controlled studies did not specifically assess suicidal ideation/behavior or depression using validated scales or prospective assessment, with results based solely on reported adverse events.

Second, the only study that included systematic psychiatric assessments using validated instruments (Patient Health Questionnaire-9, Columbia Suicide Severity Rating Scale, and Center for Epidemiological Studies Depression Scale for Children) was Study MEDI-MM36-301, that was terminated early for business reasons by the applicant, resulting in limited data availability.

Nonetheless, overall the results appear reassuring and do not show a major psychiatric AE signal for difamilast, which also makes mechanistic sense as it is a topical drug with minimal expected systemic exposures.

Inclusion in Section 5 of Prescribing Information:

We do not recommend that any information about the increased risk of psychiatric disorders or SI/B associated with difamilast be included in Section 5 (Warnings and Precautions) of the PI.

Postmarketing Studies:

DP views dedicated studies to assess SI/B as difficult to design, power, and interpret. At this time, based on the psychiatric safety signal results in the program to date, we do not feel such a dedicated study is necessary.

However, should a postmarketing study be recommended by the DDD review team, in order to more accurately ascertain any psychiatric signals, we recommend including:

1. An adequate assessment of depressive symptoms using a validated rating scale
2. Collection at every visit (including telehealth/phone visits) and prospective monitoring of scores using an assessment scale that maps to Columbia Classification Algorithm of Suicide Assessment (C-CASA) criteria, such as the C-SSRS, and including collection of third-party information in cases of complete suicide, as feasible.

These measures may help quantify the risk, identify potential risk factors, and develop appropriate risk mitigation strategies for patients receiving difamilast if needed in the future.

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/

ROBERTA RASETTI
08/25/2025 02:15:01 PM

BERNARD A FISCHER on behalf of JEAN S KIM
08/25/2025 02:27:51 PM

BERNARD A FISCHER
08/25/2025 02:28:36 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	August 8, 2025
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 219474
Product Name, Dosage Form, and Strength:	Adquey (difamilast) ointment, 1%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Acrotech Biopharma Inc.
FDA Received Date:	February 13, 2025
TTT ID #:	2025-13356
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

---

1 INTRODUCTION

As part of the approval process for Adquey (difamilast) ointment, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Adquey Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The proposed Adquey Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling may be improved to promote 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 for the Division of Dermatology and Dentistry (DDD) in Section 4 and for Acrotech Biopharma Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the proprietary name is denoted by the placeholder "TRADENAME"	We refer to our April 28, 2025, Proprietary Name Request Conditionally Acceptable letter indicating that the proprietary name, Adquey, was found conditionally acceptable.	We recommend replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name "Adquey" throughout the PI.
Highlights of Prescribing Information			
1.	The dosage statement lacks clarity surrounding how much of the	For clarity and alignment with the dosage information included in the	Revise the statement of dosage to: "Apply a thin layer of

Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	ointment to apply twice daily.	Full Prescribing Information.	ADQUEY twice daily to affected areas."
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, Section 2 contains the statement (b) (4)	Lack of clarity.	Clarify the statement by defining (b) (4) for example, revise to specify (b) (4) etc., as appropriate.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Currently the storage information in the Patient Package Insert (PPI) includes the statement "Store away from direct sunlight, heat and moisture." This statement is not included in the storage information of the PI.	Consistency between the PPI and prescribing information will help to minimize storage errors.	Add "Store away from direct sunlight, heat and moisture." to the storage information of the prescribing information.
Patient Package Insert (PPI)			
1.	As currently presented, the proprietary name is denoted by the placeholder "TRADENAME"	We refer to our April 28, 2025, Proprietary Name Request Conditionally Acceptable letter indicating that the proprietary name, Adquey, was found conditionally acceptable.	We recommend replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name "Adquey" throughout the PPI.

5 RECOMMENDATIONS FOR ACROTECH BIOPHARMA INC.

Table 3. Identified Issues and Recommendations for Acrotech Biopharma Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The established name is not at least half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2), which states that <i>the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.</i>	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
2.	As currently presented, critical product information (e.g., established name, strength, dosage form, route of administration) lack prominence relative to the company name and logo on the principal display panel.	The proprietary name and established name along with the product strength, route of administration, dosage form, and warnings or cautionary statements (if any) should be the most prominent information on the principal display panel (PDP). See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to	We recommend increasing the prominence of the established name, strength, dosage form, and route, for example, by increasing the font size and decreasing the prominence of your company name and logo relative to the prominence of the critical product information on the principal display panel.

Table 3. Identified Issues and Recommendations for Acrotech Biopharma Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Minimize Medication Errors (May 2022). ^a	
3.	As currently presented, the proprietary name is denoted by the placeholder "Tradenname."	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our April 28, 2025, Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Adquey, was found conditionally acceptable. We recommend replacing the placeholder "Tradenname" with the conditionally acceptable proprietary name, Adquey, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
4.	The net quantity statement lacks adequate spacing between the number and the unit of measure.	Lack of adequate spacing may impact readability.	We recommend placing adequate space between the net quantity number and unit of measure (e.g., 85 g instead of 85g) to improve readability.
5.	The storage statement currently includes the abbreviation for Celsius (i.e., C) in place of where Fahrenheit (i.e., F) should be indicated within the parentheses i.e., Store at 20°C to 25°C (68°C to 77°C); excursions permitted to 15°C to 30°C (59°C to 86°C) [see USP	Lack of clarity.	Revise the statement to read "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>

