CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219474Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA 219474 Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	219474
Priority or Standard	Standard
Submit Date(s)	February 13, 2025
Received Date(s)	February 13, 2025
PDUFA Goal Date	February 13, 2026
Division/Office	Division of Dermatology and Dentistry/ Office of Inflammation and Immunology (DDD/OII)
Review Completion Date	February 10, 2026
Established/Proper Name	difamilast ointment
(Proposed) Trade Name	ADQUEY (difamilast) ointment, 1%
Pharmacologic Class	Phosphodiesterase 4 inhibitor
Code name	OPA-15406 and OPC-271
Applicant	Acrotech Biopharma Inc
Dosage form	Ointment
Applicant proposed Dosing Regimen	twice daily to affected areas
Applicant Proposed Indication(s)/Population(s)	for the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	24079001 | Atopic dermatitis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the topical treatment of adults and pediatric patients 2 years of age and older with mild to moderate atopic dermatitis
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	24079001 | Atopic dermatitis (disorder)
Recommended Dosing Regimen	Apply twice daily to affected areas

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Reviewers of Multi-Disciplinary Review and Evaluation

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

Additional Reviewers of Application

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
DMPP	Helen Young, Barbara Fuller
ADL	Matthew White

Abbreviations: DEPI, Division of Epidemiology; DIIP, Division of Inflammation and Immune Pharmacology; DMEPA, Division of Medication Error Prevention and Analysis; DPM, Division of Pharmacometrics; DPT-II, Division of Pharmacology Toxicology for Immunology & Inflammation; DRISK, Division of Risk Management; OCP, Office of Clinical Pharmacology; OII, Office of Immunology & Inflammation; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; OTS, Office of Translational Science

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmaceutical Quality Team Lead	Baoqing Ma, PhD	OPQ/OPQAII	Section: 4.2	**Select one:** ___X Authored ___ Approved
	Signature:			
Nonclinical Reviewer	Renqin Duan, Ph.D.	OII/DPT-II	Sections: 5, 17.3	**Select one:** ___X Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Jianyong Wang, M.D., Ph.D.	OII/DPT-II	Sections: 5, 17.3	**Select one:** ___ Authored __X_ Approved
	Signature:			
Clinical Pharmacology Reviewer	James Mease, Pharm.D.	OTS/OCP/DIIP	Sections: 6, 17.4	**Select one:** _x_ Authored ___ Approved
	Signature:			
PBPK Reviewer	Ying-Hong Wang, Ph.D.	OTS/OCP/DPM	Sections: 17.4.3	**Select one:** __ Authored _x_ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Chinmay Shukla, M.S., Ph.D.	OTS/OCP/DIIP	Sections: 6, 17.4	**Select one:** ___ Authored _x_ Approved
	Signature:			
PBPK Team Leader	Yuching Yang, Ph.D.	OTS/OCP/DPM	Sections: 17.4.3	**Select one:** __ Authored _x_ Approved
Clinical Pharmacology Supervisor	Jianmeng Chen, M.D., Ph.D.	OTC/OCP/DIIP	Section: 6, 17.4	**Select one:** ___ Authored _x_ Approved
	Signature:			
Clinical Reviewer	K. Dev Verma, MD	OII/DDD	Sections: 1, 2, 3, 4, 7, 8.2, 8.4, 9, 10, 12, 17.1, 17.2	**Select one:** _X__ Authored ___ Approved
	Signature:			
Deputy Division Director	Carmen Booker, Ph.D.	OII/DPT-II	Sections: 5, 17.3	**Select one:** ___ Authored _x_ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Melinda McCord, MD	OII/DDD	Sections: 1, 2, 3, 4, 7, 8.2, 8.4, 9, 10, 12, 17.1, 17.2	**Select one:** ___ Authored _X__ Approved
	Signature:			
Cross-Disciplinary Team Leader	Melinda McCord, MD	OII/DDD	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature:			
Associate Director for Therapeutic Review (Clinical)	Gordana Diglisic, MD	OII/DDD	Sections: All	**Select one:** ___ Authored __X_ Approved
	Signature:			
Statistical Reviewer	Matthew Guerra, Ph.D.	OTS/OB/DBIII	Sections: 8.1, 8.2, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature:			
Statistical Team Leader	Matthew Guerra, Ph.D.	OTS/OB/DBIII	Sections: 8.1, 8.2, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature:			
Office Director	Nikolay Nikolov, M.D.	OND/OII	Sections: All	**Select one:** _14_ Authored _ X _ Approved
	Signature:			

Glossary

AD	atopic dermatitis
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BLQ	below the limit of quantitation
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COA	Clinical Outcome Assessment
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
CYP	cytochrome P450
DDI	drug-drug interaction
EASI	Eczema Area and Severity Index
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
FAS	full analysis set
FDA	Food and Drug Administration
hERG	human Ether-à-go-go Related Gene
HLM	human liver microsomes
IC_{50}	half-maximal inhibitor concentration
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IGA-AD	Investigator’s Global Assessment for Atopic Dermatitis
IL	interleukin
IND	Investigational New Drug
IRT	Interdisciplinary Review Team
IRT-CS	Interdisciplinary Review Team for Cardiac Safety Studies
LLOQ	lower limit of quantitation
MAD	multiple ascending dose

MDD	maximum daily dose
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
MIP	macrophage inflammatory protein
MRHD	maximum recommended human dose
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NCA	noncompartmental analysis
NDA	new drug application
NME	new molecular entity
NOAEL	no-observed-adverse-effect level
NRI	non-responder imputation
OCP	Office of Clinical Pharmacology
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
PBPK	physiologically based pharmacokinetic
PDE-4	phosphodiesterase Type 4
PHQ	Patient Health Questionnaire
PIF	photo irritation factor
PK	pharmacokinetic(s)
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
QT-IRT	QT-Interdisciplinary Review Team
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	System Organ Class
TCS	topical corticosteroids
TDI	time-dependent inhibition
TEAE	treatment-emergent adverse event
TQT	thorough QT/QTc

1 Executive Summary

1.1.Product Introduction

The Applicant, Acrotech Biopharma Inc., submitted a New Drug Application (NDA 219474) for Difamilast Ointment, 1% for the proposed indication of the "topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older." The Applicant developed the product under the 505(b)(1) regulatory pathway.

Difamilast is an inhibitor of phosphodiesterase type 4 (PDE-4). Difamilast's inhibition of PDE-4 (a major cyclic adenosine monophosphate (cAMP)-metabolizing enzyme) activity leads to accumulation of intracellular cyclic AMP and decreased productions of various cytokines and chemokines. However, the specific mechanism(s) by which difamilast exerts its therapeutic action is not well defined.

The proposed dose and dosing regimen is to "Apply a thin layer of TRADENAME twice daily to affected areas and rub in completely."

The Agency concluded that the proposed proprietary name, ADQUEY, was acceptable from both a promotional and safety perspective under NDA 219474 (Proprietary Name Review by Mishale Mistry, PharmD, PMPH Division of Medication Error Prevention and Analysis [DMEPA] dated April 28, 2025).

1.2.Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled phase 3 trials (271-102-00007 and 271-102-00008) that evaluated difamilast ointment, 1%, applied twice daily (BID) versus vehicle in subjects with mild to moderate atopic dermatitis (AD). Efficacy was evaluated using the Investigator's Global Assessment (IGA) scale, which assessed overall AD severity on a 5-point scale ranging from 0 (clear) to 4 (severe/very severe). Difamilast ointment, 1%, was superior to vehicle ($p<0.001$) in both trials for the primary endpoint of IGA success at Week 4, defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

In Trial 271-102-00007 (subjects ≥15 years), difamilast ointment, 1%, achieved IGA success in 70/182 (38.5%) subjects compared to 23/182 (12.6%) receiving vehicle, representing a 25.9% absolute treatment difference (95% CI: [17.5%, 34.4%]; $p<0.001$). In Trial 271-102-00008 (pediatric subjects 2-14 years), 40/85 (47.1%) subjects achieved IGA success versus 15/83 (18.1%) receiving vehicle, with a 28.7% absolute difference (95% CI: [15.0%, 42.5%]; $p<0.001$).

The efficacy of difamilast ointment, 1%, was additionally supported by consistent dose-response relationships observed across three phase 2 trials (271-12-205, 271-15-001, and 271-102-00002), where the difamilast ointment, 1%, group had higher response rates than the 0.3% group, and both active treatment groups had higher response rates than vehicle. In the multinational phase 2 trial (271-12-205), which enrolled subjects from the United States (US),

Australia, and Poland, IGA success was achieved in 9/43 (20.9%) subjects receiving difamilast 1% versus 1/37 (2.7%) receiving vehicle (difference 18.2%, 95% CI: [5.0%, 31.5%]; p=0.017).

Therefore, the review team concluded that the Applicant has provided substantial evidence of effectiveness to support the indication for the topical treatment of mild to moderate atopic dermatitis in adults and pediatric patients 2 years of age and older.

The team notes that a US phase 3 trial MEDI-MM36-301 (−301) was terminated early for business reasons by the Applicant after enrolling 153 of 336 planned subjects and showed no treatment effect difference between difamilast ointment, 1% and vehicle (11.7% versus 11.9%, p=0.702). However, the early termination limits meaningful interpretation of efficacy results from this trial and does not preclude a demonstration of substantial evidence of effectiveness.

1.3.Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Difamilast ointment, 1%, represents a new molecular entity, topical phosphodiesterase Type 4 (PDE-4) inhibitor for the treatment of mild to moderate atopic dermatitis in adults and pediatric patients 2 years of age and older. The benefit-risk assessment is based on data from multiple phase 2 and phase 3 controlled trials, long-term safety trials, and comprehensive nonclinical evaluations that collectively support a favorable benefit-risk profile for the proposed indication.

Benefit

Substantial evidence of effectiveness has been demonstrated through two pivotal Japanese phase 3 trials that showed statistically significant and clinically meaningful improvements in atopic dermatitis severity. In Trial 271-102-00007 (subjects ≥15 years), difamilast ointment, 1%, achieved Investigator's Global Assessment (IGA) success in 70/182 (38.5%) subjects compared to 23/182 (12.6%) receiving vehicle, representing a 25.9% absolute treatment difference (95% CI: [17.5%, 34.4%], p<0.001). Similarly, in Trial 271-102-00008 (pediatric subjects 2-14 years), 40/85 (47.1%) subjects achieved IGA success versus 15/83 (18.1%) receiving vehicle, with a 28.7% absolute difference (95% CI: [15.0%, 42.5%], p<0.001). The efficacy findings are supported by consistent dose-response relationships observed across all phase 2 trials, where the difamilast ointment, 1%, group had higher response rates than the 0.3% group, and both active treatment groups had higher response rates than vehicle.

Additional supportive evidence comes from three phase 2 trials, including multinational cohorts, with IGA success rates consistently favoring difamilast 1% over vehicle, though with smaller treatment effect magnitudes than observed in the pivotal phase 3 trials. The multinational phase 2 trial (271-12-205), which enrolled subjects from Australia, Poland, and the US, showed IGA success rates of 9/43 (20.9%) for difamilast 1% versus 1/37 (2.7%) for vehicle, representing an 18.2% treatment difference (95% CI: [5.0%, 31.5%], p=0.017), which was notably smaller than the 25.9% and 28.7% differences observed in the Japanese phase 3 trials. A terminated US phase 3 trial MEDI-MM36-301 showed no treatment effect difference between difamilast 1% and vehicle (11.7% versus 11.9%, p=0.702), though the early termination of this trial for “business reasons” limits meaningful interpretation of the efficacy results in the US population and does not preclude a demonstration of substantial evidence of effectiveness.

Safety Profile

The safety evaluation included data from 429 subjects receiving difamilast 1% in vehicle-controlled trials and 857 subjects in long-term uncontrolled trials, providing adequate exposure data to characterize the safety profile. In the vehicle-controlled trials, difamilast 1%

demonstrated an acceptable safety profile across all age groups with no clinically significant safety signals identified. No treatment-emergent adverse events (TEAEs) occurred with an incidence rate difference of ≥1% between the difamilast group and vehicle group. The most frequently reported TEAEs were nasopharyngitis (4.9% versus 4.6%) and viral infections (2.8% versus 2.6%), both occurring at similar rates between treatment groups.

Serious adverse events (SAEs) were infrequent and unrelated to treatment. No serious TEAEs occurred in the pivotal trials pool, and only one serious TEAE (thyroid cancer) occurred in the broader vehicle-controlled trials pool. Long-term safety data from 857 subjects with mean treatment duration of 225.5 days showed an exposure-adjusted SAE incidence rate of 1.93 per 100 person-years.

Local Tolerability

Local tolerability represents the most clinically relevant safety consideration. In vehicle-controlled trials, difamilast showed similar or improved local tolerability compared to vehicle, with lower rates of moderate to severe burning symptoms at Week 4 (4.3% vs. 10.2%). Local tolerability symptoms (burning, stinging, and itching) and application site reactions (erythema, papulation/vesiculation, and edema) when present were predominantly mild in severity across age groups, with improvement observed over time. However, local reactions led to trial discontinuation in 1/386 (0.26%) subjects in vehicle-controlled trials and 13/857 (1.52%) subjects in long-term trials. The most common reactions leading to discontinuation were application site pain, application site pruritus, and contact dermatitis. Contact dermatitis cases appeared to be primarily irritant rather than allergic hypersensitivity based on limited patch testing data.

Absence of Systemic PDE-4 Inhibitor Class Effects

Treatment with difamilast ointment, 1% was not associated with weight loss observed with systemic PDE-4 inhibitors. Pediatric growth analysis using z-score methodology showed age-appropriate weight gain comparable to CDC standards, with no overall clinical signal for drug-related weight loss.

Similarly, treatment with difamilast ointment, 1% was not associated with suicidal ideation and behavior, depression or other psychiatric disorders observed with systemic PDE-4 inhibitors.

Population Applicability and Generalizability

Although the majority of subjects in the safety database were from Japan, the epidemiological characteristics of atopic dermatitis are comparable between Japan and the US, with prevalences of approximately 10% in both populations and similar distributions of severity. Given the uninformative clinical efficacy data from the early terminated US phase 3 trial MEDI-MM36-301, to further inform the relevance of the data

derived from the phase 3 studies in Japan to the US population, the review team considered the efficacy and safety information from the multinational phase 2 trial (271-12-205), which enrolled an US representative population. While the overall treatment effect was smaller in that trial, the data were supportive of a treatment effect of difamilast ointment in the adult US population. The totality of safety data from controlled and long-term trials demonstrates a consistent safety profile for difamilast across Japanese and US populations, with no population-specific safety signals identified. Based on this information, the team concluded that the data from the phase 3 Japanese trials is relevant and may be extrapolated to the US population, provided that the efficacy information from phase 2 trial (271-12-205) is described in product labeling, to better inform prescribers of the treatment effect that may be expected in the US population.

Risk Management Strategy

The identified risks are appropriately managed through routine pharmacovigilance and product labeling. Local tolerability reactions will be addressed through appropriate labeling in section 6 (Adverse Reactions) and patient counseling regarding potential application site reactions. No additional risk evaluation and mitigation strategies are warranted given the favorable safety profile and topical route of administration with minimal systemic exposure.

Postmarketing Requirement

A postmarketing requirement will specify that the Applicant conduct an adequate and well-controlled trial in subjects ages 3 months to <2 years with mild-to-moderate atopic dermatitis . In view of the absence of data in the US population from this age group, the Applicant will be required to conduct the trial in the US. This trial will evaluate the pharmacokinetics (PK) of difamilast under maximal use conditions in a sub-set of subjects with disease at the upper range of severity, with Final Protocol Submission by 6/2026, Study Completion by 1/2029, and Final Report Submission by 6/2029.