Table 3. Identified Issues and Recommendations for Acrotech Biopharma Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Controlled Room Temperature].		
6.	Currently the storage information in the Patient Package Insert (PPI) includes the statement "Store away from direct sunlight, heat and moisture." This statement is not included in the storage information on the container labels and carton labeling.	Consistency between the PPI and the container labels and carton labeling will help to minimize storage errors.	Add "Store away from direct sunlight, heat and moisture." to the storage information of the container labels and carton labeling.
7.	The placeholder for the lot number is missing.	The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Add the placeholder for the lot number in accordance with 21 CFR 201.10(i)(1).
8.	The placeholder for the expiration date is missing.	The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholder for the expiration date in accordance with USP General Chapter <7> and clarify the intended format. The USP Chapter <7> Labeling requires the expiration date to appear on the immediate container and all other packaging. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be

Table 3. Identified Issues and Recommendations for Acrotech Biopharma Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use.
9.	The statement of dosage lacks clarity surrounding how much of the ointment to apply twice daily.	For clarity and alignment with the dosage information included in the Prescribing Information.	Revise the statement of dosage to: "Apply a thin layer twice daily to affected areas."
Container Labels			
1.	As currently presented, there are two types of barcodes (linear and 2D matrix) on the container labels located in close proximity to each other.	The linear drug barcode is often used as an additional verification during the medication use process. The presence of barcodes in close proximity to one another could lead to scan errors.	We recommend moving the 2D matrix barcode that does not contain the NDC to appear away from the linear barcode containing the NDC number and present it in a size that does not compete with nor distract from the presentation of other required or recommended information on the label. Alternatively, consider removing the 2D matrix barcode.
Carton Labeling			
1.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug	Add the product identifier to the carton labeling. For additional information, see Guidance for Industry: Product

Table 3. Identified Issues and Recommendations for Acrotech Biopharma Inc.
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in (to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).^b Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.

---

^b Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. July 2021. Available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Adquey received on February 13, 2025 from Acrotech Biopharma Inc.

Table 4. Relevant Product Information for Adquey													
Initial Approval Date	N/A												
Active Ingredient	difamilast												
Indication	the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older												
Dosage Form	ointment												
Strength	1%												
Route of Administration	topical												
Dose and Frequency	Apply a thin layer of TRADENAME twice daily to affected areas (b) (4) and rub in completely.												
How Supplied	3 g professional sample tube 27 g tube 85 g tube												
Storage	Store at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–86°F). [see USP Controlled Room Temperature]. Keep tube tightly closed.												
Container Closure	Table 1: Packaging Configurations <table border="1"> <thead> <tr> <th>Ointment / Tube</th> <th>Container (Tube)</th> <th>Closure (Cap)</th> </tr> </thead> <tbody> <tr> <td>27-g fill</td> <td>30-g empty aluminum sealed orifice</td> <td>#20 (b) (4) screw cap</td> </tr> <tr> <td>85-g fill</td> <td>90-g empty aluminum sealed orifice</td> <td>#20 screw cap</td> </tr> <tr> <td>3-g fill *</td> <td>5-g empty aluminum sealed orifice</td> <td>#12 screw cap</td> </tr> </tbody> </table> * physician samples	Ointment / Tube	Container (Tube)	Closure (Cap)	27-g fill	30-g empty aluminum sealed orifice	#20 (b) (4) screw cap	85-g fill	90-g empty aluminum sealed orifice	#20 screw cap	3-g fill *	5-g empty aluminum sealed orifice	#12 screw cap
Ointment / Tube	Container (Tube)	Closure (Cap)											
27-g fill	30-g empty aluminum sealed orifice	#20 (b) (4) screw cap											
85-g fill	90-g empty aluminum sealed orifice	#20 screw cap											
3-g fill *	5-g empty aluminum sealed orifice	#12 screw cap											

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Adquey labels and labeling submitted by Acrotech Biopharma Inc.

- Prescribing Information received on February 13, 2025, available from <\\CDSESUB1\EVSPROD\nda219474\0001\m1\us\114-labeling\114a-draft-label\20250207-difamilast-uspi-draft-1-5-final-ectd-v3.pdf>
- Patient Package Insert received on February 13, 2025, available from <\\CDSESUB1\EVSPROD\nda219474\0001\m1\us\114-labeling\114a-draft-label\difamilast-ppi-final.pdf>
- Container labels received on February 13, 2025
- Carton labeling received on February 13, 2025
- Professional Sample Container Label received on February 13, 2025
- Professional Sample Carton Labeling received on February 13, 2025

B.2 Container Labels and Carton Labeling Images

Container Labels:



---

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

KRISTINE P NEEDLEMAN
08/08/2025 08:24:27 AM

VALERIE S VAUGHAN
08/08/2025 08:27:46 AM

Interdisciplinary Review Team for Cardiac Safety Studies
QT Study Review

Submission	NDA 219474
Submission Number	0001
Submission Date	2/13/2025
Date Consult Received	4/2/2025
Drug Name	Difamilast Ointment
Indication	Treatment of mild to moderate atopic dermatitis (AD)
Therapeutic Dose	Apply twice daily to affected area
Clinical Division	DDD
Protocol Review	06/07/2021 (See Section 5)

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

This review responds to your consult dated 4/2/2025 regarding the Applicant’s QT evaluation. We reviewed the following materials:

- Previous IRT reviews of IND 112973/SDN0100 dated 10/23/2018 ([link](#)), IND 112973/SDN0118 dated 06/07/2021 ([link](#)), IND 112973/SDN0122 dated 08/04/2021 ([link](#)), IND 112973/SDN0122 dated 08/24/2021 ([link](#)), IND 112973/SDN0123 dated 08/26/2021 ([link](#)) in DARRTS;
- Clinical trial report of ECG substudy MEDI-MM36-302 (NDA 219474 / SN001; [link](#));
- Investigator’s brochure (NDA 219474 / SDN 001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (NDA 219474 / SDN 001; [link](#)) – see Table 32.