Overall Benefit-Risk Conclusion

The benefit-risk profile of difamilast ointment, 1%, is favorable for the proposed indication. The demonstrated substantial evidence of effectiveness, combined with an acceptable safety profile characterized primarily by manageable local tolerability reactions and absence of concerning systemic effects, supports approval for the topical treatment of mild to moderate atopic dermatitis in adults and pediatric patients 2 years of age and older. The availability of an additional safe and effective therapeutic option addresses an unmet medical need in a patient population where treatment may be complicated by inadequate response, loss of response, and adverse reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Atopic dermatitis (AD) is a chronic, relapsing, inflammatory cutaneous disorder which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. It is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy) (Eichenfield et al. 2014b) . • Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. For most patients, the disease resolves by adulthood. However, for 10 to 30% of individuals, AD persists into the adult years, and, for a smaller proportion of subjects, the disease initially presents in adulthood. The prevalence of AD in adults in the US has been reported to be 3% (Silverberg and Hanifin 2013) but may be as high as 7.3% (Chiesa Fuxench et al. 2019). Comorbidities may include asthma, allergic rhino-conjunctivitis, and food allergies. • Comorbidities may include asthma, allergic rhino-conjunctivitis, and food allergies.	Although AD is not a life-threatening condition, it can be serious. AD may profoundly impact the quality of life of the patient and family members. Pruritus is a hallmark of the condition and is responsible for much of the disease burden for patients and their families (Weston and Howe 2020). The intense pruritus may disrupt sleep, resulting in chronic fatigue. The dysfunctional skin barrier, further compromised by scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. The disease may also impact mood and affected individuals may experience depression and feelings of social isolation (Drucker et al. 2017).
Current Treatment Options	• For mild to moderate AD, available FDA-approved topical treatments include topical corticosteroids, crisaborole ointment and roflumilast cream, 0.15%. Second-line treatments include pimecrolimus cream and ruxolitinib cream.	There are several FDA-approved products with an acceptable benefit-risk profile for topical treatment of mild-to-moderate AD. Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Chronic use of topical corticosteroids are associated with multiple potential adverse effects; and the use of pimecrolimus cream and ruxolitinib cream for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		mild-to-moderate AD is reserved for patients with refractory disease. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.
Benefit	Substantial evidence of effectiveness was demonstrated through two pivotal Japanese phase 3 trials. Trial 271-102-00007 (subjects ≥15 years) showed difamilast ointment, 1%, achieved IGA success in 70/182 (38.5%) subjects compared to 23/182 (12.6%) receiving vehicle, with difference from vehicle (95% CI) of 25.9 (17.5, 34.4) and p-value<0.001. Trial 271-102-00008 (pediatric subjects 2-14 years) showed 40/85 (47.1%) subjects achieving IGA success versus 15/83 (18.1%) receiving vehicle, with difference from vehicle (95% CI) of 28.7 (15.0, 42.5) and p-value<0.001. Consistent dose-response was observed across all phase 2 trials where difamilast ointment, 1%, group had higher response rates than 0.3% group, and both active treatment groups had higher response rates than vehicle. Supportive phase 2 evidence from multinational trial 271-12-205 (US, Australia, Poland) showed IGA success of 9/43 (20.9%) for difamilast 1% versus 1/37 (2.7%) for vehicle (difference 18.2%, 95% CI: 5.0-31.5%, p=0.017), though with smaller treatment effect than phase 3 trials. The primary uncertainty stems from the terminated US phase 3 trial MEDI-MM36-301 which was terminated early for "business reasons" after enrolling 153 of 336 planned subjects, showing no treatment effect (11.7% versus	The pivotal Japanese phase 3 trials provide substantial evidence of effectiveness with statistically significant and clinically meaningful treatment effects (25.9% and 28.7% absolute differences from vehicle). Consistency of efficacy findings across multiple phase 2 and phase 3 trials, clear dose-response relationships, and established PDE-4 inhibitor mechanism support therapeutic benefit. The review team concludes that demographics of the study population are sufficiently representative of the target population in the US. While terminated US phase 3 trial creates uncertainty regarding direct US population data, totality of evidence from well-designed, adequately powered vehicle-controlled trials demonstrates substantial evidence of effectiveness for the proposed indication in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	11.9%, p=0.702). Applicant declined to provide an efficacy analysis of terminated US trial data. The efficacy results from the trials conducted in Japan are generalizable to the US population because the prevalence (~10%) and epidemiological characteristics of AD are comparable between the two populations, and the distribution of AD severities are similar despite some differences in clinical presentation and genetic variability.	adults and pediatric patients 2 years of age and older with mild to moderate atopic dermatitis.
Risk and Risk Management	**Overall Safety Profile:** In the vehicle-controlled trials pool (271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301), difamilast ointment, 1% demonstrated an acceptable safety profile across all age groups with no clinically significant safety signals identified. Among 386 subjects receiving difamilast ointment, 1% compared to 348 subjects receiving vehicle, no treatment-emergent adverse events (TEAEs) occurred with an incidence rate difference of ≥1% between the difamilast group and vehicle group. The most frequently reported TEAEs in the difamilast ointment, 1% group compared with the vehicle group were nasopharyngitis (4.9% versus 4.6%) and viral infections (2.8% versus 2.6%). Both TEAEs occurred at similar rates in each treatment group. **Serious Adverse Events:** Serious adverse events (SAEs) were infrequent in the development program, and most were not related to treatment with difamilast ointment, 1%. No serious TEAEs occurred in the pivotal trials pool (271-102-00007 and 271-102-00008). In the vehicle-controlled trials pool, one SAE of thyroid cancer occurred in a subject who received Difamilast ointment, 1%. Neither the	The overall safety profile of difamilast ointment, 1%, supports approval for the proposed indication. The most clinically significant safety considerations relate to local tolerability reactions, which are manageable through appropriate patient counseling and labeling. The absence of systemic safety signals characteristic of oral PDE-4 inhibitors (e.g., weight loss, psychiatric effects) supports the favorable benefit-risk profile for topical administration. Based on the comprehensive safety evaluation across controlled and long-term studies, no population-specific safety signals were identified, and the safety profile was generally consistent across all demographic subgroups evaluated. The review team concludes that routine pharmacovigilance and proposed labeling are adequate to manage the identified risks, with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	investigator nor this reviewer assessed the SAE of thyroid cancer as related to treatment. **Local Tolerability:** Active assessments of local tolerability (burning, stinging, and itching) and application site reactions (erythema, papulation/ vesiculation, and edema) were conducted only in US Trials MEDI-MM36-301 and MEDI-MM36-302. Local tolerability symptoms of burning, stinging, and itching when present were predominantly mild in severity across age groups, with both pediatric and adult subjects showing decreasing symptom severity from baseline values. Application site reactions of erythema, papulation/vesiculation, and edema when present were also predominantly mild in severity, with most subjects experiencing no application site reactions or improvement in these parameters over the treatment period. However, several subjects experienced clinically significant local reactions that led to trial discontinuation. In the vehicle-controlled trials, 1/386 (0.26%) subjects receiving difamilast 1% discontinued due to local reactions (contact dermatitis). In the long-term trials, 13/857 (1.52%) subjects discontinued due to local reactions, including application site pain (5 subjects), application site pruritus (4 subjects), contact dermatitis (4 subjects), with additional cases of application site erythema, application site vesicles, blistering, and burning. **Weight and Growth Effects:** The weight monitoring data suggest that the use of difamilast ointment, 1% does not result in the weight loss observed with systemic PDE-4 inhibitors. No subjects experienced severe weight loss (≥10% from baseline) during the 4-week controlled trials. Analysis of pediatric growth using weight z-score	no additional risk evaluation and mitigation strategies warranted at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	changes (equal numbers of subjects had weight loss and weight gain) support the conclusion that there was no safety signal for weight loss. **Psychiatric Safety:** The clinical trial data are insufficient to support a causal link between the use of difamilast ointment, 1% and adverse events of suicidal ideation and behavior (SI/B), depression or other psychiatric disorders. In the vehicle-controlled trials, only one psychiatric AE (depression) occurred in a subject who received difamilast ointment, and none in subjects who received vehicle. There were no events of SI/B. However, the only trial that included systematic psychiatric assessments using validated instruments was Trial MEDI-MM36-301, that was terminated early for business reasons by the Applicant. **Population Safety Differences:** The totality of safety data from controlled and long-term trials demonstrates a consistent safety profile for difamilast across Japanese and US populations. The absence of population-specific safety signals, combined with comparable adverse event rates and types between populations, supports the applicability of Japanese safety data to the US population to support approval. **Laboratory and Vital Signs:** There were no clinically meaningful changes or trends in laboratory parameters or vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) for subjects treated with Difamilast ointment, 1%, compared to vehicle in any of the clinical trials.	

1.4.Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		☐	Patient-reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

Patient Focused Drug Development Meeting that occurred on September 23, 2019, included U.S Food and Drug Administration (FDA) participants. A key message from patients was that additional safe and effective therapies for children and adults with AD continues to be an important goal.

2 Therapeutic Context

2.1.Analysis of Condition

Atopic dermatitis is a chronic, relapsing, inflammatory cutaneous disorder which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals (Weston and Howe 2020). Shaw et al. reported the prevalence of AD in the US in individuals 4-8 years of age to be 10.63% and in those 9-12 years of age to be 9.96% (Shaw et al. 2011). For 10-30% of individuals, AD persists into the adult years (Eichenfield et al. 2014b).

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is similar to that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the Wrists (Weston and Howe 2020). AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction (Eichenfield et al. 2014b). Irregularities in the terminal differentiation of the epidermal epithelium led to a faulty stratum corneum which permits the penetration of environmental allergens (Leung and Guttman-Yassky 2014). The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies (Leung and Guttman-Yassky 2014).

Acute AD is associated with cytokines produced by T helper type 2 (Th2) cells (as well as other [T-cell subsets and immune elements) (Leung and Guttman-Yassky 2014). These cytokines are thought to play an important role in the inflammatory response of the skin, and interleukin (IL)-4 and IL-13 may have distinct functional roles in Th2 inflammation (Bao and Reinhardt 2015). IL-4 has been shown to stimulate immunoglobulin E (IgE) production from B cells (May and Fung 2015). IL-13 expression correlates with disease severity and flares (Leung and Guttman-Yassky 2014). IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL- 13Rα1 and subsequent recruitment of IL-4Rα, forming a signaling complex (May and Fung 2015). IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases6. Dupilumab inhibits IL-4 and IL-13 by blocking the shared IL- 4Rα subunit (Regeneron Pharmaceuticals 2022). Tralokinumab binds to human IL- 13 and inhibits its interaction with the IL-13Rα1, IL-13Rα2, and IL-13Rα1/IL-4Rα receptor complex (LEO Pharma 2024).

Common comorbidities include asthma, allergic rhinitis/rhino-conjunctivitis, and food allergies (Eichenfield et al. 2014b; Bao and Reinhardt 2015). Comorbidities involving the eyes include atopic keratoconjunctivitis, a chronic, intensely pruritic, allergic disease that is most often seen in adults with AD (Hamrah and Dana 2026). Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning (Camfferman et al. 2010). Sleep disturbance in the affected individual may also disrupt the sleep of family members, impacting the quality of life for all (Camfferman et al. 2010). Affected children may experience depression and anxiety (Yaghmaie et al. 2013), social isolation, and impaired psychosocial functioning (Drucker et al. 2017).

Patients with AD are predisposed to colonization or infection by microbes, particularly Staphylococcus aureus and herpes simplex virus. The susceptibility to S. aureus is related to multiple factors, including the abnormal skin barrier function and the production of serine proteases that degrade the skin barrier (Leung and Guttman-Yassky 2014).

The most common laboratory finding is an elevated IgE (Shaw et al. 2011). Up to 80% of the AD population has elevated IgE, often with accompanying eosinophilia1. IgE levels may fluctuate with disease severity; however, some patients with severe AD present with normal IgE levels (Weston and Howe 2020).

2.2.Analysis of Current Treatment Options

The management of atopic dermatitis involves both pharmacologic and non-pharmacologic interventions. Nonpharmacologic care is critical to management of atopic dermatitis and includes attention to bathing practices and the regular use of moisturizers, which are available in several dosage forms, such as creams, ointments, oils, lotions. Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease. They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification. Moisturizers themselves may be the principal treatment for mild disease. The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control the disease (Eichenfield et al. 2014a).[1]

The FDA-approved or FDA-licensed treatments for AD (of any severity) fall in the categories of corticosteroids (topical and systemic), topical calcineurin inhibitors (pimecrolimus and tacrolimus), topical PDE-4 inhibitors (crisaborole and roflumilast), IL-4 receptor antagonist (dupilumab), IL-13 antagonist (tralokinumab), and Janus Kinase Inhibitors (topical ruxolitinib and oral abrocitinib, upadacitinib). In addition, phototherapy (ultraviolet A and ultraviolet B) is considered a safe and effective treatment for patients with AD who are candidates for systemic therapy. Systemic immunomodulating agents (e.g., cyclosporine, azathioprine, methotrexate,

[1] Sections 2.1 and 2.2 of this review were adapted from the review of sNDA 761055/S-020 (Dupilumab) on May 22, 2020, by Brenda Carr, MD with updates.

and mycophenolate mofetil) are also used off-label to treat (moderate to severe) AD, including in pediatric patients, with variable effectiveness and safety profiles (Sidbury et al. 2014).

The standard approach to the initial treatment of mild to moderate atopic dermatitis is intermittent topical corticosteroid therapy with consistent use of emollients. Other topical agents may be included in a treatment regimen to minimize adverse events (AEs) from chronic use of topical corticosteroids. Systemic therapies may be used as the initial treatment option in patients with moderate to severe disease or those insufficiently responsive to topical therapies or for whom topical therapies are contraindicated.

Topical corticosteroids (TCS) are the first-line pharmacologic treatment for AD and represent the cornerstone of anti-inflammatory treatment of AD in all age groups (Eichenfield et al. 2014a). Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits (Sidbury et al. 2014). Potential adverse effects of corticosteroids administered by any route include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment. Labeling for systemic corticosteroids do not specify any limitations on the age of indication.

There are two topical PDE-4 inhibitors that are FDA approved for the treatment of mild to moderate AD. EUCRISA (crisaborole ointment), 2%, is approved for the topical treatment of mild to moderate AD in adult and pediatric patients 3 months of age and older. (Approved January 30, 2017). Warnings and Precautions section 5.1 of labeling includes hypersensitivity reactions and Adverse Reactions section 6.1 of labeling includes application site pain. In addition, ZORYVE (roflumilast) cream, 0.15% topical treatment of mild to moderate AD in adult and pediatric patients 6 years of age and older (Approved July 9, 2024).

Pimecrolimus cream, 1% (topical calcineurin inhibitors) is indicated for the treatment of mild to moderate AD in pediatric patients (2 years and older) as second-line therapy. However, pimecrolimus cream is labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable; and it carries boxed warnings advising that the safety

of its long-term use has not been established. More specifically, the boxed warnings describe rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors; a causal relationship has not been established.

Ruxolitinib cream, 1.5% is a Janus Kinase inhibitor indicated for the topical short-term and noncontinuous chronic treatment of mild to moderate AD in non- immunocompromised adult and pediatric patients (12 years of age and older) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

3 Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

The Applicant, Acrotech Biopharma Inc. (Acrotech), in partnership with Otsuka Pharmaceutical Co. Ltd. (Otsuka), developed Difamilast Ointment, 1%, (also known as OPA-15406, OPC-271, MM36, and its commercial name Moizerto® Ointment) for the treatment of mild to moderate AD in adults and children ≥2 years of age under the 505(b)(1) regulatory pathway. Difamilast Ointment, 1%, was approved in Japan on September 27, 2021, for the treatment of AD and introduced into the Japanese marketplace on June 1, 2022.

3.2.Summary of Presubmission/Submission Regulatory Activity

Otsuka initiated product development in the US with the submission of Investigational New Drug (IND) 112973 on October 25, 2011. The IND and US sponsorship was subsequently transferred to Medimetriks Pharmaceuticals, Inc. on October 11, 2016 (IND SN 0076) and further transferred to Acrotech Biopharma LLC (Acrotech) on December 30, 2021 (IND SN 0127).

The Key interactions with the FDA included:

Early Development Phase (2011-2014)

- **February 6, 2012**: Study May Proceed Letter for IND-opening trial, a phase 1 first-in-human trial (271-11-202 to assess the tolerability, safety, and pharmacokinetics (PK) of difamilast ointment in 32 healthy adult subjects (single and multiple doses applied to a 10-cm² area under occlusion).
- **November 22, 2013**: Type C Meeting (written responses)- FDA provided guidance on pediatric development
- **September 25, 2014:** Teleconference - FDA addressed safety concerns regarding body surface area (BSA) exposure limits. FDA required modification of phase 2 multinational trial 271-12-205 to limit BSA treatment to 40% maximum, with subject discontinuation if BSA exceeded this threshold.

CMC and Nonclinical Development

- **March 23, 2016:** Final CAC Report - Executive Carcinogenicity Assessment Committee provided recommendations for 2-year dermal carcinogenicity studies in both mice and rats, with specific dose recommendations and study conduct requirements.
- **January 3, 2018 and March 16, 2018:** Advice Letters - FDA provided guidance on carcinogenicity study termination criteria and mortality management protocols.

End-of-Phase 2 Meeting and Phase 3 Planning, and Modified Development Program

- **October 31, 2018**: End-of-Phase 2 Meeting - Comprehensive discussion of phase 3 development program.
  - The Sponsor proposed to conduct two adequate and well controlled phase 3 trials. Agreements were reached with regards to the proposed dose (concentration of difamilast Ointment, 1%), the time point for the evaluation of efficacy, the size of the safety database, and study endpoints.
  - **Primary Endpoint**: FDA agreed that *"the proportion of subjects achieving a score of 'clear (0)' or 'almost clear (1)', with at least a 2-grade reduction from baseline at a prespecified timepoint based on an adequate Investigator's Global Assessment scale is acceptable."*
  - **IGA Scale Concerns**: FDA stated preference that *"the category of 'Almost clear' include no induration/papulation"* to maintain distinction from mild category.
  - **Safety Monitoring**: FDA required systematic assessment of depression and suicidal ideation, stating: *"Depression and suicidal ideation or behavior should be assessed in a systematic and prospective manner, with validated instruments such as the Patient Health Questionnaire (PHQ-9) and the C-SSRS, respectively."*
- **Completion of Japanese P3 Trials:** The Applicant completed the Japanese phase 3 trials by **December 2019**. Trial 271-102-00007, which enrolled adults aged 15 to 70 years, was conducted from March 25, 2019 to December 28, 2019. Trial 271-102-00008, which enrolled pediatric subjects aged 2 to 14 years, was conducted from May 7, 2019 to December 13, 2019. Both Japanese phase 3 trials were therefore completed between the EOP2 meeting held on October 31, 2018 and the Type C meeting held on September 11, 2020, when the Sponsor proposed the modified development strategy below.
- **September 11, 2020: Type C Meeting (written responses)** - Discussion of Sponsor's proposed modified development program that included a single phase 3 trial (MEDI-MM36-301) to be conducted in the US (rather than 2 US trials) with supportive data from the completed Japanese phase 3 trials. FDA advised: "*In principle, well-designed and conducted non-IND clinical trials with study design (population and endpoints) and statistical analysis plan that are similar with IND trials can serve as supportive evidence to support the assessment of efficacy and safety in the US population. The extent of support will be a review issue driven by the aforementioned considerations*." FDA also expressed concerns about safety database adequacy, noting: "*The safety data from the completed trials in Japan may not be adequate to characterize the risks of depression/suicidal ideation and other Adverse Events of Special Interest (AESI) from exposure to your drug product*." The Sponsor then submitted Protocol MEDI-MM36-301 with a request for review under Special Protocol Assessment (SPA) (**July 23, 2021 -see below).**

Pediatric Development

- **July 16, 2019: Agreed Initial Pediatric Study Plan (iPSP**) - The agreed iPSP included a waiver of assessments in the pediatric population 0 to 3 months of age and a deferral of assessments in pediatric subjects ≥3 months to <2 years of age with AD.

Cardiac Safety Assessment

- **June 25, 2021 and August 30, 2021**: IRT Advice Letters - FDA agreed that a substudy with comprehensive electrocardiogram (ECG) monitoring could be conducted as part of Trial MEDI-MM36-302 in lieu of a dedicated thorough QT study, with specific recommendations for ECG data collection and analysis.

Special Protocol Assessment Process

- **July 23, 2021:** The Sponsor (Medimetriks Pharmaceuticals) submitted the US Phase 3 protocol MEDI-MM36-301 for Difamilast Ointment, 1% under SPA.
- **September 3, 2021:** SPA No Agreement Letter for US trial MEDI-MM36-301 - Initial SPA submission was not agreed upon. Issues included:
  - Disagreement with the validated Investigator's Global Assessment for Atopic Dermatitis (IGA-AD) scale definition for "almost clear." FDA reiterated position that "the score of 'almost clear' should be characterized only by 'barely perceptible erythema'. The inclusion of induration/papulation and lichenification blurs the distinction between the categories of 'almost clear' and 'mild'
  - Issues with proposed secondary endpoints
  - Concerns about exploratory endpoints for individual AD signs assessment
  - Questions about the CBCL assessment tool for pediatric depression monitoring
  - Problems with the proposed application site assessment scale: For Individual Signs Assessment FDA recommended "that the investigator evaluate the signs of AD (erythema, induration/papulation, exudation, excoriation and lichenification) using separate 4-point scales (0 = none, 1 = mild, 2 = moderate, or 3 = severe)."
  - Assessment of depression in the pediatric population: FDA provided advice on appropriate tools to assess for depression in the pediatric population.
- **October 13, 2021:** Type A Meeting - Discussion of SPA disagreements.
- **May 5, 2022: SPA Agreement Letter** - Final agreement was reached for the US Phase 3 trial protocol after addressing FDA concerns

The development program proceeded with one US Phase 3 trial (MEDI-MM36-301) under SPA agreement. However, the US Phase 3 trial under the SPA was subsequently terminated early by the sponsor for "business reasons" after enrolling approximately half of the planned sample size (153 of 336 planned subjects) between October 26, 2022 and July 19, 2023.

No pre-NDA meeting was held and the Applicant (Acrotech Biopharma LLC) proceeded with NDA submission on **February 13, 2025.** The Applicant declined to provide efficacy analysis of the terminated US trial MEDI-MM36-301 data despite FDA requests, maintaining that

substantial evidence of efficacy had been demonstrated through results of the other completed Japanese phase 3 trials and multinational phase 2 trial.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1.Office of Scientific Investigations

The overall quality of the clinical information contained in this submission was adequate. The Office of Scientific Investigations (OSI) selected sites for inspection by based on number of enrolled subjects, prior inspectional history, site success rate, and filing of financial disclosure. The findings of the clinical inspections (Clinical Inspection Summary by Dr. Stephanie Coquia, dated November 13, 2025) are summarized in Table 1.