1 SUMMARY

We previously agreed that the QTc assessment for difamilast ointment could be based on a QTc substudy included in an open-label extension study in patients with mild to moderate atopic dermatitis (study MEDI-MM36-302), along with an integrated nonclinical risk assessment. Our agreement was predicated on the assumption that the difamilast exposure in the QTc substudy would be representative of the therapeutic exposures in the intended patient population. On the contrary, we have determined that difamilast exposure in the QTc substudy is not representative of the exposure in the overall Phase 3 population as the mean (SD) body surface area affected in the QTc substudy (5.5% [3%]) is lower than that in the overall Phase 3 population (10% [11%]). In addition, the mean steady-state C_{max} in the QTc substudy is substantially lower than the mean C_{max} reported in the maximum use study, which included patients with moderate to severe atopic dermatitis (0.5 ng/mL vs. 14 ng/mL, respectively). As the QTc

substudy does not appear to represent the intended patient population, the Applicant has not adequately evaluated the effects on the QTc interval. The Applicant therefore needs to perform a dedicated QTc study to evaluate the effects on the QTc interval. We defer to the Division concerning the timing of this study. Until the effects on the QTc interval have been characterized, we recommend inclusion of a statement in the label describing the inadequate characterization of the QTc interval.

2 RECOMMENDATIONS

2.1 PROPOSED LABEL

The Applicant did not propose QTc labelling language in Section 12.2 ([link](#)).

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

[There is insufficient information to characterize the effect of TRADENAME on the QTc interval.](#)

Reviewer's comment: We recommend describing in the label that the effects on the QTc interval have not been adequately characterized.

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

The Applicant, Acrotech Biopharma Inc, is seeking approval of difamilast ointment (10 mg/g) for the treatment of mild to moderate atopic dermatitis. The proposed therapeutic dose is application of a thin layer to the affected areas twice daily.

Initially, the Applicant proposed a QTc assessment based on an integrated nonclinical risk assessment together with a QTc assessment in the maximum use study (MEDI-MM-206). We did not agree that study MEDI-MM-206 could be used as a substitute for a TQT study because of the lack of placebo and it was unclear if the timing of ECG collection was adequate. We recommended that the Applicant conducted a TQT study. (DARRTS [10/23/2018](#))

The Applicant subsequently responded that they did not believe that a conventional TQT study would provide clinically meaningful data because suprathreshold exposures could not be achieved in healthy volunteers. The Applicant therefore proposed a QTc assessment based on clinical data from study MEDI-MM36-302 together with an integrated nonclinical risk assessment based on a repeat hERG and in vivo QTc study to follow best practice recommendations. Overall, we agreed with the proposal but noted that it was unclear if a repeat hERG assay was necessary. This agreement was based on an understanding of the concentrations in the MEDI-MM36-302 being reflective of therapeutic concentrations. We conveyed that if the Applicant wanted to repeat the hERG assay, we recommended following best practice recommendations in ICH E14/S7B Q&A

2.1. We also noted that considering the 3Rs we did not recommend repeating the in vivo QT study and instead recommended that the Applicant provided PK data from other in vivo QT studies to support the safety margin for the 30 mg/kg single subcutaneous (SC) in the completed study (Study No. 028658 / Report No. 023319). (DARRTS [06/07/2021](#)) The requested information for the in vivo QT study was later submitted by the Applicant and found to be acceptable. (DARRTS [08/04/2021](#); [08/24/2021](#))

The Applicant subsequently requested confirmation on the proposed ECG monitoring in MEDI-MM36-301. We responded that it was acceptable. (DARRTS [08/26/2021](#))

A review of the Applicant's clinical QTc assessment plan based on Study MEDI-MM36-302 is presented in Section 5 (Appendix 5).

As noted elsewhere, the concentrations in study MEDI-MM36-302 are sub-therapeutic. We therefore re-assessed study MEDI-MM-206 and confirmed that the study included ECGs on Days 1, 15, and 29. Based on the PC dataset, almost all the ECGs on Days 1 and 15 were pre-dose. Consequently, the data from this study are not supportive of QTc assessment. Another potential study (271-12-204; [CSR](#)) was also identified. This study included two Phases, the Phase with the highest exposures (Phase 2) had a few completers (n=11), which is not a sufficient sample size to support QTc assessment. Additionally, the study also only included post-dose ECGs on Day 1 (2 and 4 h).

3.1.1 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety. Briefly, difamilast is appreciably absorbed after topical administration and time to peak concentration varied by dose and study population or dosing condition. The drug exhibited less-than dose-proportional increase in C_{max} between 0.3% (15 mg) to 3% (150 mg) single dose applications. Although steady state accumulation was observed in healthy subjects (Study 271-14-001, Day 14 over Day 1 C_{max} ratio of 1.26 – 1.52) no accumulation was observed in pediatric patients with atopic dermatitis (Study MEDI-MM36-206).

Difamilast is metabolized to several metabolites with significant systemic exposures (metabolite/parent AUC₀₋₁₂ ratio ranging from 0.259 to 0.670).

Impact of intrinsic and extrinsic factors on PK of difamilast have not been characterized. According to the Applicant, no obvious impact is expected from age, sex, race, and renal impairment; hepatic impairment is likely to increase difamilast exposure, but no hepatic impairment study has been conducted.

Difamilast is a substrate of CYP3A4 and CYP1A2. Predictions from the Applicant's PBPK model indicate that strong CYP3A4 inhibition is likely to increase difamilast C_{max} by 1.3-fold. Therefore, tentative high clinical exposure scenario is 1.3-fold increase in C_{max} with strong CYP3A4 inhibition. The Applicant postulates 5-fold increase in C_{max} with hepatic impairment.

The proposed dosing regimen (1% (10 mg/g) difamilast ointment applied as thin layer on affect parts) under maximal use condition ($\geq 35\%$ and $\geq 25\%$ of BSA in children 2-12 years and 12 – 18 years old respectively) provided geometric mean C_{max} of 14.3 ng/mL after first dose (median T_{max} = 4 hours) and geometric mean C_{max} of 11.0 ng/mL on day

15 of twice daily dosing (30 mg – 88 mg BID)[See [CSR MEDI-MM36-206, Table 22, page 103 of 367](#)]

The C_{max} in the QTc substudy (0.5 ng/mL) is sub-therapeutic.