Table 1: Clinical Site Inspection Summary

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification
Site # 307 Toyofuku, Kazutomo 3-2-5, Takadanababa Friend-Building F3 SHINJUKU-KU, TOKYO 169-0075 JPN	27110200007	41	NAI
Site # 313 Kume, Akihiro 1-65-2, Otorihigashimachi, Nishi-Ku SAKAI-SHI, OSAKA 593-8324 JPN	27110200007	17	NAI
Tsujino, Yoshiaki 5-9-26, Uozakikitamachi, Higashinada- Ku KOBE-SHI, HYOGO 658-0082 JPN	27110200008	15	NAI

Source: Clinical Inspection Summary by Dr. Stephanie Coquia, dated November 13, 2025
Abbreviations: NAI, No Action Indicated

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

4.2.Product Quality

Acrotech Biopharma Inc. submitted NDA 219474 for ADQUEY® (difamilast) ointment, 1%, for topical use via 505 (b)(1) regulatory pathway for the treatment of mild to moderate AD. The Applicant developed difamilast under IND 112973.

The drug substance, difamilast, is referred to DMF (b) (4). It is a white to off-white crystals or crystalline powder. It exists in two crystal forms (b) (4), in which (b) (4) is the stable form. (b) (4). The drug substance manufacturer, Otsuka, (b) (4), all phase 3 studies and commercial production will use (b) (4) crystals. It has established a (b) (4) months retest date; however, the drug product manufacturer, (b) (4), has an (b) (4) retest interval.

Ointment formulation with 0.1%, 0.3%, 1% and 3% strength has been used in phase 1 clinical trial, 1% strength was evaluated in the clinical phase 3 trial. Difamilast is formulated as a semi-

solid ointment. The difamilast (b) (4) Propylene Carbonate, (b) (4) White petrolatum, Paraffin Wax, Mineral Oil and White Beeswax. The resulting ointment is filled into (b) (4) tubes.

Difamilast Ointment, 1%, is packaged with 3 g, 27 g and 85 g three configurations in (b) (4) aluminum tubes sealed with (b) (4) cap. 3 g fill tube is a physician sample. 19 bulk batches including clinical and registration with each package of at least 3 batches manufactured at (b) (4) have been provided with their Clinical Outcome Assessments (COAs).

The Applicant provided up to 36 months long-term stability data at 25°C/60%RH and 6 months accelerated data at 40°C/75%RH for three primary registration batches for three package configurations. The proposed expiry period for the drug product is 36 months for commercial 27g fill tube and 85g fill tube, and 18 months for 3g fill physician sample tubes when stored at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. (b) (4).

The Applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.

The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.

Overall, this application is approvable from a chemistry, manufacturing, and controls perspective.

4.3.Clinical Microbiology

Not applicable for this NDA.

4.4.Devices and Companion Diagnostic Issues

Not applicable for this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Difamilast is a PDE-4 inhibitor. The applicant submitted an original 505(b)(1) NDA application for Difamilast Ointment, 1%, indicated for the treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older.

The toxicity profile of difamilast has been adequately evaluated in a full battery of safety pharmacology studies, repeat-dose subcutaneous (SC) toxicity studies with treatment durations up to 39 weeks in dogs, dermal toxicity studies with treatment durations up to 26 weeks in rats and 39 weeks in minipigs, a standard battery of genotoxicity tests, two 2-year dermal carcinogenicity studies in rats and mice, a fertility and early embryonic development study in rats, two embryofetal development studies in rats and rabbits, a prenatal and postnatal development study in rats, and two juvenile animal toxicity studies in rats. Toxicity studies with drug product impurities were also provided.

PDE-4 is present in many types of immune cells and specifically degrades intracellular cAMP. Difamilast inhibits the activity of PDE-4 in in vitro studies, e.g., increasing intracellular cAMP levels in inflammatory cells and inhibiting/suppressing the productions of various cytokines and chemokines. Difamilast showed efficacy in a mouse model of chronic contact dermatitis. The mechanism of the anti-inflammatory effects of difamilast involves macrophage inflammatory protein (MIP)-1α and MIP-2 in the mouse dermatitis model.

There were no significant effects on the central nervous system (CNS) in rats at single SC doses up to 200 mg/kg or cardiovascular or respiratory parameters in conscious dogs at single SC doses up to 30 mg/kg. In an in vitro human Ether-à-go-go Related Gene (hERG) assay, the half-maximal inhibitor concentration (IC_{50}) value for the inhibition on hERG K^+ current was 2.54 µM.

In a 39-week SC repeat-dose toxicity study in dogs, there were no test article-related adverse effects. The no-observed-adverse-effect level (NOAEL) was the high dose of 3 mg/kg/day for both males and females (36 times the maximum recommended human dose (MRHD) for males and 23 times the MRHD for females, respectively, based on area under the plasma concentration-time curve [AUC] comparison).

In a 26-week dermal rat toxicity study, a decrease in body weight gain was the only significant systemic toxicity. The NOAEL was the low dose of 0.9 (male) or 1.1 mg/kg/day (female) (0.3% ointment applied to 3% BSA) based on a significant decrease in body weight gain noted at high dose (0.4 times the MRHD for males and 1.1 times the MRHD for females, respectively, based on AUC comparison).

In a 39-week dermal minipig toxicity study, the NOAEL was the maximum feasible dose (MFD), 3% ointment applied to 10% of BSA, for both males (8.1 mg/kg/day) and females (8.3 mg/kg/day) based on no systemic or local toxicity at the MFD (0.38 times the MRHD for males and 0.30 times the MRHD for females, respectively, based on AUC comparison).

Difamilast was negative in a standard battery of genotoxicity tests, including the Ames test, the mouse lymphoma assay, and an in vivo micronucleus study in rats.

In 2-year dermal carcinogenicity studies in rats and mice, no test article-related neoplastic findings were observed in rats or mice that received difamilast at dermal doses up to 3% (3.7 to 10 times the MRHD based on AUC comparison). The results of these two carcinogenicity studies were reviewed by the Executive Carcinogenicity Assessment Committee (ECAC).

In a fertility and early embryonic development rat study, the NOAEL for reproductive function and early embryonic development was the mid dose of 10 mg/kg/day in males and females (19.8 times the MRHD for males and 30.3 times the MRHD for females, respectively, based on AUC comparison), based on irregular estrus cycles, sperm abnormalities, increased preimplantation loss rate, decreased copulation and fertility indexes observed at the high dose of 100 mg/kg/day.

In embryofetal development studies, fewer live fetuses, decreased fetal weight, retarded ossification, and increased membranous ventricular septum defect were noted in rats at the high dose of 100 mg/kg/day. Skeletal variations (increase in supernumerary lumbar vertebra and for full supernumerary rib) were observed in rabbits at the high dose of 3 mg/kg/day. The NOAEL for embryofetal development was the mid doses of 10 mg/kg/day in rats and 1 mg/kg/day in rabbits (30.3 times the MRHD for rats and 3.0 times the MRHD for rabbits, respectively, based on AUC comparison).

In a prenatal and postnatal development study in rats, the NOAEL was the mid dose of 0.3 mg/kg/day for general toxicity in dams and the high dose of 3 mg/kg/day for the reproductive function of dams, prenatal and postnatal development of offspring, and implantation and viability of embryos (12.7 times the MRHD based on AUC comparison).

In an 8-week repeat-dose dermal toxicity study in juvenile rats with starting age of 25 days, suppressed body weight gain and decreased food consumption were observed in females at the high dose of 3% ointment, but there was no toxicity specific to the juvenile animals. The NOAEL was 3% ointment in males (3.1 times the MRHD based on AUC comparison) and 1% ointment in females (equivalent to the MRHD based on AUC comparison).

In a 10-week repeat-dose subcutaneous toxicity study in neonatal rats (focusing on potential central nervous system effects), rats aged 4 days received multiple SC administrations of difamilast at 1, 3, and 10 mg/kg/day. Suppressed body weight gain and decreased brain weight, which is considered likely to be a secondary effect due to neonatal low body weight, were observed in males and females at 10 mg/kg/day. These changes tended to resolve during a 4-week recovery period. There were no effects on central nervous system function, brain morphology or histopathology. The NOAEL for central nervous system effects was 10 mg/kg/day for both males and females (31 times the MRHD for males and 43 times the MRHD for females, respectively, based on AUC comparison).

Difamilast Ointment, 1%, does not contain any novel excipients or excipients of human or animal origin. There are no significant safety issues with impurities, extractables/leachables or major human metabolites.

This NDA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical postmarketing commitment (PMC)/postmarketing requirement (PMR) for this NDA.

5.2.Referenced NDAs, BLAs, DMFs

DMF (b) (4) OPA-15406 drug substance

In nonclinical studies, OPA-15406 and OPC-271 were used as codenames for difamilast.

5.3.Pharmacology

PDE-4 is present in many types of immune cells and specifically degrades intracellular cAMP. Difamilast inhibits the activity of PDE-4 in in vitro studies, e.g., increasing intracellular cAMP levels in inflammatory cells and inhibiting/suppressing the productions of various cytokines and chemokines. Difamilast showed efficacy in a mouse model of chronic contact dermatitis. The mechanism of the anti-inflammatory effects of difamilast involves MIP-1α and MIP-2 in the mouse dermatitis model.

There were no significant effects on CNS in rats at single SC doses up to 200 mg/kg or cardiovascular or respiratory parameters in conscious dogs at single SC doses up to 30 mg/kg. In an in vitro hERG assay, the IC_{50} value for the inhibition on hERG K^+ current was 2.54 μM.

5.4.ADME/PK

Table 2: Summary of PK/TK Data for Difamilast

Type of Study	Major Findings
Absorption	
Plasma concentrations of OPC-271 and its metabolites in male and female rats after single percutaneous, subcutaneous, oral and intravenous administration of OPC-271 (Study# B081070) (only dermal results here)	Rat (single dermal dose) $T_{1/2}$: 0.3 mg/kg (0.1%): 9.8 hr (m) 0.9 mg/kg (0.3%): 9.6 hr (m) 3 mg/kg (1%): 17.1 hr (m), 8.9 hr (f) 9 mg/kg (3%): 11 hr (m) 3 mg/kg (1%, abraded skin): 8.6 hr (m) C_{max} (ng/ml): 0.3 mg/kg (0.1%): 3.0 (m) 0.9 mg/kg (0.3%): 8.2 (m) 3 mg/kg (1%): 17.9 (m), 52.6 (f) 9 mg/kg (3%): 17.6 (m) 3 mg/kg (1%, abraded skin): 35.1 (m) T_{max}: 0.3 mg/kg (0.1%): 8 hr (m) 0.9 mg/kg (0.3%): 16 hr (m) 3 mg/kg (1%): 8 hr (m), 8. hr (f) 9 mg/kg (3%): 28 hr (m) 3 mg/kg (1%, abraded skin): 8 hr (m) $AUC_{0\text{-}inf}$ (ng*hr/ml): 0.3 mg/kg (0.1%): 80.1 (m) 0.9 mg/kg (0.3%): 234.6 (m) 3 mg/kg (1%): 578.5 (m), 1418 (f) 9 mg/kg (3%): 688.1 (m) 3 mg/kg (1%, abraded skin): 926.3 (m) Bioavailability (%): 0.3 mg/kg (0.1%): 29.8 (m) 0.9 mg/kg (0.3%): 29.2 (m) 3 mg/kg (1%): 20.9 (m), 30.3 (f) 9 mg/kg (3%): 8.2(m) 3 mg/kg (1%, abraded skin): 34.7 (m)

Type of Study	Major Findings
Pharmacokinetic study of ^{14}C-OPC-271 in male Beagle dogs–absorption, distribution, metabolism, and excretion after single subcutaneous administration (Study# B080979)	*Dog (single subcutaneous dose)* $T_{1/2}$: 0.1 mg/kg: 18.5 hr (m) 0.3 mg/kg: 195.6 hr (m) 1 mg/kg: 52.5 hr (m) 3 mg/kg: 48.4 hr (m) C_{max} (ng/ml): 0.1 mg/kg: 4.8 (m) 0.3 mg/kg: 10.7 (m) 1 mg/kg: 34 (m) 3 mg/kg: 61.3 (m) T_{max}: 0.1 mg/kg: 9 hr (m) 0.3 mg/kg (0.3%): 9 hr (m) 1 mg/kg: 9.7 hr (m) 3 mg/kg: 19 hr (m) $AUC_{0\text{-}inf}$ (ng*hr/ml): 0.1 mg/kg: 68.8 (m) 0.3 mg/kg: 968.6 (m) 1 mg/kg: 1233 (m) 3 mg/kg: 2971 (m) Bioavailability (%): 0.1 mg/kg: 31 (m) 0.3 mg/kg: 34.3 (m) 1 mg/kg (1%): 29.9 (m) 3 mg/kg (3%): 23.3 (m)

Type of Study	Major Findings
Plasma concentrations of OPC-271 and its metabolites in miniature pigs after single percutaneous and intravenous administration of OPC-271 (Study# 031349)	*Minipig (single dermal dose)* $T_{1/2}$: 0.15 mg/kg (0.3%): 16.7 hr (m) 0.5 mg/kg (1%): 41.2 hr (m) 1.5 mg/kg (3%): 44.7 hr (m) 0.5 mg/kg (1%, abraded skin): 39.8 hr (m) C_{max} (ng/ml): 0.15 mg/kg (0.3%): 0.4 (m) 0.5 mg/kg (1%): 1.2 (m) 1.5 mg/kg (3%): 0.9 (m) 0.5 mg/kg (1%, abraded skin): 1.2 (m) T_{max}: 0.15 mg/kg (0.3%): 12 hr (m) 0.5 mg/kg (1%): 16 hr (m) 1.5 mg/kg (3%): 28 hr (m) 0.5 mg/kg (1%, abraded skin): 16 hr (m) $AUC_{0\text{-}inf}$ (ng*hr/ml): 0.15 mg/kg (0.3%): 9.5 (m) 0.5 mg/kg (1%): 39.1 (m) 1.5 mg/kg (3%): 57.1 (m) 0.5 mg/kg (1%, abraded skin): 45.8 (m) Bioavailability (%): 0.15 mg/kg (0.3%): NC (m) 0.5 mg/kg (1%): 4.7 (m) 1.5 mg/kg (3%): NC (m) 0.5 mg/kg (1%, abraded skin): 5.4 (m)

Type of Study	Major Findings
Distribution	
Summary information	Radioactivity was widely distributed to most tissues after a dermal or subcutaneous dose of 3 mg/kg 14C-OPA-15406 to rats. Distribution of radioactivity was slow, with t_{max} observed in most tissues 8-24 hr after a dermal dose and 4-8 hr after a subcutaneous dose. Radioactivity decreased in tissues over the course of the study, although radioactivity was present in most tissues at 168 hr postdose, suggesting a slow elimination rate. Tissue concentrations of 14C-OPA-15406 radioactivity were highest in the brown and white adipose tissue, liver, kidney, adrenal, skin, stomach, and small intestine, whereas the cerebrum, cerebellum, medulla oblongata, and cerebral spinal fluid had tissue concentrations less than plasma, indicating that 14C-OPA-15406-dependent radioactivity did not readily cross the blood brain barrier. Concentrations of radioactivity were consistently higher in female rats than in male rats. The bone marrow, testis, seminal vesicle, ovary, and uterus had tissue concentrations less than or equivalent to that in plasma. In pregnant rats, distribution of radioactivity was similar to non-pregnant animals, except for the mammary gland, which had tissue concentrations 4.3- to 8.2-fold higher than blood. Tissue concentrations of radioactivity in the fetus and in fetal blood, liver, kidney, and lung were higher than maternal blood, indicating 14C-OPA-15406-dependent radioactivity crosses the placental barrier. However, radioactivity concentrations in fetal brain were lower than maternal blood, indicating 14C-OPA-15406-dependent radioactivity did not readily cross the fetal blood-brain barrier. Distribution of radioactivity to the cellular component of blood was low in rats and dogs (<10% at 1 hr after a SC dose of 3 mg/kg). Serum protein binding was high (>99%) in serum in the tested concentration range of 30-3000 ng/ml, from all tested species, including mouse, rat, rabbit, dog, minipig, and human.

Type of Study	Major Findings
Metabolism	
Summary information	^{14}C-OPA-15406 underwent in vitro biotransformation to 25 metabolites, including three major metabolites MAP-15484, MAP-15485, and MAP-15497, in hepatic S9 fractions from all species. MAP-15485 (O-deethylated metabolite of OPA-15406) was the major metabolite in rat, rabbit, and human hepatic S9 fractions, with maximum abundances of 16.9%, 13.8%, and 15.0% of total sample radioactivity, respectively. In dog S9 fractions, MAP-15497 (ring-hydroxylated metabolite of OPA-15406) was the major metabolite and accounted for 17.5% of sample radioactivity. Based on metabolite profiles, biotransformation of OPA-15406 by human hepatic S9 fractions most closely resembled that from dogs, and no human specific metabolite was observed. In human hepatic S9 fractions and human hepatic microsomes, OPA-15406 was extensively metabolized to MAP-15485 (major) and MAP-15497 (minor) by CYP3A4/5 and CYP1A2, respectively. The metabolite pathways of OPA-15406 in vivo were consistent with the biotransformation in vitro with hepatic S9 fractions. Metabolism of OPA-15406 was extensive in rats, dogs, and rabbits, with different metabolite profiles across species. In rats, OPA-15406 was extensively metabolized to MAP-15485 and subsequent Phase II conjugates of MAP-15485 and was predominantly excreted as metabolites in bile and feces. The second highest exposure was metabolite MAP-15484. Metabolic clearance was the predominant route of elimination of OPA-15406 in rats. The metabolite profile of OPA-15406 in dogs was different from that of rats. OPA-15406 was the major circulating component in dog's plasma and MAP-15497 was the most abundant metabolite followed by MAP-15485 and MAP-15484. Fecal excretion of metabolites was the predominant route of elimination with minimal unchanged parent drug present in excreta. Metabolic clearance also appeared to be the major route of elimination of OPA-15406 in dogs. In rabbits, OPA-15406 was extensively metabolized to MAP-15485 and multiple Phase II conjugates of MAP-15485.

Type of Study	Major Findings
Excretion	
Summary information	In rats, fecal excretion was the major route of elimination of radioactivity after dermal or SC dosing of 14C-OPA-15406, accounting for 16.9% and 25.0% of the administered dose or 62.7% and 72.3% of the absorbed dose in male and female rats, respectively, by 168 hr postdose. Urinary excretion was a minor route of elimination after a dermal dose to intact skin and accounted for 3.6% and 4.9% of the administered dose or 14.0% and 14.1% of the absorbed dose in male and female rats, respectively, by 168 hr postdose. Biliary excretion was demonstrated as the major pathway of elimination in bile duct-cannulated rats and accounted for 71.4% of the administered SC dose, by 72 hr postdose. After intraduodenal administration of bile collected from 14C-OPA-15406 treated rats, biliary excretion of radioactivity was high, indicating enterohepatic recirculation of radioactivity from bile was substantial. In dogs, fecal excretion of radioactivity was also the major route of elimination and cumulatively accounted for 100.81% of the administered dose by 168 hr postdose. Urinary excretion of radioactivity was minor and accounted for 1.47% of the administered dose by 168 hr postdose. When 14C-difamilast was subcutaneously administered to lactating rats at a single dose of 3 mg/kg, the concentration of radioactivity in milk was higher than that in blood (with milk/blood ratios for C_{max} and AUC_{∞} of 13.7 and 5.4, respectively). Thus, it was considered that difamilast and some of its derived compounds were excreted into milk.
TK data from general toxicology studies	Difamilast: D MAP-15484: M1 MAP-15485: M2 MAP-15497: M3
A 6-month dermal toxicity study in rats (Study# P140515)	*Rat (dermal daily dosing for 6 months)* AUC_{24h} (ng*h/mL) at Week 26: Males: 0.3%: 92.8 (D), 37.4 (M1), 99.2 (M2), 0.8 (M3) 1%: 270.8 (D), 160.4 (M1), 436.9 (M2), 3 (M3) 3%: 706.2 (D), 243.5 (M1), 806.3 (M2), 7.3 (M3) Females: 0.3%: 267 (D), 66.9 (M1), 231.6 (M2), 4.3 (M3) 1%: 761.7 (D), 209.5 (M1), 627.2 (M2), 14.1 (M3) 3%: 1627 (D), 486.9 (M1), 1488 (M2), 43.4 (M3)
A 9-month subcutaneous toxicity study in beagle dogs (Study# 037208)	*Dog (subcutaneous daily dosing for 9 months)* AUC_{24h} (ng*h/mL) at Week 39: Males: 0.3 mg/kg/day: 508.2 (D), 36.8 (M1), 104.6 (M2), 139.6 (M3) 1 mg/kg/day: 833.7 (D), 114.1 (M1), 176 (M2), 353 (M3) 3 mg/kg/day: 8444 (D), 404.6 (M1), 929 (M2), 1614 (M3) Females: 0.3 mg/kg/day: 744.5 (D), 54.8 (M1), 98.9 (M2), 166.9 (M3) 1 mg/kg/day: 3215 (D), 315 (M1), 609.3 (M2), 694.5 (M3) 3 mg/kg/day: 5422 (D), 565.3 (M1), 884 (M2), 1229 (M3)

Type of Study	Major Findings
A 9-month dermal toxicity study in minipigs (Study# 675234)	*Minipig (dermal daily dosing for 9 months)* AUC_{24h} (ng*h/mL) on Day 273: Males: 1%: 80.7 (D), 0.08 (M1), 2.6 (M2), NC (M3) 3%: 90.2 (D), 1.3 (M1), 1.6 (M2), NC (M3) Females: 1%: 47.9 (D), NC (M1), 1.8 (M2), NC (M3) 3%: 71.3 (D), 0.6 (M1), 2.4 (M2), NC (M3)
A 4-week subcutaneous toxicity study in rats (Study# B100031) (TK data were used for rat FEED and EFD studies)	*Rat (subcutaneous daily dosing for 4 weeks)* AUC_{24h} (ng*h/mL) at Week 39: Males: 1 mg/kg/day: 572.5 (D), 135.3 (M1), 472.1 (M2), 3.6 (M3) 10 mg/kg/day: 4699 (D), 977.3 (M1), 2748 (M2), 88.3 (M3) 100 mg/kg/day: 27430 (D), 8454 (M1), 12230 (M2), 889.8 (M3) Females: 1 mg/kg/day: 911.2 (D), 115.2 (M1), 550 (M2), 8.8 (M3) 10 mg/kg/day: 7179 (D), 1074 (M1), 4230 (M2), 107.9 (M3) 100 mg/kg/day: 62230 (D), 7438 (M1), 14690 (M2), 960.7 (M3)
A 4-week subcutaneous toxicokinetics study in female rats (Study# 037254) (TK data were used for rat PPND study)	*Rat (subcutaneous daily dosing for 4 weeks)* AUC_{24h} (ng*h/mL) on Day 28: Females: 0.1 mg/kg/day: 111.5 (D), 14.9 (M1), 64.3 (M2), NC (M3) 0.3 mg/kg/day: 320.8 (D), 52.8 (M1), 188.6 (M2), 1.9 (M3) 3 mg/kg/day: 3002 (D), 400.5 (M1), 1771 (M2), 22.6 (M3)
A 13-day subcutaneous toxicokinetics study in female rabbit (Study# 032776) (TK data were used for rabbit EFD study)	*Rabbit (subcutaneous daily dosing for 13 days)* AUC_{24h} (ng*h/mL) on Day 13: Females: 0.1 mg/kg/day: 80.1 (D), NC (M1), 45.2 (M2), NC (M3) 0.3 mg/kg/day: 214.6 (D), 1.5 (M1), 120.4 (M2), NC (M3) 1 mg/kg/day: 700.3 (D), 23.1 (M1), 530.3 (M2), NC (M3 3 mg/kg/day: 3256 (D), 109 (M1), 3138 (M2), NC (M3)
TK data from reproductive toxicology studies	TK analysis was not conducted in reproductive toxicology studies. TK data from repeat-dose toxicity studies were used for reproductive toxicity studies.
An 8-week dermal juvenile toxicity study in rats (Study# GH13265)	*Rat (dermal daily dosing for 8 weeks)* AUC_{24h} (ng*h/mL) at Day 56: Males: 0.3%: 117.9 (D), 34.6 (M1), 89.6 (M2), 1.3 (M3) 1%: 369.8 (D), 108.5 (M1), 276 (M2), 3.3 (M3) 3%: 731.8 (D), 247.6 (M1), 639 (M2), 9.2 (M3) Females: 0.3%: 248.6 (D), 40.4 (M1), 168.3 (M2), 3.2 (M3) 1%: 817.2 (D), 163.2 (M1), 635.5 (M2), 12.8 (M3) 3%: 1440 (D), 410.4 (M1), 1441 (M2), 31.6 (M3)

Type of Study	Major Findings
A 10-week subcutaneous juvenile toxicity study in rats (Study# GH13266)	*Rat (subcutaneous daily dosing for 10 weeks)* AUC_{24h} (ng*h/mL) at Day 70: Males: 1 mg/kg/day: 1231 (D), 323.9 (M1), 619 (M2), 5.8 (M3) 3 mg/kg/day: 2472 (D), 1023 (M1), 1185 (M2), 15.2 (M3) 10 mg/kg/day: 7347 (D), 2592 (M1), 2920 (M2), 92.6 (M3) Females: 1 mg/kg/day: 1458 (D), 275 (M1), 702.9 (M2), 10.1 (M3) 3 mg/kg/day: 3818 (D), 1039 (M1), 1779 (M2), 33.2 (M3) 10 mg/kg/day: 10240 (D), 2178 (M1), 3853 (M2), 139.9 (M3)
TK data from Carcinogenicity studies	
A 2-year dermal carcinogenicity study in rats (Study# B-8051)	*Rat (dermal daily dosing for 2 years)* AUC_{24h} (ng*h/mL) at Week 26: Males: 0.3%: 165.7 (D), 39.4 (M1), 183 (M2), 1.6 (M3) 1%: 386.8 (D), 163.6 (M1), 463 (M2), 4.3 (M3) 3%: 873 (D), 356.5 (M1), 1124 (M2), 12.4 (M3) Females: 0.3%: 324.4 (D), 51.1 (M1), 291 (M2), 4.4 (M3) 1%: 920 (D), 171.5 (M1), 777 (M2), 12.8 (M3) 3%: 2419 (D), 618.4 (M1), 2197 (M2), 65 (M3)
A 2-year dermal carcinogenicity study in mice (Study# B-8052)	*Mouse (dermal daily dosing for 2 years)* AUC_{24h} (ng*h/mL) at Week 26: Males: 0.3%: 136.4 (D), 21 (M1), 7.1 (M2), 4.8 (M3) 1%: 545.7 (D), 84.3 (M1), 28.6 (M2), 30.6 (M3) 3%: 1106 (D), 223.3 (M1), 93 (M2), 110.3 (M3) Females: 0.3%: 132.3 (D), 46.8 (M1), 10.3 (M2), 14.2 (M3) 1%: 322 (D), 124.8 (M1), 23.5 (M2), 33 (M3) 3%: 867.6 (D), 363.2 (M1), 77.3 (M2), 101.5 (M3)

Abbreviations:; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from 0 to infinity; AUC_{24h}, area under the plasma concentration-time curve from 0 to 124 hours; C_{max}, maximum plasma concentration; CYP, cytochrome P450; EFD, embryo-fetal development; FEED, fertility and early embryonic development; PK, pharmacokinetic; PPND, pre- and post-natal development; SC, subcutaneous; $T_{1/2}$, half-life; T_{max}, time of C_{max}; TK, toxicokinetic

5.5.Toxicology

5.5.1. General Toxicology

Pivotal repeat-dose toxicity studies were conducted in rats (dermal), dogs (subcutaneous), and minipigs (dermal). There were no significant systemic or dermal toxicities noted in these studies, except a decrease in body weight gain observed in a 26-week dermal toxicity study in rats.

Study Title/ Number: Twenty-Six-Week Repeated Percutaneous Dose Toxicity Study of OPC-271 Ointments in Rats/ Study Number: P140515

- A decrease in body weight gain was the only significant systemic toxicity.

- The NOAEL for systemic toxicity was the low dose of 0.9/1.1 mg/kg/day for males and females, respectively (0.3% ointment applied once daily at 0.008 ml/cm^2 to 3% BSA).
- The NOAEL for local effects was the high dose of 9.0/11.0 mg/kg/day for males and females, respectively (3% ointment applied once daily at 0.008 ml/cm^2 to 3% BSA).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (white petrolatum), 0 (vehicle), 0.3%, 1% and 3%, equivalent to 0, 0, 0.9/1.1, 3.0/3.7, and 9.0/11.0 mg/kg/day for males and females, respectively, once daily for 26 weeks
Route of administration:	Dermal
Formulation/Vehicle:	Ointment/ (b) (4) % white petrolatum, (b) (4) % paraffin, (b) (4) % mineral oil, (b) (4) % white wax, and (b) (4) % propylene carbonate
Species/Strain:	Rat/ SD
Number/Sex/Group:	15
Age:	6 weeks
Satellite groups/ unique design:	TK groups: 3/sex/group for vehicle control, 6/sex/group for treatment groups
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major Findings**
Mortality	No mortality occurred.
Clinical signs	There were no significant treatment-related findings.
Body weights	Significant decreases in body weight (mid dose: ¯9.4% in males, ¯10.7% in females; high dose: ¯14.3% in males, ¯9.9% in females, when compared to control group) and body weight gains (mid dose: ¯13.1% in males, ¯18.3% in females; high dose: ¯20% in males, ¯19.9% in females, when compared to control group) in both males and females at mid and high doses.
Food consumption	There were no significant treatment-related findings.
Ophthalmoscopy	There were no significant treatment-related findings.
Hematology	There were no significant treatment-related findings.
Clinical chemistry	There were no significant treatment-related findings.
Urinalysis	There were no significant treatment-related findings.
Gross pathology	There were no significant treatment-related findings.
Organ weights	There were no significant treatment-related findings.
Histopathology Adequate battery: Yes (including skin treated sites)	There were no significant treatment-related findings.

Study Title/ Number: Thirty-Nine-Week Repeated Subcutaneous Dose Toxicity Study of OPA-15406 in Beagle Dogs/ Study Number: 037208

- No test article-related adverse effects were noted in this study. The NOAEL was the high dose of 3 mg/kg/day for both males and females.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (corn oil), 0.3, 1 and 3 mg/kg/day, once daily for 39 weeks
Route of administration:	Subcutaneous
Formulation/Vehicle:	Corn oil
Species/Strain:	Dog/ beagle
Number/Sex/Group:	4
Age:	7 months
Satellite groups/ unique design:	N/A
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major Findings**
Mortality	No mortality occurred.
Clinical signs	There were no significant treatment-related findings.
Body weights	There were no significant treatment-related findings.
Food consumption	There were no significant treatment-related findings.
Ophthalmoscopy	There were no significant treatment-related findings.
ECG	There were no significant treatment-related findings.
Hematology	There were no significant treatment-related findings.
Clinical chemistry	There were no significant treatment-related findings.
Urinalysis	There were no significant treatment-related findings.
Gross pathology	There were no significant treatment-related findings.
Organ weights	There were no significant treatment-related findings.
Histopathology Adequate battery: Yes	There were no significant treatment-related findings.
Body temperature	There were no significant treatment-related findings.

Study title/ Number: Thirty-Nine-Week Repeated Percutaneous Dose Toxicity Study of OPC-271 Ointments in Miniature Pigs/ Study Number: 675234

- No test article-related adverse effects were noted in this study. The NOAEL was the high dose of 8.1 and 8.3 mg/kg/day for males and females, respectively (also the MFD: 3% ointment applied once daily at 0.008 ml/cm^2 to 10% BSA)

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (white petrolatum), 0 (vehicle), 1% and 3%, equivalent to 0, 0, 2.7/2.8, and 8.1/8.3 mg/kg/day for males and females, respectively, once daily for 39 weeks
Route of administration:	Dermal
Formulation/Vehicle:	Ointment/ (b) (4)% white petrolatum, (b) (4)% paraffin, (b) (4)% mineral oil, (b) (4)% white wax, and (b) (4)% propylene carbonate
Species/Strain:	Minipig/Gottingen
Number/Sex/Group:	4
Age:	7 months
Satellite groups/ unique design:	N/A
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major Findings**
Mortality	No mortality occurred.
Clinical signs	There were no significant treatment-related findings.
Body weights	There were no significant treatment-related findings.
Ophthalmoscopy	There were no significant treatment-related findings.
ECG	There were no significant treatment-related findings.
Hematology	There were no significant treatment-related findings.
Clinical chemistry	There were no significant treatment-related findings.
Urinalysis	There were no significant treatment-related findings.
Gross pathology	There were no significant treatment-related findings.
Organ weights	There were no significant treatment-related findings.
Histopathology Adequate battery: Yes (including skin treated sites)	There were no significant treatment-related findings.
Cumulative skin irritation	There were no significant treatment-related findings.

5.5.2. Genetic Toxicology

Difamilast was not mutagenic or clastogenic in an in vitro bacterial reverse mutation (Ames) test (study# M-08-042), an in vitro mammalian cell forward mutation test in mouse lymphoma cells (study# G-08-053) or an in vivo rat bone marrow micronucleus test (study# B090145).

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Mutagenicity Test of OPC-271 With bacteria/ Study# M-08-042

Key Study Findings:

- There were no significant increases in revertant colonies at any dose, with or without S9, compared with negative control.
- Difamilast was not mutagenic under the study conditions.

GLP compliance: Yes

Test system: Difamilast was tested up to the maximum dose of 5040 µg/plate in five bacteria strains, including *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537.

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ Number: Mutation Assay of OPC-271 in L5178Y Mouse Lymphoma Cells/ Study# G-08-053

Key Study Findings:

- Using the global evaluation factor approach, the induced mutant frequencies were all below 126 x 10^{-6}, the global evaluation factor.
- Difamilast was not mutagenic under the study conditions.

GLP compliance: Yes

Test system: Difamilast was tested in L5178Y $TK^{+/-}$ mouse lymphoma cells at 20, 30, 70, 100, 200, 300, 700, and 1000 µM for 3 hr treatment without S9, 1, 3, 10, 30, 70, and 100 µM for 3 hr treatment with S9, and 7, 10, 20, 30, 70, and 85 µM for 24 hr treatment without S9. The high dose was selected based on cytotoxicity.

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title/ Number: CTP-543: In Vivo Rat Bone Marrow Micronucleus Assay / Study# 8348335

Key Study Findings:

- Difamilast did not significantly induce micronucleated erythrocytes in male rat bone marrow under the study conditions.
- Difamilast was not clastogenic under the study conditions.

GLP compliance: Yes

Test system: Difamilast was tested at two daily subcutaneous doses of 0 (vehicle: corn oil), 100, 200, and 400 mg/kg. The high dose of 400 mg/kg is the maximum available dose for corn oil preparation.

Study is valid: Yes

5.5.3. Carcinogenicity

In a 2-year dermal carcinogenicity study in rats (study# B-8051), no test article-related neoplastic findings were observed in male or female rats that received difamilast at dermal doses up to 3% ointment, i.e., 8.2 mg/kg/day for males and 10.2 mg/kg/day for females, respectively (3.7 times the MRHD for males and 10 times the MRHD for females, respectively, based on AUC comparison).

In a 2-year dermal carcinogenicity study in mice (study# B-8052), no test article-related neoplastic findings were observed in male or female mice that received difamilast at dermal doses up to 3% ointment, i.e., 51.8 mg/kg/day for males and 56.8 mg/kg/day for females, respectively (4.7 times the MRHD for males and 3.7 times the MRHD for females, respectively, based on AUC comparison).

These two 2-year dermal carcinogenicity studies have been reviewed by the ECAC. The Committee concluded that the studies were adequate and there was no evidence of drug-related neoplasms in either study. Refer to Section 17.3 for the detailed review of the studies.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ Number: Fertility and Early Embryonic Development Study of OPC-271 Subcutaneously Administered to Rats/ Study Number: 100131

Key Study Findings

- Decreased sperm motility, increased abnormal sperm morphology, and decreased number of sperm in males; irregular estrus cycles and decreased copulation and fertility indexes in females, and increased preimplantation loss rate were observed at high dose of 100 mg/kg/day.
- The NOAEL for reproduction and early embryonic development was 10 mg/kg/day.
- The NOAEL for general toxicity was 1 mg/kg/day for males and 10 mg/kg/day for females due to body weight loss.

Conducting laboratory and location (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (corn oil), 1, 10 and 100 mg/kg/day, once daily
Route of administration:	Subcutaneous
Formulation/Vehicle:	Solution/ corn oil
Species/Strain:	Rat/ SD
Number/Sex/Group:	20
Satellite groups:	None
Study design:	SD rats received SC difamilast once daily, from 2 weeks prior to mating, through the mating period (up to 14 days), and up to the day before necropsy in parental males, and from 2 weeks prior to mating, through the mating period, and up to Day 7 of gestation in parental females. Additional mating: 18 males (all surviving males) that had been treated at 100 mg/kg for 35 days and 18 untreated females were paired in ascending order of the animal number and put together on a one-to-one basis from the evening to the next morning for 14 days at the longest. Second mating: 12 females (all females which had failed to copulate in the 1st mating) of the 100 mg/kg group which had been allowed a 14-day recovery period and 12 males of the control group which had been treated for 56 days were paired in ascending order of the animal number and put together on a one-to-one basis from the evening to the next morning for 12 days (all pairs copulated). Day of caesarean section: Day 13 of gestation.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major Findings**
Mortality	3 male and 4 female mortalities at high dose.
Clinical signs	Decreased locomotor activity, hypothermia, and diarrhea in males and females. Abdominal distension and soiled fur in females at high dose.
Body weights	Significant decreases in body weight (males: ¯18.6% at mid dose, ¯35.9% at high dose; females: ¯15.7% at high dose, when compared to control group) and body weight gains (males: ¯55.6% at mid dose, ¯29.2% at high dose; females: ¯63.6% at high dose, when compared to control group) in males at mid and high doses and females at high dose.

Parameters	Major Findings
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	Decreased sperm motility [motile sperm rate: ↓18.5%, progressive sperm rate: ↓45.2%, path velocity (μm/s): ↓20.9%, straight line velocity (μm/s): ↓20.7%, curvilinear velocity (μm/s): ↓20.3%, amplitude of lateral head displacement (μm): ↓15.2%, when compared to control group], increased abnormal sperm morphology (abnormal sperm rate: ↑ 15.5 times, abnormal head rate: ↑15.2 times, when compared to control group; abnormal tail rate: 0.4% at high dose versus 0% in control group), and decreased number of sperm (number of sperms in left cauda epididymis: ↓33.4%, number of sperms/weight of left cauda epididymis (g): ↓24.2%) in males, and irregular estrus cycles (number of estrous cases during dosing period before start of pairing: 1.8 at high dose versus 3.5 in control) and decreased copulation (↓78.9% compared to control group) and fertility indexes (↓75% compared to control group) in females were observed at high dose. Preimplantation loss rate tended to increase in untreated females mated with males treated at 100 mg/kg/day. When the high dose females were entered into a recovery period with return of normal estrus cycling and mated with parental males in the vehicle control group, no abnormal copulation index or fertility index or adverse effects on uterine parameters were noted. No significant findings were noted at low or mid doses. Therefore, the NOAEL for reproduction and early embryonic development was the mid dose of 10 mg/kg/day.