3.1.2 Nonclinical Safety Pharmacology Assessments

In vitro hERG assay

We have previously reviewed the hERG assay and no new hERG assays were submitted by the Applicant.

Briefly, the GLP hERG study (022275, study ID: 028269; [link](#)) assessed the potential effects of difamilast on the hERG current in CHO cells. The hERG current was assessed at room temperature ($23 \pm 1^\circ\text{C}$), using a step-step voltage protocol (from a holding potential of -80 mV to a depolarizing pulse of 20 mV for 1.5 s, followed by a repolarizing pulse to -40 mV for 1.5 s) that is different from the recommended hERG current protocol by the FDA. The positive control (1 μM E-4031) inhibited the hERG currents by 97.2%. Samples of the test article formulation solutions collected from the targeted stock solutions (prior to perfusion) were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of difamilast at all test concentrations were within $\pm 5.0\%$ of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects.

Difamilast concentration dependently inhibited the hERG currents with an IC_{50} of 2.54 μM , which corresponds to a hERG safety margin of 7931-fold (MW: 446.5 g/mol; PB: 99%) using the C_{max} in study MEDI-MM36-206 (14.3 ng/mL).

Reviewer's Comment: *The hERG assay showed deviations (room temperature; a lack of proper positive control; solution samples collection for drug concentration verification were not collected from the recording chamber). The results showed that difamilast has a safety margin of 7931x, suggesting that difamilast may have low risk for QTc prolongation by direct interaction with hERG channel at therapeutic exposure. The limitations of the hERG assay may not substantially impact this large safety margin (7931x).*

In vivo QT study

The in vivo cardiovascular pharmacology study (023319, [link](#)) assessed the effects of difamilast on ECG parameters following SC administration of difamilast at 0 (vehicle control), 3, 10, and 30 mg/kg doses to conscious male beagle dogs.

ECGs were collected and evaluated before administration and 0.5, 1, 2, 3, 4, and 5 hours after the administration of the vehicle and test articles.

No PK data were available in this study. In a repeat dose tox study (023810, [link](#)), the C_{max} values were 131 ng/mL, 329 and 1409 ng/mL on Day 1, for dose levels of 3, 10 and 30 mg/kg/day, respectively. The protein binding in dogs exceeded 99%.

No drug-related changes in heart rate, QTcV, QRS, and PR intervals were observed in the in vivo study.

Reviewer's Comment: *No QTc prolongation was observed at exposure 98x the C_{max} of study MEDI-MM36-206 in the in vivo dog study.*

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

In the Applicant's by-time analysis, the maximum upper bound for difamilast ointment 1% was <10 msec for Δ QTcF, showing no prolongation effect at this drug dose.

Applicant also presented by-time analysis results for HR, PR and QRS intervals, which did not show significant changes.

Reviewer's comment: *The Applicant's analysis was similar to the reviewer's analysis. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the Applicant.

3.2.2 Categorical Analysis

Per the Applicant's analysis for QTc there was one patient having QTcF values greater than 500 msec but no one with >60 msec over baseline; for HR, no subject had a HR <40 or >110 beats/min at any timepoint; for PR, one patient had 3 timepoints greater than 220 msec but less than 25% over baseline; for QRS, no patient with value >120 msec and 25% over baseline.

Reviewer's comment: *The reviewer's analysis results are similar to the Applicant's for all intervals with slightly different cutoffs. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The Applicant developed linear, quadratic, and cubic models for difamilast and its metabolites. Although AIC were comparable between models, the Applicant selected a quadratic model for difamilast and cubic models for each of 3 metabolites of difamilast (i.e., MAP-15484, MAP-15497, and MAP-15485) as the final model for prediction of QTc effect. None of the selected models indicate significant C-QTc relationship and the predicted Δ QTcF (mean and upper bound of 90% CI) are not clinically significant (i.e., upper bound of 90% CI was <10 msec for all models).

Reviewer's comment: *The Applicant's analyses differ from the reviewer's analysis reported in Section 4.5. Despite the difference, the reviewer's C-QTc analysis also indicate absence of C-QTc relationship.*

3.2.4 Safety Analysis

In summary, difamilast administration was observed to have no clinically relevant effects on the ECG and specifically was not associated with evidence of cardiac repolarization 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

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., $|\text{mean}| > 10$ beats/min) were observed (section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to date and time. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.3 BY-TIME ANALYSIS

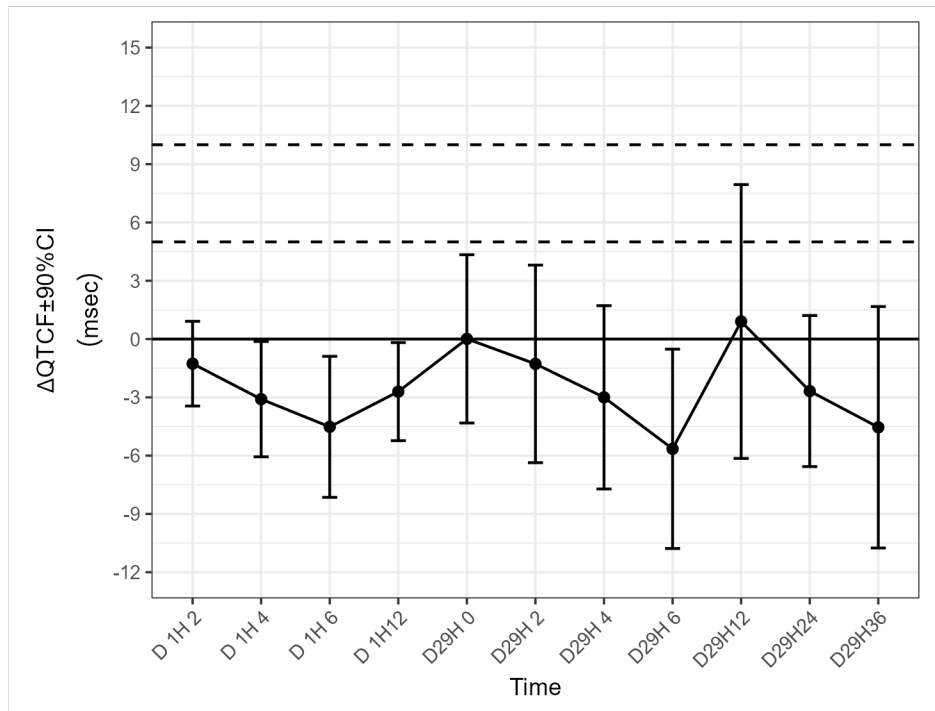
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. One subject withdrew in Day 1 and thereafter.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The model includes time (as a categorical variable), and baseline as a covariate. The model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for difamilast ointment 1%.