Embryo-Fetal Development

Study Title/ Number: Embryo-Fetal Development Study of OPC-271 Subcutaneously Administered to Rats/ Study Number: 200131

Key Study Findings

- Increased post-implantation loss, decreased fetal weight, retarded ossification and increased visceral abnormalities were noted at high dose of 100 mg/kg/day.
- The NOAEL for reproduction in dams and embryofetal development was 10 mg/kg/day.
- The NOAEL for general toxicity in dams was 1 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (corn oil), 1, 10 and 100 mg/kg/day, once daily
Route of administration:	Subcutaneous
Formulation/Vehicle:	Solution/ corn oil
Species/Strain:	Rat/SD
Number/Sex/Group:	20 females/group
Satellite groups:	None
Study design:	Pregnant rats were administered subcutaneously during the period of organogenesis (from gestation Days 7 to 17). The dams were euthanized on Gestation Day 20.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major Findings**
Mortality	No mortality occurred.
Clinical signs	Decreased locomotor activity, vaginal hemorrhage, soiled hair (perineal region), diarrhea, and dark red spots in the stomach glandular mucosa were noted at high dose.
Body weights	Significant decreases in body weight (¯7.5% at mid dose, ¯20.6% at high dose on GD20, when compared to control group), body weight gains (¯27.1% at mid dose, ¯75.7% at high dose on GD20, when compared to control group) and food consumption (¯14.9% at high dose on GD 17, when compared to control group) were noted at mid and high doses.
Necropsy findings Cesarean section data	There were no significant treatment-related findings in corpora lutea, number of implantation sites, implantation rate, or pre-implantation losses in any treatment groups.
Necropsy findings Offspring	Statistically significant retarded ossification (number of ossified bones: sternebrae: 4.5 at the high dose versus 5.4 in control, metacarpal: 6.7 at high dose versus 7.3 in control) was noted at high dose. Fewer live fetuses (¯18.3%, number of live fetuses: 205 at high dose versus 251 in control), increased post-implantation loss (-3.5 times, 21.4% at high dose versus 6.1% in control), decreased fetal weight (¯4.6% in males, ¯2.7% in females, when compared to control group) and increased visceral abnormalities (membranous ventricular septum defect) were also noted at the high dose (incidence of fetuses with visceral variations: -2.3 times, 1.8% at high dose versus 0.8% in control). However, these findings were not statistically significant. There were no significant treatment-related findings in sex ratio, or external, skeletal or placental morphology.

Study Title/ Number: Embryo-Fetal Development Study of OPC-271 Subcutaneously Administered to Rabbits/ Study Number: 250131

Key Study Findings

- The NOAEL for general toxicity in dams was 3 mg/kg/day.

- Two abortions and increased skeletal variations were noted at high dose of 3 mg/kg/day.
- The NOAEL for reproduction in dams and embryofetal development was 1 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (corn oil), 0.1, 0.3, 1 and 3 mg/kg/day, once daily
Route of administration:	Subcutaneous
Formulation/Vehicle:	Solution/ corn oil
Species/Strain:	Rabbit/Kbl:NZW
Number/Sex/Group:	20 females/group
Satellite groups:	None
Study design:	Pregnant rabbits were administered subcutaneously during the period of organogenesis (from gestation Days 6 to 18). The dams were euthanized on Gestation Day 28.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major Findings**
Mortality	No mortality occurred.
Clinical signs	Two abortions at high dose. Small amount of feces at 1 and 3 mg/kg.
Body weights	No treatment-related significant changes in body weight, body weight gains or food consumption were noted.
Necropsy findings Cesarean section data	There were no significant treatment-related findings in corpora lutea, number of implantation sites, implantation rate, or pre-implantation losses in any treatment groups.
Necropsy findings Offspring	Statistically increased skeletal variations (-2.7 times in supernumerary lumbar vertebra, number of fetuses with variations: 48% at high dose versus 18% in control) were noted at 3 mg/kg. There were no significant treatment-related findings in post-implantation losses, the number of live fetuses, sex ratio, fetal weight, or ossification in any groups.

Prenatal and Postnatal Development

Study title/ Number: Study for Effects of OPC-271 Administered Subcutaneously on Prenatal and Postnatal Development, Including Maternal Function, in Rats/ Study Number: GH14034

Key Study Findings

- The NOAEL for reproductive functions of dams, development of offspring (F1) and embryos (F2) was the high dose of 3 mg/kg/day.

- The NOAEL for general toxicity in dams was 0.3 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (corn oil), 0.1, 0.3, and 3 mg/kg/day, once daily
Route of administration:	Subcutaneous
Formulation/Vehicle:	Solution/corn oil
Species/Strain:	Rat/SD
Number/Sex/Group:	21-22 females/group
Satellite groups:	None
Study design:	Pregnant rats were administered subcutaneously from Day 7 of gestation to Day 20 of lactation, the days that correspond to the period from implantation to weaning of rats.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	**Major Findings**
F0 Dams	No deaths. Suppressed body weight gain (↓14.9% during gestation, ↓30.8% during lactation period, compared with control) at the high dose. No effects on reproductive functions of F0 dams (maintenance of pregnancy, delivery and nursing behavior) were noted.
F1 Generation	There were no significant treatment-related findings (including pre- and post-natal development and reproductive performance).
F2 Generation	There were no significant treatment-related findings (including viability and implantation)

5.5.5. Other Toxicology Studies

Juvenile Animal Toxicity

In an 8-week repeat-dose dermal juvenile toxicity study (study# GH13265), difamilast ointments at concentrations of 0 (white petrolatum), 0 (vehicle: (b) (4)% white petrolatum, (b) (4)% paraffin, (b) (4)% mineral oil, (b) (4)% white wax, and (b) (4)% propylene carbonate), 0.3%, 1% and 3% were dermally applied to 10% BSA of SD rats from 25 days of age in a dose volume of 0.008 mL/cm^2 once daily for 8 weeks (10/sex/group), with a 4-week recovery period (5/sex/group for control and high dose groups). The parameters evaluated included mortality, clinical observations (including dosing site), body weights, food consumption, ophthalmology, functional observational battery, conditioned avoidance response, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, observation of genital development, vaginal smears, observation of mating ability, gross pathology of males after observation of

mating ability, gross pathology of females which failed to mate, observation at cesarean section, and TK analysis.

Significant test article-related decreases in body weight were observed in females at mid (↓7.7%) and high doses (↓15.4%) when compared to control group, which was partially recovered during the 4-week recovery period. Significant decreases in thymus weight (↓23.6%) and spleen weight (↓39.9%) were also observed in females at high dose when compared to control group. With no histopathological correlates, these changes were considered to be minimal toxic effects. For functional observational battery, the decreased grip strength was noted in females at high dose during the treatment period and at mid and high doses during the recovery period. This was considered to be a secondary change due to physical growth retardation and considered to be a minimal change of no toxicological significance. There were no new or specific toxicities to the juvenile animals. The NOAEL was 3% ointment for males and 1% ointment for females, respectively, based on significant body weight decrease noted in high dose females. The corresponding AUC_{24h} values were 731.8 ng·h/mL for males and 817.2 ng·h/mL for females, respectively, which are 3 and 3.4 times the MRHD based on AUC comparison.

In a 10-week repeat-dose SC juvenile toxicity study (focusing on potential central nervous system effects, study# GH13266), subcutaneous doses of 0 (vehicle: corn oil), 1, 3, and 10 mg/kg/day difamilast were administered to juvenile SD rats (4 days old, 10/sex/group) once daily for 10 weeks, with a 4-week recovery period (5/sex/group for vehicle control and high dose groups).

Significant test article-related decreases in body weight were observed in males (↓15.4%) and females (↓10.3%) at 10 mg/kg/day when compared to the vehicle control group. There were no test article-related changes in CNS function, brain morphology, or histopathology. Decreases in brain weight were observed in males (↓6.5%) and females (↓3.5%) at 10 mg/kg/day, which was considered likely to be a secondary effect due to neonatal low body weight and tended to resolve during a 4-week recovery period. The NOAEL for CNS effects was 10 mg/kg/day. The corresponding AUC_{24h} values were 7347 ng·h/mL for males and 10240 ng·h/mL for females, respectively, which are 31 and 43 times the MRHD based on AUC comparison.

Ocular Irritation

In a primary eye irritation study in female New Zealand White rabbits (study# 028745), OPA-15406 powder (0.1 ml, equivalent to ~60.0 mg) was applied into the conjunctival sac of the right eye of 3 male rabbits. After application, the rabbits were assessed for signs of ocular damage/irritation under gross observation and observation using a slit lamp microscope, according to Draize's evaluation criteria at 1, 3, 6, 24, 48, and 72 hr postdose.

No corneal or iridial effects were noted during the observation period. Conjunctival effects (redness, chemosis, and/or discharge) were noted in all animals. The effects were classified as a very slight reaction, and they were no longer noted by 24 hr postdose.

In a primary eye irritation study in rabbits (study# P100233), 0.1 ml OPC-271 ointments (0%, 0.1%, 0.3%, 1%, and 3%) were applied into the conjunctival sac of the right eye of female New Zealand White rabbits (3/group). The eye reaction (for cornea, iris, and conjunctiva) was observed at 1, 3, 24, 48, 72, and 96 hr after application.

No eye reaction was observed in the cornea, iris, or conjunctiva in any animal. All the tested difamilast ointments (0%, 0.1%, 0.3%, 1%, and 3%) were classified as "nonirritant."

Dermal Sensitization

In a skin sensitization study in guinea pigs (study# 031169), Hartley Guinea pigs were sensitized with intradermal injections (0.1 ml, first sensitization, on Day 1) and an occluded patch (second sensitization, 0.2 ml, on Day 8) of white petrolatum (negative control) or 0%, 0.1%, 0.3%, 1% or 3% OPA-15406 ointments (9 for negative control, 5/group for OPA-15406 ointments). 2, 4-dinitro-1-chlorobenzene (DNCB, 0.1% solution) was used as a positive control (3 animals in the positive control group). On Day 22, 0.1 ml of the test article was applied using a closed patch as the challenge dose. Assessment for skin reactions was made under gross observation prior to challenge and at 24 hr (Day 24) and 48 hr (Day 25) after the challenge patches were removed.

No allergic skin reactions following challenge were noted in OPA-15406 ointment treated animals. OPA-15406 ointments did not show skin sensitization potential in guinea pigs under the study conditions.

Phototoxicity

In an in vitro phototoxicity test (study# F-09-193), BALB/3T3 cells were treated with the test article for 60 min in an incubator, then were irradiated (UVA irradiance: approximately 2.5 mW/cm^2) or kept in the dark for 50 min. The tested concentrations for the test article were 1.6, 3.1, 6.3, 13, 25, 50, 100, and 200 µg/ml (serial dilution ratio of 2 from the maximum concentration 200 µg/ml). Chlorpromazine hydrochloride was used as a positive control, with tested concentrations of 0.016-2.0 µg/ml for irradiation condition and 0.31-40 µg/ml for non-irradiation condition. A solar simulated light source was used to generate irradiation of UVA, UVB, and visible light. The irradiation intensity was measured, and the results were shown in the next section.

Cell survival rates were measured with an Neutral Red Uptake (NRU) assay on the next day. The IC_{50} value (i.e., the concentration with a 50% relative survival rate) was calculated. Then the photo irritation factor (PIF) was calculated as: PIF = IC_{50} value of non-irradiation/IC_{50} value of irradiation.

When a PIF is 5 or greater, the test article is judged to be phototoxic, when a PIF is less than 2, the test article is judged to be non-phototoxic; when a PIF is between 2 and 5, it is judged to be probably phototoxic.

A PIF of 42.2 for chlorpromazine hydrochloride showed that the positive control was valid in this study. For OPC-271, IC_{50} values were 34 µg/ml without irradiation and 43 µg/ml with

irradiation. The PIF for OPC-271 was calculated to be 0.79, which indicated that OPC-271 was not phototoxic under the study conditions.

In a phototoxicity test in guinea pigs (study# 030920), twelve Hartley guinea pigs were treated with topical applications of white petrolatum (negative control) or 0%, 0.1%, 0.3%, 1% or 3% OPA-15406 ointments (50 µl/site, 5 irradiated and 5 non-irradiated sites for each test article). Thirty minutes after the application, the animals were irradiated with solar simulators (irradiation dose of 10 J/cm2, wavelength 300-780 nm) and assessed for signs of skin reactions according to Draize's evaluation criteria at 24, 48, and 72 hr after irradiation. 8-methoxypsoralen (8-MOP, 0.1% solution) was used as a positive control.

8-MOP induced a phototoxic skin reaction (moderate to severe erythema and edema). Under the conditions of this study, no skin reactions were noted in either the irradiated or the non-irradiated areas in any animals treated with OPA-15406 ointments at any observation time point. OPA-15406 ointments did not induce phototoxicity in this study.

Drug Excipient Evaluation

Difamilast ointment, 1%, does not contain any novel excipients or excipients of human or animal origin. All the inactive ingredients are at the same or below approved levels for the dermal route of administration listed in the FDA's inactive ingredient database.

Potential Drug Impurity Evaluation

The Applicant provided an impurity characterization and control strategy, or the impurities have been qualified in studies described below. The potential impurities that are evaluated and controlled include product-related impurities, process-related impurities, elemental impurities, and contaminants. The proposed control strategy is considered acceptable. There are no safety concerns for potential impurities contained in this product.

Acceptance criteria for four potential impurities are higher than the qualification thresholds in accordance with the International Conference on Harmonization (ICH) guideline on impurities in final products. The acceptance criteria are defined as the concentration of the specification limit of impurities in difamilast contained in the ointment. These criteria in difamilast ointment, 1% are (b) (4) .

(b) (4)

The maximum daily dose (MDD) of the drug product, difamilast ointment, 1%, is 14 g (i.e., 140 mg difamilast) based on the information the applicant provided. The proposed acceptance criterion is (b) (4)% for (b) (4) in the 1% ointment. Therefore, the MDD for (b) (4) would be (b) (4)% x 1% x 14 g = (b) (4) mg/day.

(b) (4) was a genotoxic carcinogen and its carcinogenic potency (TD_{50}) is (b) (4) mg/kg/day as shown in the Carcinogenic Potency Database, based on a dietary carcinogenicity study in mice (Gold et al. 2008).

As per the ICH M7(R1) guidance, for known genotoxic carcinogens, compound-specific risk assessments to derive acceptable daily intakes (ADIs) should be applied when sufficient carcinogenicity data exist.

The ADI for (b) (4) = (b) (4) mg/kg/day / (b) (4) mg/day.

The proposed MDD is slightly higher than the ADI. However, considering that this is a topical product with limited dermal absorption, the acceptance criterion is acceptable.

(b) (4)

The acceptance criteria are (b) (4)% for (b) (4) and (b) (4) and (b) (4)% for (b) (4) The safety of these impurities was evaluated in two genotoxicity and two 13-week repeat-dose toxicity studies conducted using difamilast spiked with each impurity at an amount equivalent to or double that of the acceptance criteria.

(b) (4) were negative in a bacterial reverse mutation test conducted using difamilast (dissolved in DMSO) spiked with (b) (4), (b) (4) and (b) (4) (study# 032964) and a micronucleus test in male rats conducted using difamilast (suspension in corn oil) spiked with (b) (4), (b) (4) and (b) (4) (study# 035481).

In a 13-week repeat-dose SC toxicity study in Beagle dogs using difamilast solution spiked with (b) (4), (b) (4) and (b) (4), there were no new toxicities or significant enhancement of the toxicities related to these impurities (study# 035168).

In a 13-week repeat-dose dermal toxicity study in Göttingen minipigs using difamilast ointment spiked with (b) (4), (b) (4) and (b) (4), there were no test article-related effects (study# 645132).

Considering that this is a topical product with limited dermal absorption, there are no significant safety concerns for these impurities at the proposed levels.

Overall, there are no safety concerns for potential impurities contained in this product from a pharmacology/toxicology perspective.

Extractable/Leachable Evaluation

Difamilast drug substance is packaged in a (b) (4) . The packaging material that comes into contact with the drug substance is made of (b) (4) and complies with 21 Code of Federal Regulations (CFR) 177.1520 (US) regulations.

The final container closure system for the ADQUEY product is an aluminum tube (i.e., a physician sample 3 g fill tube, early marketing planning 27 g fill tube and current marketing demand 85 g fill tube). Extractable and leachable studies were conducted for the container closure system.

The applicant followed the ICH M7 (R1) guidance to set analytical thresholds for the extractable and leachable studies. No extractable compounds, leachable compounds, or elements were detected based on the analytical thresholds set for these studies.

Therefore, there are no safety concerns for the extractables or leachables from either the drug substance storage container closure system or the final product container closure system.

Major Human Metabolite Evaluation

There are three major human metabolites: MAP-15484, MAP-15485 and MAP-15497. Overall, these three major metabolites were well covered with the pivotal nonclinical toxicology studies. The dog is the most appropriate animal species for the major metabolites. There are no significant safety concerns with these major metabolites.

Reasonable margins of exposure (based on $AUC_{0\text{-}24h}$) for these three major metabolites were obtained in SC toxicity studies. In rats, following 4 weeks of dosing, exposures were 1.7 to 3.9 times higher than the exposures at the MRHD for two of the three major metabolites. In the chronic toxicity study in dogs, exposures to these three major metabolites were 5.8 to 9.9 times higher than the exposures at the MRHD. There were no test article-related adverse effects.

In 2-year dermal carcinogenicity studies in mice and rats, the exposures to the three major metabolites were 0.62 to 16 times higher than the exposures at the MRHD in at least one species. No test article-related neoplastic findings were observed in rats or mice.

Overall, there are no significant safety concerns for these three major metabolites from a pharmacology/ toxicology perspective.

6 Clinical Pharmacology

6.1.Executive Summary

Background:

On February 13, 2025, the Applicant (Acrotech Biopharma, Inc.) submitted an original NDA (NDA 219474) for difamilast ointment, 1% (ADQUEY; OPA-15406), in which they are seeking approval for the treatment of mild-to-moderate AD in adults and pediatric patients 2 years of age and older. The active pharmaceutical ingredient of ADQUEY, difamilast, is a PDE-4 inhibitor. 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 is not well defined. Of note, other topical PDE-4 inhibitors have been previously approved, including crisaborole ointment 2% (Eucrisa, NDA 207695; approved for AD) roflumilast foam 0.3% (Zoryve, NDA 217242; approved for seborrheic dermatitis and plaque psoriasis) and roflumilast cream 0.05%, 0.15%, and 0.3% (Zoryve, NDA 215985; approved for AD [0.05% and 0.15%] and plaque psoriasis [0.3%]).