Figure 1. Mean and 90% CI of Δ QTcF Time-Course (Unadjusted CIs)



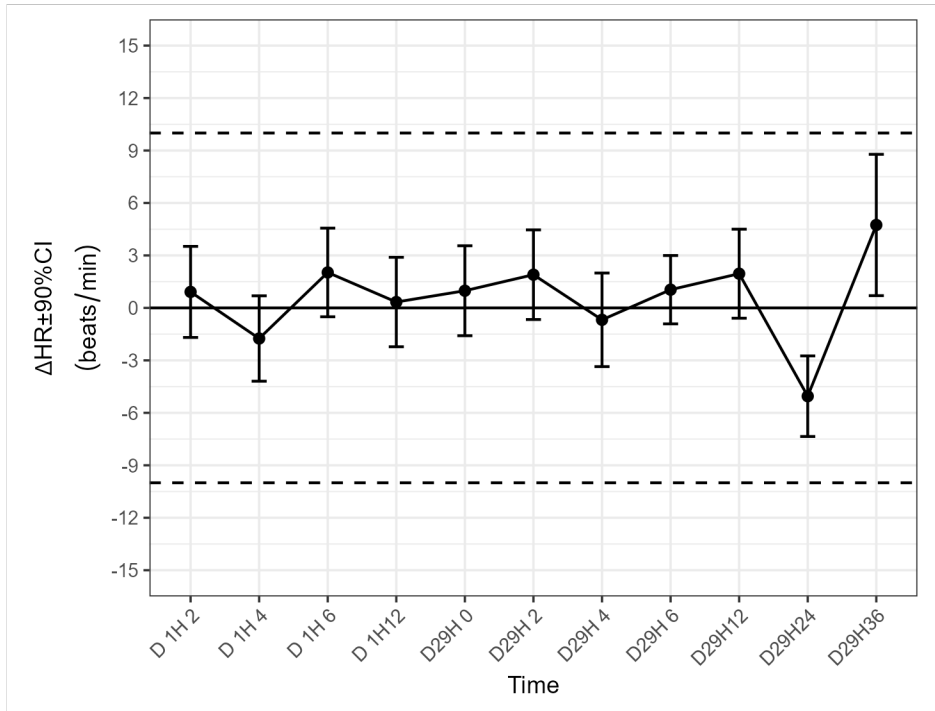
4.3.1.1 Assay Sensitivity

Not applicable

4.3.2 HR

Figure 2 displays the time profile of Δ HR for difamilast ointment 1%.

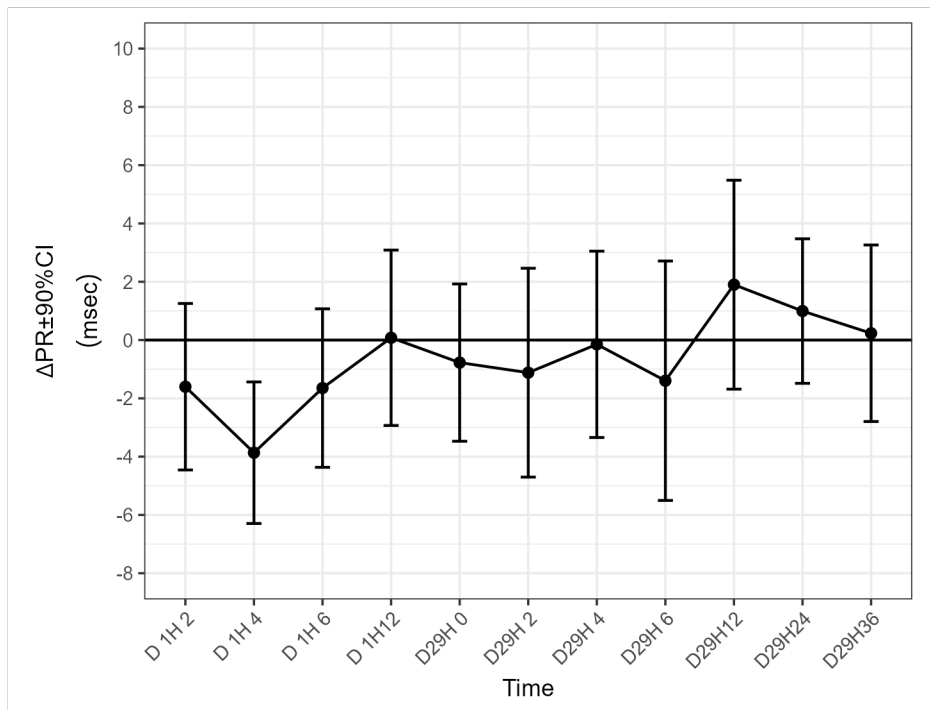
Figure 2. Mean and 90% CI of Δ HR Time-Course



4.3.3 PR

Figure 3 displays the time profile of Δ PR for difamilast ointment 1%.

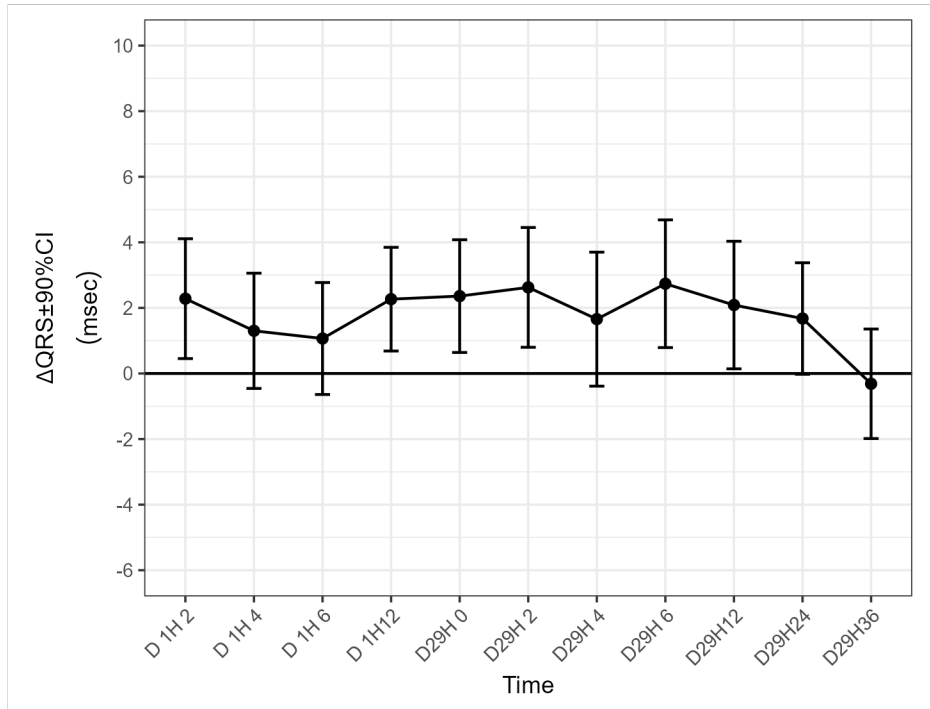
Figure 3. Mean and 90% CI of Δ PR Time-Course



4.3.4 QRS

Figure 4 displays the time profile of Δ QRS for difamilast ointment 1%.

Figure 4. Mean and 90% CI of Δ QRS 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

Table lists the number of subjects, as well as the number of observations with QTcF values of ≤ 450 msec, >450 and ≤ 480 msec, >480 and ≤ 500 msec, and >500 msec with or without a change from baseline >60 msec. There was one subject ((b) (6)) who experienced QTcF values >500 msec and changes from baseline >60 msec. The QTc was prolonged at isolated time-points and that subject had prolonged QTc (>590 msec) at two pre-dose time-points (Hours 6 and 12).

Table 1. Categorical Analysis for QTcF (Maximum)

Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		Value >500 msec & <=60 msec	Value >500 msec & >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Obs.	# Subj.	# Obs.
Difamilast Ointment 1%	31	321	29 (93.5%)	315 (98.1%)	1 (3.2%)	3 (0.9%)	1 (0.3%)	1 (3.2%)	2 (0.6%)

Table lists the categorical analysis results for Δ QTcF (<30 msec, >30 and <60, and >60 msec). There was one subject who experienced changes of QTcF values from baseline >60 msec.

Table 2. Categorical Analysis for Δ QTcF (Maximum)

Actual Treatment	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Difamilast Ointment 1%	31	321	29 (93.5%)	316 (98.4%)	1 (3.2%)	3 (0.9%)	1 (3.2%)	2 (0.6%)

4.4.2 HR

Table lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 3 subjects who experienced HR values >100 msec.

Table 3. Categorical Analysis for HR (Maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Difamilast Ointment 1%	31	325	28 (90.3%)	322 (99.1%)	3 (9.7%)	3 (0.9%)

4.4.3 PR

No subjects had observed PR >220 with 25% increase over baseline.

4.4.4 QRS

No subjects had observed QRS >120 msec.

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 (n = 31). One subject ((b) (6)) had high baseline QTcF at 6 and 12 hours on Day -1. This subject was not excluded from analysis.