Proposed Dosing in Mild-to-Moderate AD:

The recommended dosing regimen of difamilast ointment, 1%, for the treatment of mild-to-moderate AD in adults and pediatrics 2 years of age and older is as follows:

- Apply a thin layer BID to affected areas and rub in completely

Major Clinical Pharmacology Review Findings:

- Following absorption into systemic circulation, difamilast undergoes metabolism via cytochrome P450 (CYP) 3A4, CYP1A2, and non-enzymatic hydrolysis to form three major metabolites, including MAP-15485, MAP-15497, and MAP-15484, respectively. Although the Applicant has not conducted a mass balance study in humans, based on the totality of available evidence, elimination of the parent drug occurs primarily via hepatic metabolism with minimal renal elimination.
- Support for systemic safety is furnished by PK and safety findings from a maximal use trial conducted in pediatric subjects 2 to <18 years of age with AD at the upper range of disease severity, which resulted in substantially greater systemic exposure as compared to that observed in phase 2 and phase 3 trials and demonstrated a favorable safety profile with no serious systemic adverse events (SAEs). Additional data to inform the systemic safety are derived from phase 3 trials.
- The Applicant has not adequately assessed the potential QT prolongation risk of difamilast ointment, 1%. As a result, a statement will be included in section 12.2 of the label to state that there is insufficient information to characterize the effect of this product on the QTc interval. However, based on the totality of available clinical, nonclinical, and clinical pharmacology data, a dedicated QTc study was not considered

necessary for this topical product. Section 12.2 will include the following language to convey this conclusion, "ADQUEY ointment is not expected to cause clinically significant QTc interval prolongation at the recommended dosages."

- No dedicated clinical trials were conducted to investigate the impact of intrinsic factors on difamilast PK. However, the available clinical safety data and safety margins based on animal toxicity data do not warrant any dose restrictions for intrinsic factors, including body weight, age, sex, race, renal impairment, and hepatic impairment.
- No dedicated clinical drug-drug interaction (DDI) trials were conducted. Based on in vitro studies, the potential for difamilast and its major metabolites to act as inhibitors of major transporters and CYP enzymes is low at the not anticipated at the expected systemic exposures. The potential impact of coadministration with CYP3A4/CYP1A2 inhibitors on the PK of difamilast has not been adequately characterized. However, clinically significant increases in difamilast PK are not expected based on the totality of clinical safety data, including a limited number of subjects with concomitant administration of CYP3A4 or CYP1A2 inhibitors.

Recommendation:

The Office of Clinical Pharmacology (OCP), Division of Inflammation and Immune Pharmacology (DIIP) has reviewed the information submitted under NDA 219474. This application is approvable from a clinical pharmacology perspective.

Post Marketing Requirements (PMRs):

Conduct an adequate and well-controlled trial in subjects ages 3 months to <2 years with mild-to-moderate AD. Evaluate the PK of difamilast under maximal use conditions in a sub-set of subjects with disease at the upper range of severity.

- **Final Protocol Submission:** 6/2026
- **Study Completion:** 1/2029
- **Final Report Submission:** 6/2029

6.2.Overview of Clinical Pharmacology Program

In total, the Applicant provided clinical pharmacology data from eight studies conducted in adults and pediatric subjects 2 years of age and older. Two phase 1 (SAD/MAD studies were completed in healthy subjects (271-11-202 and 271-14-001). All other clinical pharmacology studies were conducted in patients with mild-to-severe AD, including a phase 1b proof-of-concept study (271-12-204), three phase 2 dose-ranging studies (271-12-205, 271-15-001, and 271-102-00002), one maximal use PK and safety study (MEDI-MM36-206), and a phase 3, open-label extension (OLE), long-term safety and efficacy trial (MEDI-MM36-302), which included a QTc sub-study to characterize the potential QTc prolongation risk of difamilast ointment, 1%. A tabulated summary of clinical pharmacology studies is provided below in Table 3.

Study reports and results for all clinical pharmacology studies, including pivotal clinical pharmacology studies MEDI-MM36-206 and MEDI-MM36-302, are described in the OCP appendices in Section 17.4.1. Of note, given that all PK samples for healthy US adult subjects enrolled in Study 271-11-202 were below the limit of quantitation (BLQ), this study is not discussed further in this review.

Table 3: Summary of Clinical Pharmacology Trials Supporting NDA 219474

Study ID	Description	PK Population (N)[a]	Difamilast Dose(s) and Strength[b]	Treatment Duration
271-11-202	Phase 1, FIH, DB, PC, SAD/MAD study	Healthy U.S. adults (48)	**SAD:** Difamilast ointment, 0.1%, 0.3%, 1%, and 3% once **MAD:** Difamilast ointment, 0.1%, 0.3%, 1%, and 3% QD	**SAD:** Single-dose **MAD:** 14 days
271-14-001	Phase 1, DB, PC, SAD/MAD study	Healthy Japanese adults (24)	**SAD:** Difamilast ointment, 0.3%, 1%, and 3% once **MAD:** Difamilast ointment, 0.3%, 1%, and 3% BID	**SAD:** Single-dose **MAD:** 14 days
271-12-204	Phase 1b, randomized, two-part, placebo- and active comparator-controlled POC study	US adult subjects with mild-to-moderate AD (60)	**Part 1:** Difamilast ointment, 0.3%, 1%, and 3% BID **Part 2:** Difamilast ointment, 1% and 3% BID	Part 1: 4 weeks Part 2: 4 weeks
MEDI-MM36-206	Phase 2, OL, maximal use PK and safety study	Pediatric subjects 2 to <18 years of age with mild-to-severe AD (31)	Difamilast ointment, 1% BID	4 weeks
271-12-205	Phase 2, randomized, DB, PC, parallel, dose-ranging study	Adult and pediatric subjects ≥10 years of age with mild-to-moderate AD (9)	Difamilast ointment, 0.3% and 1% BID	8 weeks
271-15-001	Phase 2, randomized, DB, PC, parallel, dose-ranging study	Adult and pediatric Japanese subjects ≥15 years of age with mild-to-moderate AD (125)	Difamilast ointment, 0.3% and 1% BID	8 weeks
271-102-00002	Phase 2, randomized, DB, PC, parallel, dose-ranging study	Pediatric Japanese subjects 2 to 14 years of age with mild-to-moderate AD (45)	Difamilast ointment, 0.3% and 1% BID	4 weeks
MEDI-MM36-302 (QTc sub-study)	Phase 3 OL, long-term safety and efficacy study	Adult and pediatric subjects ≥2 years of age with mild-to-moderate AD (31)	Difamilast ointment, 1% BID	52 weeks

Source. Adapted from Summary of Clinical Pharmacology Studies (Table 5, pg. 17)
[a] Reflects number of subjects for which evaluable PK data are available
[b] Only difamilast treatment arms are shown. Studies 271-11-202, 271-14-001, 271-12-204 (Part 1), 271-12-205, 271-15-001, and 271-102-00002 also included placebo arms. Study 271-12-204 (Part 2) also included an active-comparator treatment arm (tacrolimus ointment, 0.1% BID).
Abbreviations: AD, atopic dermatitis; BID, twice daily; DB, double-blind; FIH, first-in-human; MAD, multiple ascending dose; N, number of subjects; NDA, new drug application; OL, open-label; PC, placebo-controlled; PK, pharmacokinetic; POC, proof-of-concept; QD, once daily; SAD, single ascending dose

6.2.1. General Dosing and Therapeutic Individualization

General Dosing:

The recommended dosage and administration instructions of difamilast ointment, 1%, for the treatment of mild-to-moderate AD in adults and pediatrics 2 years of age and older is as follows:

- Apply a thin layer BID to affected areas and rub in completely. Wash hands after application.
- For topical use only and not for ophthalmic, oral, or intravaginal use.
- Avoid areas of the skin that are infected.

Therapeutic Individualization:

No dosage adjustments or restrictions are recommended based on any intrinsic or extrinsic factors.

Outstanding Issues:

None.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Key clinical pharmacology information about difamilast ointment, 1%, is summarized below in Table 4.

Table 4: Summary of Clinical Pharmacology and Pharmacokinetics (PK)

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Phosphodiesterase 4 (PDE-4) inhibitor
Mechanism of action	Difamilast is a PDE-4 inhibitor. 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 is not well defined.
Active moieties	Difamilast Pharmacologic activity of major metabolites MAP-15484, MAP-15485, and MAP-15497 has not been characterized. However, given that metabolism occurs downstream of the local site of drug application and action (topical), metabolites are not expected to contribute appreciably to efficacy.

Characteristic	Drug Information
QT prolongation	There is insufficient information to characterize the effect of difamilast on the QTc interval. However, following inter-disciplinary discussion and risk assessment based on the totality of available clinical, nonclinical, and clinical pharmacology data, clinically significant QTc interval prolongation is not anticipated at expected systemic exposure following clinical use. Therefore, the review team concluded that further TQT assessment was not warranted.
	General Information
Bioanalysis	Four bioanalytical assays utilizing protein precipitation followed by liquid chromatography with tandem mass spectroscopy (LC-MS/MS) were developed for the quantitation of difamilast and its major metabolites (MAP-15484, MAP-15485, and MAP-15497) in human plasma and urine in the submitted clinical pharmacology studies. The method used in the QTc sub-study of the phase 3 OLE trial MEDI-MM36-302 (MN21007) was successfully validated for determination of difamilast, MAP-15495, and MAP-15497 (over a range of 0.050 to 50.0 ng/mL), and MAP-15484 (over a range of 0.125 to 125 ng/mL), in human plasma. The method used in the maximal use trial MEDI-MM36-206 (OPAHHP) was successfully validated for determination of difamilast over a range of 0.200 to 40.0 ng/mL in human plasma. However, significant issues were identified with the validation and performance of this assay for quantitation of plasma concentrations of MAP-15484, MAP-15485, and MAP-15497, including unacceptable selectivity data, substantial matrix effects, and poor QC performance. Therefore, metabolite PK data in Study 206 were not considered reliable.
Healthy subjects versus patients	Following single- and multiple-dose topical BID administration of difamilast ointment, 1%, for 14 days in healthy US adults, plasma concentrations in all samples were BLQ (Study 271-11-202). Following topical BID administration of difamilast ointment, 1%, in US adult subjects with mild-to-moderate AD (Study MEDI-MM36-302), dose-normalized mean steady-state C_{max} and AUC_{0-12h} of difamilast were approximately 7.6- and 6.3-fold higher, respectively, compared to healthy Japanese adults (Study 271-14-001).
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	In US pediatric patients 2 to <18 years of age with moderate-to-severe AD, the mean (SD) steady-state C_{max} and AUC_{0-8h} of difamilast were 16.9 (21.9) ng/mL and 86.2 (79.6) ng*h/mL, respectively, following topical BID administration of difamilast ointment, 1%, for 14 days under maximal use conditions (Study MEDI-MM36-206). In adult patients with mild-to-moderate AD, the mean (SD) steady-state C_{max} and AUC_{0-12h} of difamilast were 0.76 (1.16) ng/mL and 6.10 (8.85) ng*h/mL, respectively, following topical BID administration of difamilast ointment, 1%, for 4 weeks (Study MEDI-MM36-302). It should be noted that this study was not conducted under maximal use conditions.

Characteristic	Drug Information
Range of effective dose(s) or exposure	Three dose-ranging studies were conducted in adults and pediatric subjects 2 years of age and older with mild-to-moderate AD, including one US trial (Study 271-12-205) and two Japanese trials (Studies 271-15-001 and 271-102-00002). All three trials explored two difamilast dosing regimens: Difamilast ointment, 0.3% BID Difamilast ointment, 1% BID Both the 0.3% and 1% difamilast ointment strengths were subsequently evaluated in pivotal phase 3 efficacy and safety trials.
Maximally tolerated dose or exposure	In Study MEDI-MM36-206, difamilast ointment, 1%, was administered under maximal use conditions in pediatric subjects 2 to <18 years of age with AD at the upper range of severity. Maximal use conditions were defined as the following: Application to ≥35% BSA for subjects 2 to <12 years of age Application to ≥25% BSA for subjects 12 to <18 years of age In this trial, the mean (SD) average daily ointment applied was 8.5 (4.2) g/day, ranging from 3.3 to 23.3 g/day. This corresponded to a mean (SD) predicted difamilast dose of approximately 42.7 (21.1) mg difamilast per dose application (range: 16.7 to 117 mg). There were no serious adverse events and difamilast appeared to be generally well-tolerated, supporting systemic safety at expected therapeutic exposures following administration under typical clinical use conditions.
Dose proportionality	Not applicable
Accumulation	There was no accumulation of difamilast following topical BID administration of difamilast ointment, 1%, under maximal use conditions for 14 days (Study MEDI-MM36-206).
Time to achieve steady-state	Steady state is expected to be reached within 14 days of BID dosing in patients with AD.
Bridge between to-be-marketed and clinical trial/study formulations	Two crystalline forms ([(b) (4)]) were used throughout clinical development. [(b) (4)] was used throughout the phase 1 and 2 trials, whereas [(b) (4)] (to-be-marketed formulation) was used in the pivotal efficacy and safety trials. No dedicated clinical relative bioavailability studies were done to bridge these two formulations. However, a formulation bridge was established based on comparative in vitro dissolution data, which demonstrated equivalent drug release between [(b) (4)] at the 1% ointment strength.
	Absorption
Bioavailability	Absolute bioavailability of difamilast ointment, 1%, was not determined.
T_{max}	Median T_{max} of difamilast was approximately 4 hours after both single- and multiple-dose topical administration of difamilast ointment, 1%,.
Food effect (fed/fasted) Geometric least square mean and 90% CI	Not applicable
	Distribution
Volume of distribution	Not applicable
Plasma protein binding	The plasma protein binding ratios of difamilast, MAP-15484, MAP-15485, and MAP-15497 are 99%, 98%, 99%, and 99%, respectively, based on in vitro assessments.
Drug as substrate of transporters	Based on in vitro studies, difamilast is a substrate of BCRP (≥1 μM).

Characteristic	Drug Information
	Elimination
Mass balance results	A mass balance study was not conducted in humans.
Clearance	Not applicable
Half-life	Based on limited PK data in 5 adult subjects with mild-to-moderate AD, mean (SD) terminal elimination half-life was approximately 8.6 (3.3) hours following BID administration of difamilast ointment, 1%, for 28 days (Study MEDI-MM36-302). This half-life estimate is not considered reliable.
Metabolic pathway(s)	Difamilast is predominantly metabolized by CYP3A4, CYP1A2, and non-enzymatic hydrolysis to form three major metabolites, including MAP-15485, MAP-15497, and MAP-15484, respectively. The primary metabolic pathways are briefly described below: CYP1A2-mediated hydroxylation to form MAP-15497, followed by subsequent glucuronidation CYP3A4-mediated *O*-deethylation to form MAP-15485, followed by sulfation (MAP-15583), glucuronidation (MAP-15585), and/or further oxidation and subsequent conjugation (MAP-15606) Non-enzymatic hydrolysis to form MAP-15484
Primary excretion pathways (% dose)	No mass balance study was conducted in humans. However, based on urine PK data derived from a SAD/MAD study conducted in healthy Japanese adults, urinary concentrations of difamilast and its metabolites were very low (i.e., f_e <0.1%) or undetectable at all timepoints, suggesting minimal renal elimination (Study 271-14-001).
	Intrinsic Factors and Specific Populations
Body weight	No dedicated studies have been conducted to evaluate the impact of body weight on the PK of difamilast.
Age	No dedicated studies have been conducted to evaluate the impact of age on difamilast PK. Based on cross-study PK comparison, dose-normalized steady-state exposure of difamilast was approximately 2- to 3-fold higher in pediatric subjects with AD compared to adults. Among pediatric subjects 2 to <18 years of age with AD from Study 206, children 6 to <12 years of age had the lowest systemic exposure on Day 1, despite having the greatest BSA involvement (47.2%) and receiving the highest predicted topical difamilast dose (61.4 mg per dose application). Conversely, the highest systemic exposure was observed in adolescents 12 to <18 years of age, who had the lowest BSA involvement (36.9%). Dose-normalized PK parameters in the lowest age group (children 2 to <6 years of age) were approximately 2-fold higher relative to the overall study population. Based on these data, no clear age-dependent trend among pediatric age sub-groups was identified. Overall, age (2 to 70 years) did not appear to meaningfully influence the PK of difamilast and no dose adjustments or restrictions are recommended.
Sex	No dedicated studies have been conducted to evaluate the impact of sex on difamilast PK. Nominal steady-state exposure (C_{max} and AUC) of difamilast was approximately 2- to 3-fold higher in females compared to males, although dose-normalized exposure was comparable regardless of patient sex (Study MEDI-MM36-302). Overall, sex did not appear to meaningfully influence the PK of difamilast and no dose adjustments or restrictions are recommended.

Characteristic	Drug Information
Race/Ethnicity	No dedicated studies have been conducted to evaluate the impact of race/ethnicity on difamilast PK. Based on cross-study PK comparison, dose-normalized systemic exposure of difamilast was generally comparable between White and Black subjects, with slightly higher dose-normalized exposure observed in Asians. Overall, race/ethnicity did not appear to meaningfully influence the PK of difamilast and no dose adjustments or restrictions are recommended.
Renal impairment	No dedicated studies have been conducted to evaluate the impact of renal impairment on the PK of difamilast. Based on post hoc analysis of PK data across the clinical pharmacology program, renal impairment (eGFR ≥90 mL/min/1.73 m^2 [normal, N=66]; eGFR 60 to <90 mL/min/1.73 m^2 [mild, N=26]; eGFR 30 to <60 mL/min/1.73 m^2 [moderate, N=1]) did not appear to meaningfully impact the PK of difamilast. It should be noted that there was only one subject with moderate renal impairment and no subjects with severe renal impairment. However, based on urine PK data which suggested very low fraction excreted in the urine, no specific dosing recommendations are considered necessary in subjects with renal impairment.
Hepatic impairment	No dedicated studies have been conducted to evaluate the impact of hepatic impairment on the PK of difamilast. Based on post hoc analysis of PK data across the clinical pharmacology program, CTCAE Grade 1 elevations in baseline ALP and ALT did not appear to meaningfully impact PK of difamilast. A slight trend of higher difamilast exposure was observed in subjects with Grade 1 elevations in AST compared to those with normal baseline values, although this PK difference is not considered to be clinically significant. It should be noted that there were only eleven, five, and four subjects with baseline CTCAE Grade 1 elevations in ALT, AST, and ALP, respectively, and a single subject with a baseline CTCAE Grade 2 elevation in ALT at baseline. However, based on the totality of available evidence, including the generally favorable safety profile demonstrated for difamilast across phase 2 and phase 3 trials, no specific dosing recommendations are considered necessary in subjects with hepatic impairment.
	Drug Interaction Liability (Effect of other drugs on difamilast)
Inhibition/induction of metabolism	Based on in vitro studies, difamilast and its major metabolites (MAP-15484, MAP-15485, and MAP-15497) are not inhibitors of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4, and are not inducers of CYP1A2, CYP2B6, or CYP3A4 at expected therapeutic exposures following administration under typical clinical use conditions.
Inhibition/induction of transporter systems	Based on in vitro studies, difamilast and its major metabolites (MAP-15484, MAP-15485, and MAP-15497) are not inhibitors of p-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K at expected therapeutic exposures following administration under typical clinical use conditions.