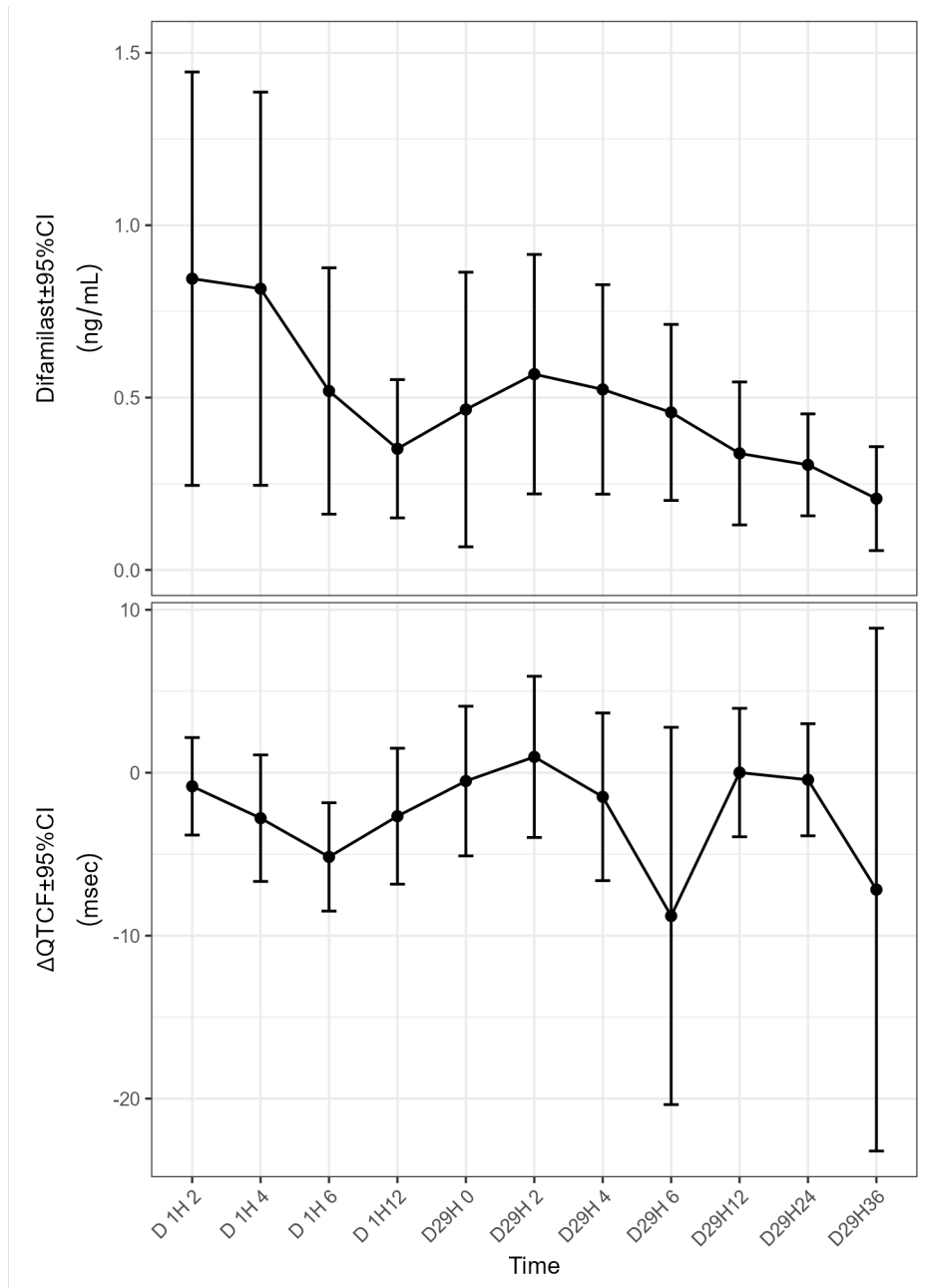
4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were 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 $\Delta QTcF$; and 3) absence of a nonlinear relationship.

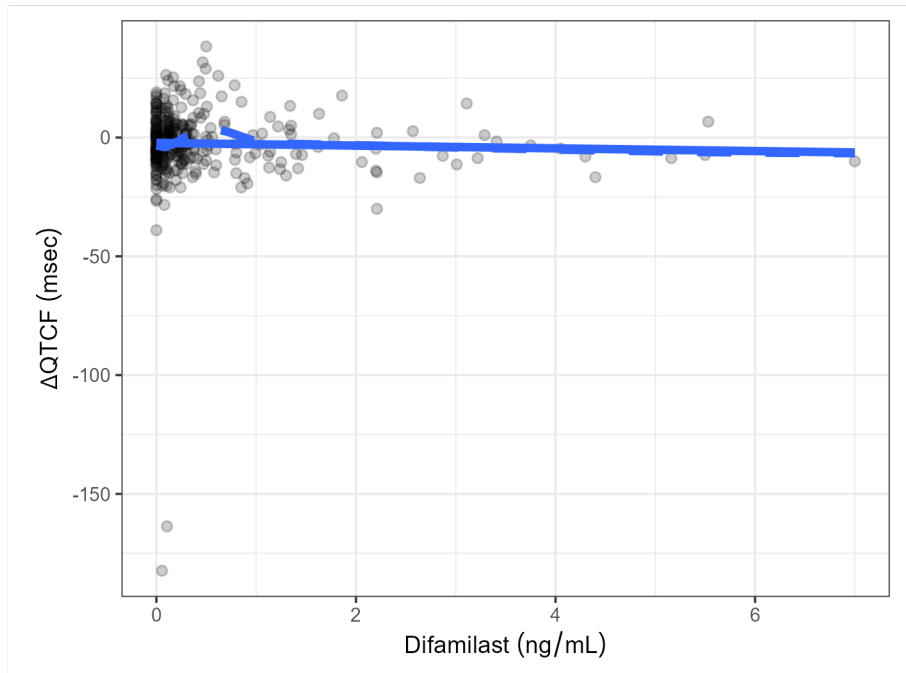
Figure 2 shows the time-course of ΔHR , with an absence of significant ΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and $\Delta QTcF$, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and $\Delta QTcF$ and supports the use of a linear model.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)¹



¹ ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

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



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4.

Figure 7. Goodness-of-Fit Plot for QTcF

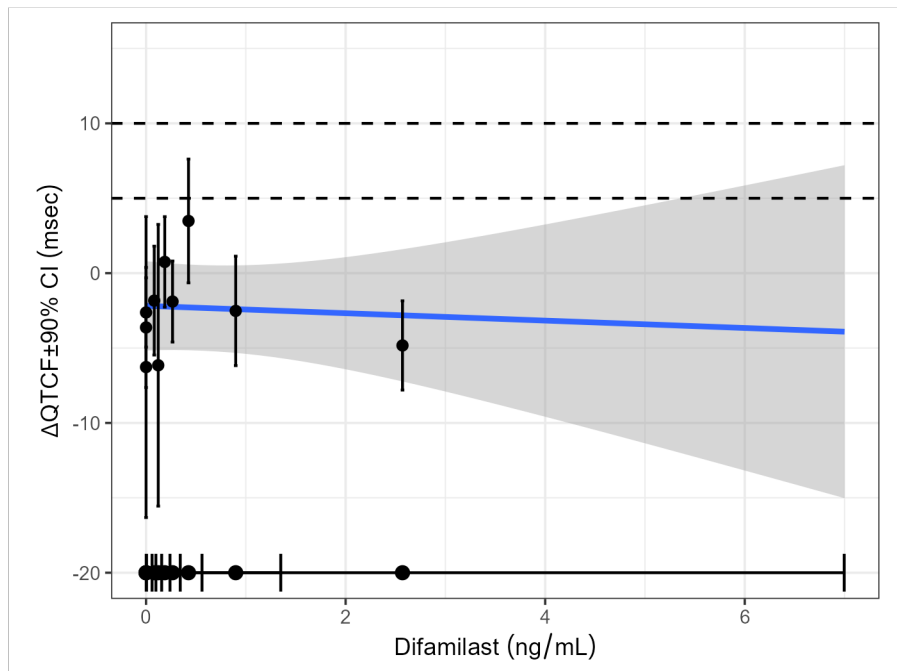


Table 4. Predictions From Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Difamilast (ng/mL)	Δ QTcF (msec)	90.0% CI (msec)
Difamilast Ointment 1%	29	0.4	-2.3	(-5.1 to 0.6)
Difamilast Ointment 1%	1	0.5	-2.3	(-5.2 to 0.6)

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

1. QT Studies					
Study	ECG Quality	Treatments		Sample Size	ECG & PK Assessments
		Arms	Dose Coverage		
Protocol Number: MEDI-MM36-302 Population: Patients Design: Other	Digital: Yes Central Read? Yes Blinded? No Replicates? Yes	Highest Dose: Difamilast Ointment 1%, BID for 4 weeks Placebo: No Positive Control: No	Therapeutic	31	Baseline: Time-matched Timing: Baseline on Day -1: 0, 1, 2, 4, 6 and 12 hours. On Day 1 and Day 29, respectively, pre-dose, 1, 2, 4, 6 and 12 hours after the first or last dose; and 24 and 36 hours after the last dose.
Reviewer's comments: Cardiovascular safety of difamilast was investigated in 31 subjects participating in a Phase III, open-label study to assess the long-term safety of difamilast Ointment 1% in the treatment of children (≥ 2 years), adolescents, and adults with mild to moderate atopic dermatitis (Study MEDI-MM36-302). Patients in this study were de-novo or rolled over from another Phase III study (Study MEDI-MM36-301). Holter recordings were used on Day -1, Day 1, Day 29, and Day 30. 12-lead ECGs were extracted on Days -1, 1 and 29 at pre-dose and at 2, 4, 6, and 12-hours post dose. On day 30 additional 12-lead ECGs were extracted at 24, and 30- hours post-dose.					

5.2 EVALUATION OF THE APPLICANT'S CLINICAL QT ANALYSIS PLAN

1. Analysis plan	
1.1 Study Objectives Related to QT	
<i>Reviewer's comment: QTc assessment based on study MEDI-MM36-302 and an integrated nonclinical risk assessment.</i>	
1.2 Data Pooling	
Data pooling?	No
Did Applicant propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A
1.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF
<i>Reviewer's comments: No HR effect was observed in the QTc sub-study.</i>	
1.4 Assay Sensitivity	
Assay sensitivity methods proposed by Applicant	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☒ Other ☐ Not applicable (objective is large mean effects)
<i>Reviewer's comments: QTc assessment is conducted in patient population as supratherapeutic exposure cannot be achieved through topical administration to healthy subjects with intact skin.</i>	
1.5 By-Time Analysis	
1.5.1 Investigational Drug	
Primary analysis	Yes
Did the Applicant use IUT or descriptive statistics?	Both

For IUT: Does the Applicant use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	MMRM
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	Yes
The ΔQTcF and its 90% confidence interval between difamilast and baseline at each time point were estimated using an analysis of covariance (ANCOVA) model with repeated measures for ΔQTcF as the dependent variable, and baseline QTcF, period, timepoint, as fixed effects, and subject by period as random effects. Reviewer's comments: <i>This model seems acceptable. However, the model doesn't describe how to incorporate repeated measures, and it seems that the SAS code was not included. Thus, we used the default model with one treatment and conducted our independent analysis.</i>	
1.5.2 Positive Control	
Primary analysis	No
Did the Applicant adjust for multiplicity?	N/A
1.6 Exposure-Response Analysis	
1.6.1 Investigational Drug	
Primary analysis	No
What is the dependent variable in the Applicant's model?	Single delta
White paper model?	No
Which concentration covariate(s) are included in the model?	Multiple - Univariate
Which methods did the Applicant use for predicting the QT effect?	☐ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
Reviewer's comments: <i>The Applicant's model included time as categorical covariate. This is a deviation from the white paper which does not recommend time covariate for studies without placebo control.</i> <i>The Applicant developed separate C-QTc model for difamilast and its three metabolites (MAP-15484, MAP-15497, and MAP-15485). All the models were non-linear. Difamilast model was quadratic while cubic models were developed for the metabolites. The</i>	

developed models are not physiologic and deviates from the White paper model. As drugs are expected to directly interact with hERG channels, linear C-QTc relationship is expected.

1.6.2 Positive Control			
Primary analysis		No	
Same model as investigational drug		N/A	
1.7 Categorical Analysis			
QTcF / Δ QTcF?	Yes	QRS?	Yes
PR?	Yes	HR?	Yes

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/

ELIFORD N KITABI
07/21/2025 01:53:04 PM

WEI LIU
07/21/2025 01:56:35 PM

YU-TING WENG
07/22/2025 08:12:35 AM

MICHAEL Y LI
07/22/2025 08:28:30 AM

DONGLIN GUO
07/22/2025 08:29:34 AM

LARS JOHANNESSEN
07/22/2025 08:30:37 AM

CHRISTINE E GARNETT
07/22/2025 08:32:01 AM