Characteristic	Drug Information
	Drug Interaction Liability (Effect of difamilast on other drugs)
Effect of CYP enzyme inhibitors/inducers	No dedicated DDI studies have been conducted to evaluate the impact of coadministration of inhibitors of CYP1A2 and/or CYP3A4 (primary metabolizing enzymes) on the PK of difamilast and its metabolites. The Applicant utilized PBPK modeling to estimate difamilast PK parameters following topical administration of difamilast ointment, 1%, (50 mg) with ketoconazole 200 mg BID (CYP3A4 inhibitor) and fluvoxamine 50 mg QD (CYP1A2 inhibitor). However, these analyses were deemed inadequate for predicting the effects of coadministration of strong inhibitors of CYP3A and CYP1A2 on difamilast plasma exposure. Since PBPK approach was found inadequate, additional data analysis was conducted based on the review of a limited number of difamilast-treated subjects across phase 2 and phase 3 studies who had concomitant administration of CYP3A4/1A2 inhibitors, the safety profile was found to be generally comparable to that of the overall population. Additional safety analyses which were conducted based on exposure quartiles of percent BSA involvement and average daily dose did not reveal any significant trends in the frequency, severity, or type of TEAEs as a function of average daily dose or percent BSA affected. Overall, analysis of the safety data generated across the clinical development program did not reveal systemic safety concerns for difamilast ointment, 1%. There appears to be a large safety margin associated with topical difamilast treatment, such that any potential DDI-mediated increases in difamilast exposure are unlikely to result in a clinically significant increase in safety events. Therefore, based on the totality of evidence, no specific dosing adjustments or restrictions are warranted for subjects receiving inhibitors of CYP3A4 and/or CYP1A2.

Source: Compiled by reviewer based on Summary of Biopharmaceutic Studies (m2.7.1) and Summary of Clinical Pharmacology Studies (m2.7.2); Reviewer's analysis based on adpc.xpt, adsl.xpt, and adpk.xpt datasets for Studies MEDI-MM36-206 and MEDI-MM36-302; Reviewer's analysis based on CSRs for Studies 271-14-001, 271-12-204, 271-12-205, 271-15-001, and 271-102-00002; Applicant's Responses to Information Requests (dated 6/5/2025, 6/30/2025, 9/18/2025, 10/1/2025, 10/29/2025, 11/24/2025, and 12/2/2025)

Abbreviations: AD, atopic dermatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMP, adenosine monophosphate; $AUC_{0\text{-}12h}$, area under the plasma concentration-time curve from 0 to 12 hours; $AUC_{0\text{-}8h}$, AUC from 0 to 8 hours; BCRP, breast cancer resistance protein; BID, twice daily; BLQ, below the limit of quantitation; CI, confidence interval; C_{max}, maximum plasma concentration; CSR, clinical study report; CTCAE, common terminology criteria for adverse events; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; DDI, drug-drug interaction; EPC, established pharmacologic class; fe, fraction eliminated in the urine; PDE-4, phosphodiesterase-4; LC-MS/MS: liquid chromatography with tandem mass spectroscopy; OLE, open-label extension; MAD, multiple ascending dose; MATE, multidrug and toxin extrusion protein; OAT, organic anion transporter; OATP, organic anion transporting peptide; OCT, organic cation transporter; P-gp, P-glycoprotein; PK, pharmacokinetic; QC, quality control; SAD, single ascending dose; SD, standard deviation; TEAE, treatment-emergent adverse event; T_{max}, time of C_{max}, TQT, thorough QT-

6.3.2. Clinical Pharmacology Major Review Questions

6.3.2.1. Clinical Pharmacology Assessment of Proposed Dosing (Safety and Effectiveness)

Overall, the proposed BID topical administration dosing regimen of difamilast ointment, 1%, for the treatment of mild-to-moderate AD in adults and pediatric subjects 2 years of age and older appears reasonable from a clinical pharmacology perspective based on observed safety and PK data derived from Studies MEDI-MM26-206 and MEDI-MM36-302.

Clinical Pharmacology Data to Support Efficacy:

Given that difamilast ointment, 1%, is a topically applied product with local effects, PK assessed under maximal use conditions supports systemic safety rather than efficacy, as plasma concentrations are not necessarily correlated with exposure at the site of action. Regarding the major metabolites MAP-15484, MAP-15485, and MAP-15497, pharmacologic activity was not characterized. However, given that metabolism occurs downstream of the local site of drug application and action, the metabolites are considered unlikely to contribute appreciably to efficacy (refer to Section 17.4.2.1). Refer to Section 8.1 for efficacy data analysis and conclusions.

Clinical Pharmacology Data to Support Systemic Safety:

Trial 206 was a maximal use trial to evaluate the PK of difamilast and its metabolites following administration of difamilast ointment, 1%, under maximal use conditions in pediatric subjects 2 to <18 years of age with AD at the upper range of disease severity. Trial 302 was a phase 3 OLE trial in which the PK of difamilast and its major metabolites was assessed following BID administration of difamilast ointment, 1%, in a sub-set of adults with mild-to-moderate AD. Refer to Section 17.4.1.1 and Section 17.4.1.2 for further details regarding the overall study designs of Trials 206 and 302, respectively. Since administration of difamilast ointment, 1%, in Trial 302 is considered representative of the typical clinical use scenario, PK, safety, and dosing data for administration under maximal use conditions in Trial 206 have been submitted as supportive evidence of systemic safety for the proposed dosing in the target patient population.

Baseline Disease Characteristics – Study 206 Versus Study 302:

The baseline disease characteristics for Trials 206 and 302 are summarized in Table 5. In general, baseline total Eczema Area and Severity Index (EASI) score, IGA-AD score, and BSA involvement were substantially higher in Trial 206 compared to Trial 302, given that the former was a maximal use trial which targeted enrollment of AD patients with a higher disease severity, whereas the latter primarily included subjects with mild-to-moderate AD.

Table 5: Summary of Baseline EASI Score, IGA-AD Score, and BSA Involvement: MEDI-MM36-206 (Maximal Use Trial) Versus MEDI-MM36-302 (Phase 3 OLE Trial)

Demographic Summary Statistics	MEDI-MM36-206 PK Population (N=31)	MEDI-MM36-302 QTc Sub-Study (N=31)	MEDI-MM36-302 Safety Population (N=537)
EASI total			
n	31	31	535
Mean (SD)	18.0 (6.9)	4.8 (3.0)	6.5 (5.3)
Median (min, max)	15.7 (7.6, 32.0)	3.6 (1.6, 15.6)	5.2 (0.0, 50.7)
IGA-AD			
N	31	31	537
0: clear	0	0	4 (0.7%)
1: almost clear	0	0	14 (2.6%)
2: mild	3 (9.7%)	7 (22.6%)	182 (33.9%)
3: moderate	23 (74.2%)	24 (77.4%)	336 (62.6%)
4: severe	5 (16.1%)	0	1 (0.2%)
BSA involvement (%)[a]			
N	31	31	537
Mean (SD)	43.9 (13.4)	5.5 (3.0)	9.6 (10.7)
Median (min, max)	41.0 (25.0, 80.0)	4.0 (3.0, 19.0)	6.0 (0.0, 86.0)

Source. Reviewer's analysis based on adsl.xpt and adpk.xpt for Study MEDI-MM36-206, and adsl.xpt and adqs.xpt for Study MEDI-MM36-302
[a] For Study 206, if BSA affected decreased during treatment period, the same amount of study medication defined at baseline would continue to be applied; if overall BSA affected worsened, additional study medication would be applied to cover the increased affected BSA
Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; IGA-AD, Investigator's Global Assessment for Atopic Dermatitis; N, number of subjects; OLE, open-label extension; PK, pharmacokinetic; SD, standard deviation

Dosing Trend of Difamilast Ointment, 1% – Study 206 Versus Study 302:

A comparison of average daily dose of difamilast ointment, 1% (g) for the maximal use and phase 3 trial populations is summarized below in Table 6. In general, larger doses were administered in Study 206 compared to Study 302. A brief descriptive summary of the dosing trend for each population is provided below:

- **Study 206:** Approximately 83% (24/29) of subjects applied *at least* 5 g ointment per day, with a mean (SD) daily ointment administration of 8.5 (4.2) g, ranging from 3.3 to 23.3 g per day. This corresponded to a mean (SD) of approximately 42.7 (21.1) mg difamilast per dose application (range: 16.7 to 117 mg).
- **Study 302 (Overall Population):** Nearly 83% (324/389) of subjects applied *less than* 5 g ointment per day, with a mean (SD) daily ointment administration of 3.0 (3.2) g, ranging from 0.1 to 31.2 g per day. This corresponded to a mean (SD) of approximately 14.8 (16.2) mg difamilast per dose application (range: 0.7 to 156 mg).
- **Study 302 (QTc Sub-Study):** Approximately 93% (28/30) of subjects applied *less than* 5 g ointment per day, with a mean (SD) daily ointment administration of 1.8 (1.8) g, ranging from 0.2 to 7.5 g per day. This corresponded to a mean (SD) of approximately 9.0 (8.8) mg difamilast per dose application (range: 1.2 to 37.5 mg).

Table 6: Average Daily Dosing Trend of Difamilast Ointment, 1%: MEDI-MM36-206 (Maximal Use Trial) Versus MEDI-MM36-302 (Phase 3 OLE Trial)

	MEDI-MM36-206	MEDI-MM36-302	
Average Daily Dose (g ointment)[a]	PK Population (N, %)	QTc Sub-Study (N, %)	Safety Population (N, %)[b]
<1 g	0	12 (40.0%)	86 (22.1%)
1 to <3 g	0	12 (40.0%)	178 (45.8%)
3 to <5 g	5 (17.2%)	4 (13.3%)	60 (15.4%)
5 to <7 g	8 (27.6%)	1 (3.3%)	32 (8.2%)
7 to <9 g	4 (13.8%)	1 (3.3%)	17 (4.4%)
9 to <11 g	7 (24.1%)	0	7 (1.8%)
11 to <13 g	1 (3.4%)	0	2 (0.5%)
13 to <15 g	2 (6.9%)	0	2 (0.5%)
15 to <17 g	1 (3.4%)	0	1 (0.3%)
>17 g	1 (3.4%)	0	4 (1.0%)
Total	29 (100%)	30 (100%)	389 (100%)

Source: Reviewer's analysis based on adpk.xpt for Study MEDI-MM36-206 and adpk.xpt and adsl.xpt for Study MEDI-MM36-302
[a] Average daily dose calculated based on the weight difference of the medication tube between visits; Subjects who did not return all the dispensed study drug tubes were excluded from this calculation
[b] Note that the counts shown for the overall phase 3 population include the 30 subjects enrolled the QTc sub-study
Abbreviations: N, number of subjects; OLE, open-label extension; PK, pharmacokinetic

PK Findings for Difamilast and Metabolites – Study 206 Versus Study 302:

A summary of PK parameters derived at Day 1 and at steady state for difamilast and its major metabolites (MAP-15484, MAP-15485, and MAP-15497) is provided below for Studies 206 and 302 in Table 7 and Table 8, respectively. Of note, PK sampling was only completed through 8 hours post-dose in Trial 206, precluding the calculation of $AUC_{0\text{-}12h}$. Given that difamilast ointment, 1%, is administered with a dosing interval of BID (i.e., Q12H), plasma concentrations at pre-dose and 12 hours post-dose are theoretically equivalent at steady-state. Therefore, to facilitate cross-study comparison of AUC between Trials 206 and 302, noncompartmental analysis (NCA) was used to estimate the steady-state $AUC_{0\text{-}12h}$ for pediatric subjects in the maximal use trial via extrapolation, whereby plasma concentration at 12 hours post-dose for each subject was set to the pre-dose concentration at Day 15.

In both trials, exposure of the parent drug was lower at Days 15/29 (steady state) compared to Day 1, whereas approximately 2- to 4-fold accumulation of the metabolites was observed based on C_{max} and AUC. Overall, nominal systemic exposure of difamilast was substantially higher in the maximal use trial, with approximately 22-, 20-, and 11-fold higher mean steady-state C_{max}, $AUC_{0\text{-}12h}$, and C_{trough} values, respectively, compared to the phase 3 PK sub-study. Metabolite exposure was also notably higher in Trial 206 compared to Trial 302, although deficiencies with the bioanalytical assay used to determine metabolite plasma concentrations in Trial 206 preclude a more detailed comparison. Refer to Section 17.4.4 for additional details regarding bioanalytical method validation and performance across the clinical pharmacology program.

Table 7: Summary of PK Parameters for Difamilast and Metabolites Following Administration of Difamilast Ointment, 1%, Under Maximal Use Conditions (MEDI-MM36-206; PK Population)[a]

	Analyte							
Study Day	Difamilast		MAP-15484		MAP-15485		MAP-15497	
PK Parameter[b]	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Day 1 (N=31)								
C_{max} (ng/mL)	31	23.1 (23.4)	31	1.25 (1.10)	31	3.68 (3.51)	31	6.03 (6.07)
AUC_{0-8h} (ng*h/mL)	31	107 (94.1)	31	4.78 (4.71)	31	17.2 (18.5)	31	29.0 (35.4)
Day 15 (N=29)								
C_{max} (ng/mL)	29	16.9 (21.9)	29	2.79 (1.60)	29	5.88 (4.32)	29	8.40 (7.92)
AUC_{0-8h} (ng*h/mL)	29	86.2 (79.6)	29	16.2 (9.35)	29	35.1 (26.8)	29	49.1 (49.5)
AUC_{0-12h} (ng*h/mL)	29	122 (103)	29	26.3 (14.8)	29	55.6 (41.5)	29	76.4 (71.4)
C_{trough} (ng/mL)[c]	29	5.15 (3.53)	29	2.47 (1.66)	29	4.11 (3.16)	29	5.39 (4.17)

Source. Reviewer's analysis based on adpc.xpt and adpk.xpt for Study MEDI-MM36-206
[a] Maximal use conditions defined as topical application of difamilast ointment, 1%, BID to ≥35% BSA for subjects 2 to less than 12 years of age and ≥25% BSA for those 12 to less than 18 years of age
[b] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[c] Steady-state AUC0-12h estimated based on extrapolation of pre-dose concentration at Day 15 to the plasma concentration at 12 hours post-dose
[d] Pre-dose plasma concentration on Day 15
Abbreviations: AUC_{0-8h}, area under the plasma concentration-time curve from 0 to 8 hours; AUC_{0-12h}, AUC from 0 to 12 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

Table 8: Summary of PK Parameters for Difamilast and Metabolites Following BID Topical Administration of Difamilast Ointment, 1% (MEDI-MM36-302; PK Sub-Study)

	Analyte							
Study Day	Difamilast		MAP-15484		MAP-15485		MAP-15497	
PK Parameter[a]	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Day 1 (N=31)								
C_{max} (ng/mL)	24	1.28 (1.94)	3	0.25 (0.13)	10	0.19 (0.16)	12	0.22 (0.17)
AUC_{0-12h} (ng*h/mL)	19	9.48 (13.0)	2	1.68 (1.82)	9	1.54 (1.46)	11	1.69 (1.51)
Day 29 (N=30)								
C_{max} (ng/mL)	28	0.76 (1.16)	5	0.58 (0.80)	19	0.24 (0.39)	19	0.28 (0.51)
AUC_{0-12h} (ng*h/mL)	27	6.10 (8.85)	4	7.15 (9.78)	18	2.29 (3.49)	19	2.52 (4.21)
C_{trough} (ng/mL)[b]	30	0.45 (1.03)	30	0.09 (0.33)	30	0.14 (0.33)	30	0.16 (0.42)

Source. Reviewer's analysis based on pc.xpt and adpk.xpt for Study MEDI-MM36-302
[a] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL for difamilast, MAP-15485, and MAP-15497; 0.125 ng/mL for MAP-15484) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Pre-dose plasma concentration on Day 29
Abbreviations: AUC_{0-8h}, area under the plasma concentration-time curve from 0 to 8 hours; AUC_{0-12h}, AUC from 0 to 12 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

Adequacy of the Maximal Use Trial to Support Systemic Safety – Overall Assessment:

Administration of difamilast ointment, 1%, under maximal use conditions in Study 206 appeared to be well-tolerated, with few treatment-emergent adverse events (TEAEs), no SAEs, and a generally favorable safety profile (refer to Section 17.4.1.1). Based on the available dosing trends and PK data derived from Studies 206 and 302, the systemic exposure of difamilast in the typical clinical use scenario is expected to be lower than that observed under maximal use conditions.

Regarding the metabolites, although PK data for MAP-15484, MAP-15485, and MAP-15497 in Study 206 are unreliable due to inadequate assay validation and performance, metabolite

exposure under typical clinical use conditions (i.e., Study 302) can reasonably be expected to be lower than that achieved in Study 206. Furthermore, the Pharmacology/Toxicology discipline did not identify significant safety concerns for any of the metabolites and confirmed the establishment of adequate safety margins based on the pivotal nonclinical animal toxicology studies (refer to Section 5 for additional details regarding the nonclinical program). When considered in tandem with the lack of any clinically significant systemic safety concerns following administration under maximal use conditions, these findings collectively support the safety of the metabolites despite the unreliable PK in Study 206.

Therefore, based on the totality of available evidence, the maximal use trial (Study 206) is supportive of systemic safety at expected therapeutic exposures following administration of difamilast ointment, 1%, under typical clinical use conditions. Refer to Section 8.2 for additional discussion of safety data of difamilast across the broader clinical program.

6.3.2.2. QTc Prolongation

The Applicant did not conduct a dedicated conventional thorough QT/QTc (TQT) trial, contending that such a study would be infeasible because supratherapeutic systemic exposures of difamilast could not be achieved for an adequate assessment of QT liability with topically applied difamilast. Therefore, in lieu of a traditional TQT study, the Agency previously agreed that the QTc assessment for difamilast ointment, 1%, could be based on a QTc sub-study conducted within the phase 3 OLE Trial MEDI-MM36-302 in conjunction with an integrated nonclinical risk assessment. This agreement was contingent on the assumption that the difamilast exposure achieved in the QTc sub-study would be representative of the expected therapeutic exposures in the typical clinical use scenario.

However, as discussed in Section 6.3.2.1, the mean BSA involvement and predicted difamilast dose were both nearly 40 to 50% lower for subjects included in the QTc sub-study relative to those included in the overall phase 3 population for Study 302. Given these considerations, the Interdisciplinary Review Team for Cardiac Safety Studies (IRT-CS) concluded that the QTc sub-study does not represent the intended patient population and that the effects on the QTc interval following administration of difamilast ointment, 1%, have not been adequately evaluated. As a result, the IRT-CS recommended that the Agency issue a PMR to the Applicant to conduct a dedicated QTc study to address this deficiency. Additionally, until this study has been completed and the effects on the QTc interval sufficiently characterized, the IRT-CS recommended inclusion of labeling statements to describe the inadequate characterization of the QTc interval (refer to the IRT-CS QT Study Review dated July 22, 2025 [DARRTS Reference ID: 5628165]).

However, following inter-disciplinary discussion and risk assessment based on the totality of available clinical, nonclinical, and clinical pharmacology data, it was ultimately concluded that a dedicated QTc study was not necessary for this topical product. Refer to Section 8.2.4 for additional details.

6.3.2.3. Therapeutic Individualization

6.3.2.3.1. Intrinsic Factors

No dedicated clinical studies were completed to investigate the potential impact of intrinsic factors, such as age, race, sex, or organ impairment (i.e., renal and hepatic impairment), on the safety, efficacy, or PK of difamilast following administration of difamilast ointment, 1%. However, this reviewer conducted cross-study analyses to compare systemic exposure of difamilast across patient populations to evaluate the potential need for therapeutic individualization based on these intrinsic factors. Additionally, in response to an information request issued by the Agency on July 23, 2025, the Applicant conducted and submitted analyses to evaluate the potential relationship between baseline markers of both renal impairment (i.e., serum creatinine [SCr], creatinine clearance [CrCl], and estimated glomerular filtration rate [eGFR]) and hepatic impairment (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, and alkaline phosphatase [ALP]) on the PK of difamilast and its major metabolites MAP-15484, MAP-15485, and MAP-15497.

Based on cross-study PK comparison, higher difamilast exposure was observed in pediatric subjects, females, and Asians, relative to adults, males, and non-Asians, respectively. However, based on the totality of safety data, these PK differences are not expected to result in a clinically meaningful impact on safety and no dosage adjustments or restrictions are recommended. Regarding organ impairment, there are limited data available for the use of difamilast ointment, 1%, in subjects with reduced renal and/or hepatic function. Based on post hoc exploratory analyses, which were conducted based on the pooled PK population across six clinical pharmacology studies, no clinically meaningful differences in difamilast PK or safety events are anticipated for subjects with baseline renal or hepatic impairment and no specific dosing recommendations or restrictions are recommended.

6.3.2.3.1.1. Age

The proposed population for topical difamilast ointment, 1%, includes treatment of adults and pediatric patients 2 years of age and older with mild-to-moderate AD. Across the clinical program, difamilast PK has been assessed following topical administration of various ointment strengths in subjects with AD ranging from 2 to 70 years of age (Table 9).

Table 9: Summary of PK Assessment in Subjects With AD Across Clinical Pharmacology Studies, Stratified by Age Sub-Group (PK Populations)

	Age Sub-Group				
Study ID	**2 to <6 yr**	**6 to <12 yr**	**12 to <18 yr**	**≥18 yr**	**Total**
271-12-204	0	0	0	60	60
MEDI-MM36-206	9	15	7	0	31
271-12-205	0	0	0	9	9
271-15-001	0	0	2	123	125
271-102-00002	12	24	9	0	45
MEDI-MM36-302	0	0	0	31	31
Total	21	39	18	223	301

Source. Compiled by reviewer based on CSRs for 271-12-204, MEDI-MM36-206, 271-12-205, 271-15-001, 271-102-00002, and MEDI-MM36-302
Abbreviations: AD, atopic dermatitis; CSR, clinical study report; PK, pharmacokinetic

To assess the impact of age on PK of difamilast, this reviewer compared PK parameters in US pediatric subjects with AD, stratified by age sub-group, derived from the maximal use study MEDI-MM36-206 (Table 10). Additionally, a summary of difamilast PK data following BID administration of difamilast ointment, 1%, in US adult subjects with AD across clinical trials 271-12-205, 271-12-204, and MEDI-MM36-302 is provided in Table 11. Note that due to limited PK sampling in trials MEDI-MM36-206, 271-12-205, and 271-12-204 (Part 2), steady-state $AUC_{0\text{-}12h}$ was estimated for these studies as previously described in Section 6.3.2.1 in order to facilitate cross-study PK comparison.

Among pediatric subjects 2 to <18 years of age from Study 206, children 6 to <12 years of age had the lowest systemic exposure at Day 1, despite having the greatest BSA involvement (47.2%) and receiving the highest predicted topical difamilast dose (61.4 mg per dose application). Conversely, the highest systemic exposure was observed in adolescents 12 to <18 years of age, who had the lowest BSA involvement (36.9%). Dose-normalized PK parameters in the lowest age group (children 2 to <6 years of age) were approximately 2-fold higher relative to the overall study population.

In general, BSA involvement and predicted difamilast doses administered in adult subjects were substantially lower than those of pediatric subjects in Trial 206. The mean predicted topical dose (51.6 mg per dose application) administered in Trial 271-12-204 (Part 2) was notably higher as compared to other adult studies and comparable to that of the overall population in Trial 206 (42.7 mg per dose application). As a result, mean nominal exposure in this trial was similar to that observed in Trial 206, although dose-normalized PK parameters were approximately 2- to 3-fold higher in the overall pediatric population. However, the high nominal exposures in Trial 271-12-204 appeared to be primarily driven by two subjects with substantially higher percent BSA involvement (45% and 66%) and estimated topical difamilast doses (90 mg and 130 mg per dose application) relative to the remaining subjects. For this reason, in addition to the small sample size from this trial, these PK data should be interpreted with caution (refer to Section 17.4.1.3).

Compared to adults in the phase 3 QTc sub-study (MEDI-MM36-302), mean BSA involvement and predicted topical dose were approximately 8- and 5-fold higher, respectively, in pediatric subjects from Trial 206. However, nominal steady-state C_{max}, $AUC_{0\text{-}12h}$, and C_{trough} were 22-, 10-,

and 11-fold higher, respectively, in pediatric subjects from Study 206, indicating a significantly higher than dose-proportional increase in exposure for pediatric subjects relative to adults.

Table 10: Summary of Difamilast PK Parameters Following Administration of Difamilast Ointment, 1%, Under Maximal Use Conditions in US Pediatric Subjects With AD, Stratified by Age Sub-Group (MEDI-MM36-206; PK Population)

	Study MEDI-MM36-206 (Maximal Use PK Study)			
Study Day **PK Parameter[a]**	**2 to 5 yr (N=9)**	**6 to 11 yr (N=15)**	**12 to 17 yr (N=7)**	**Total (N=31)**
Day 1 (No. of subj =31)				
BSA Treated (%)	44.0 (9.0)	47.2 (14.3)	36.9 (15.1)	43.9 (13.4)
Predicted Dose (mg)[b]	26.6 (8.6)	61.4 (56.9)	53.9 (28.7)	49.6 (43.9)
C_{max} (ng/mL)	20.7 (23.0)	19.7 (21.0)	33.3 (28.9)	23.1 (23.4)
$C_{max}N$ (ng/mL/mg)[c]	0.94 (1.20)	0.39 (0.35)	0.78 (0.78)	0.64 (0.79)
AUC_{0-8h} (ng*h/mL)	106 (93.0)	84.1 (71.0)	155 (130)	107 (94.1)
$AUC_{0-8h}N$ (ng*h/mL/mg)[c]	4.82 (4.94)	1.67 (1.05)	3.62 (3.54)	3.02 (3.39)
Day 15 (No. of subj =29)				
BSA Treated (%)	41.5 (5.3)	47.0 (14.8)	36.9 (15.1)	43.0 (13.2)
Predicted Dose (mg)[b]	24.9 (7.4)	47.2 (16.2)	53.9 (28.7)	42.7 (21.1)
C_{max} (ng/mL)	15.3 (10.1)	12.3 (9.4)	28.2 (41.5)	16.9 (21.9)
$C_{max}N$ (ng/mL/mg)[c]	0.74 (0.59)	0.26 (0.16)	0.60 (0.97)	0.48 (0.59)
AUC_{0-8h} (ng*h/mL)	86.9 (53.0)	70.9 (54.4)	116 (135)	86.2 (79.6)
$AUC_{0-8h}N$ (ng*h/mL/mg)[c]	4.18 (3.25)	1.49 (0.91)	2.40 (3.13)	2.45 (2.54)
AUC_{0-12h} (ng*h/mL)[d]	119 (71.3)	105 (76.4)	160 (168)	122 (103)
$AUC_{0-12h}N$ (ng*h/mL/mg)[c,d]	5.70 (4.40)	2.22 (1.26)	3.29 (3.85)	3.44 (3.31)
C_{trough} (ng/mL)[e]	4.86 (2.49)	4.89 (2.87)	6.04 (5.65)	5.16 (3.53)
$C_{trough}N$ (ng/mL/mg)[c,e]	0.23 (0.17)	0.11 (0.06)	0.11 (0.09)	0.14 (0.12)

Source. Reviewer's analysis based on adpc.xpt and adpk.xpt for Study MEDI-MM36-206
[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Reported as predicted difamilast dose administered per application (mg); Calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength (1%)
[c] Normalized according to the predicted difamilast dose (mg) per application
[d] Steady-state AUC0-12h estimated based on extrapolation of pre-dose concentration at Day 15 to the plasma concentration at 12 hours post-dose
[e] Pre-dose trough concentration on Day 15
Abbreviations: AD, atopic dermatitis; AUC_{0-8h}, area under the plasma concentration-time curve from 0 to 8 hours; AUC_{0-12h}, AUC from 0 to 12 hours; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

Table 11: Summary of Difamilast PK Parameters Following BID Dosing of Difamilast Ointment, 1%, in US Adult Subjects With AD, Stratified by Study ID

	Study ID				
Study Day	**271-12-205**	**271-12-204 (N=22)**		**MEDI-MM36-**	**Total**
PK Parameter[a]	**(N=4)**	**Part 1 (N=15)**	**Part 2 (N=7)**	**302 (N=31)**	**(N=57)**
Day 1 (No. of subj =55)					
BSA treated (%)	7.0 (1.4)	5 (0.0)	27.3 (23.0)	5.5 (3.0)	8.3 (10.7)
Predicted dose (mg)[b]	15.6 (3.0)	10 (0.0)	53.3 (45.6)	10.4 (11.7)	16.1 (223)
C_{max} (ng/mL)	4.74 (5.51)	2.15 (2.64)	30.9 (33.7)	1.28 (1.94)	5.53 (14.9)
$C_{max}N$ (ng/mL/mg)[c]	0.27 (0.29)	0.22 (0.27)	0.53 (0.62)	0.14 (0.17)	0.22 (0.31)
AUC_{0-12h} (ng*h/mL)	NC	14.0 (10.3)	NC	9.48 (13.0)	11.2 (12.1)
$AUC_{0-12h}N$ (ng*h/mL/mg)[c]	NC	1.40 (1.03)	NC	1.07 (0.92)	1.19 (0.96)

Study Day PK Parameter[a]	Study ID 271-12-205 (N=4)	271-12-204 (N=22) Part 1 (N=15)	271-12-204 (N=22) Part 2 (N=7)	MEDI-MM36-302 (N=31)	Total (N=57)
Day 28/29 (No. of subj =55)					
BSA treated (%)	7.0 (1.4)	5 (0.0)	26.8 (23.4)	5.0 (1.6)	7.7 (10.2)
Predicted dose (mg)[b]	16.7 (2.0)	10 (0.0)	51.6 (47.1)	9.0 (8.8)	14.9 (21.1)
C_{max} (ng/mL)	1.38 (0.55)	3.69 (3.51)	11.0 (14.3)	0.76 (1.16)	2.77 (5.87)
$C_{max}N$ (ng/mL/mg)[c]	0.08 (0.03)	0.37 (0.35)	0.19 (0.18)	0.12 (0.16)	0.19 (0.24)
$AUC_{0\text{-}12h}$ (ng*h/mL)[d]	13.3 (5.0)	23.1 (15.8)	91.3 (135)	6.10 (8.85)	21.3 (51.9)
$AUC_{0\text{-}12h}N$ (ng*h/mL/mg)[c,d]	0.81 (0.32)	2.31 (1.58)	1.35 (1.37)	0.99 (1.23)	1.36 (1.40)
C_{trough} (ng/mL)[d]	1.18 (0.39)	2.85 (3.20)	4.90 (9.16)	0.45 (1.03)	1.64 (3.66)
$C_{trough}N$ (ng/mL/mg)[c,e]	0.07 (0.03)	0.29 (0.32)	0.06 (0.10)	0.054 (0.07)	0.12 (0.20)

Source. Reviewer's analysis based on CSRs for Study 271-12-205 (PKT-3 [pg. 576]; PKT-12 [pg. 585]) and Study 271-12-204 (PKT-2 [pg. 557]; PKT-4, [pg. 559]; PKT-21 through PKT-26 [pg. 576-583]), and adpc.xpt and adpk.xpt for Study MEDI-MM36-206
[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the assay LLOQ (0.200 ng/mL for Studies 271-12-205 and 271-12-204; 0.050 ng/mL for Study MEDI-MM36-302) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Reported as predicted dose of difamilast administered per application (mg); In Studies 271-12-205, MEDI-MM36-302, and 271-12-204 (Part 2), this was calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength (1%); In Study 271-12-204 (Part 1), predicted dose was calculated based on assumption of approximately 1 g ointment per 5% BSA
[c] Normalized according to the predicted topical dose of difamilast (mg) per application
[d] Steady-state AUC0-12h estimated for Studies 271-12-205 and 271-12-204 (Part 2) based on extrapolation of pre-dose concentration at Day 28 to the plasma concentration at 12 hours post-dose
[e] Pre-dose trough concentration on Day 28 (271-12-205 and 271-12-204) or Day 29 (MEDI-MM36-302)
Abbreviations: AD, atopic dermatitis; $AUC_{0\text{-}8h}$, area under the plasma concentration-time curve from 0 to 8 hours; $AUC_{0\text{-}12h}$, AUC from 0 to 12 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; NC, not calculable; PK, pharmacokinetics; SD, standard deviation

Overall, there was not a clear age-dependent trend in difamilast PK across age sub-groups in pediatric subjects 2 to <18 years of age. However, nominal systemic exposure was substantially higher in pediatric subjects as compared to adults. Furthermore, following dose-normalization, pediatric PK parameters were approximately 2- to 3-fold higher as compared to adults. However, despite these findings, given the favorable safety findings reported for pediatric subjects following administration of difamilast under maximal use conditions in Trial MEDI-MM36-206, the observed age-related PK differences are not expected to confer a clinically meaningful impact on safety and therefore no dosage adjustments or restrictions are recommended based on age.

6.3.2.3.1.2. Sex

To assess the impact of sex on difamilast PK, this reviewer compared PK parameters between US adult male and female subjects enrolled in the QTc sub-study of MEDI-MM36-302 (Table 12). Mean nominal C_{max} and $AUC_{0\text{-}12h}$ were approximately 8- and 5.5-fold higher, respectively, in females compared to males on Day 1. This finding appears to be driven partially by the greater baseline BSA involvement and corresponding administration of approximately 2-fold higher topical doses in females compared to males, although this cannot fully explain the observed PK variability.

Table 12: Summary of Difamilast PK Parameters Following BID Topical Administration of Difamilast Ointment, 1%, in US Adults With AD, Stratified by Sex (Study MEDI-MM36-302)

	Study MEDI-MM36-302 (QTc Sub-Study)					
Study Day	**Males (N=13)**		**Females (N=18)**		**Total (N=31)**	
PK Parameter[a]	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Day 1						
BSA treated (%)	13	4.3 (1.5)	18	6.3 (3.5)	31	5.5 (3.0)
Predicted dose (mg)[b]	13	6.2 (5.8)	18	13.4 (13.9)	31	10.4 (11.7)
C_{max} (ng/mL)	10	0.26 (0.17)	14	2.01 (2.30)	24	1.28 (1.94)
$C_{max}N$ (ng/mL/mg)[c]	10	0.09 (0.09)	14	0.18 (0.20)	24	0.14 (0.17)
$AUC_{0\text{-}12h}$ (ng*h/mL)	7	2.39 (1.26)	12	13.6 (15.0)	19	9.48 (13.0)
$AUC_{0\text{-}12h}N$ (ng*h/mL/mg)[c]	7	0.82 (0.61)	12	1.22 (1.06)	19	1.07 (0.92)
Day 29						
BSA treated (%)	13	4.3 (1.5)	17	5.5 (1.4)	30	5.0 (1.6)
Predicted dose (mg)[b]	13	6.2 (5.8)	17	11.1 (10.1)	30	9.0 (8.8)
C_{max} (ng/mL)	11	0.34 (0.34)	17	1.03 (1.41)	28	0.76 (1.16)
$C_{max}N$ (ng/mL/mg)[c]	11	0.12 (0.20)	17	0.12 (0.13)	28	0.12 (0.16)
$AUC_{0\text{-}12h}$ (ng*h/mL)	11	2.89 (2.55)	16	8.3 (10.9)	27	6.10 (8.85)
$AUC_{0\text{-}12h}N$ (ng*h/mL/mg)[c]	11	1.06 (1.60)	16	0.94 (0.95)	27	0.99 (1.23)
C_{trough} (ng/mL)[d]	13	0.15 (0.19)	17	0.68 (1.33)	30	0.45 (1.03)
$C_{trough}N$ (ng/mL/mg)[c,d]	13	0.05 (0.08)	17	0.06 (0.06)	30	0.05 (0.06)

Source. Reviewer's analysis based on pc.xpt and adpk.xpt for Study MEDI-MM36-302
[a] PK parameters, %BSA treated, and predicted difamilast dose reported as arithmetic mean (SD); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Reported as predicted dose of difamilast administered per application (mg); Calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength (1%)
[c] Normalized according to the predicted topical dose of difamilast (mg) per application
[d] Pre-dose plasma concentration on Day 29
Abbreviations: AD, atopic dermatitis; $AUC_{0\text{-}8h}$, area under the plasma concentration-time curve from 0 to 8 hours; $AUC_{0\text{-}12h}$, AUC from 0 to 12 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

It was noted that observed Day 1 C_{max} values for the two male subjects who received the highest topical difamilast doses of 23.6 and 11.6 mg were only 0.05 and 0.39 ng/mL, respectively, which were substantially lower than those reported in female subjects receiving similar topical doses of 16.6, 19.4, 23.6, and 27.1 mg, for which observed C_{max} values were 7.00, 1.35, 5.53, and 1.4 ng/mL, respectively. These PK findings appear to highlight the extent of inter-individual PK variability of difamilast, as even among female subjects, a clear dose-dependency was not observed for systemic exposure. At Day 29, mean nominal C_{max} and $AUC_{0\text{-}12h}$ were approximately 2- to 3-fold higher in females compared to males, although dose-normalized PK parameters were comparable regardless of sex, suggesting that similar steady-state exposure can generally be expected following administration of similar topical doses.

Difamilast PK was also compared between male and female pediatric subjects enrolled in maximal use Trial 206 (Table 13). Overall, mean BSA involvement was similar between males and females throughout the treatment period. On Day 1, a higher mean nominal exposure was observed in female subjects, despite the application of a nearly 2-fold lower mean topical dose. Additionally, dose-normalized exposure was approximately 2-fold higher in females on Day 1. At steady-state (Day 15), nominal exposure (C_{max}, AUC, and C_{trough}) was slightly higher in male subjects, although dose-normalized PK parameters were comparable regardless of sex, which aligns with findings in adult subjects at steady-state from Study 302.

Table 13: Summary of Difamilast PK Parameters Following Administration of Difamilast Ointment, 1%, Under Maximal Use Conditions in US Pediatric Subjects With AD, Stratified by Sex (MEDI-MM36-206; PK Population)

Study Day	Study MEDI-MM36-206 (Maximal Use PK Study)		
PK Parameter[a]	Males (N=15)	Females (N=16)	Total (N=31)
Day 1			
BSA treated (%)	43.9 (14.2)	44.0 (13.0)	43.9 (13.4)
Predicted dose (mg)[b]	63.1 (59.0)	36.9 (16.0)	49.6 (43.9)
C_{max} (ng/mL)	17.9 (19.4)	27.9 (26.3)	23.1 (23.4)
$C_{max}N$ (ng/mL/mg)[c]	0.42 (0.49)	0.85 (0.97)	0.64 (0.79)
AUC_{0-8h} (ng*h/mL)	97.0 (99.5)	115 (91.0)	107 (94.1)
$AUC_{0-8h}N$ (ng*h/mL/mg)[c]	2.26 (2.57)	3.74 (3.96)	3.02 (3.39)
Day 15			
BSA treated (%)	43.4 (14.6)	42.7 (12.3)	43.0 (13.2)
Predicted dose (mg)[b]	49.1 (24.1)	36.7 (16.5)	42.7 (21.1)
C_{max} (ng/mL)	20.9 (29.6)	13.2 (10.4)	16.9 (21.9)
$C_{max}N$ (ng/mL/mg)[c]	0.47 (0.69)	0.49 (0.51)	0.48 (0.59)
AUC_{0-8h} (ng*h/mL)	99.9 (100)	73.4 (54.2)	86.2 (79.6)
$AUC_{0-8h}N$ (ng*h/mL/mg)[c]	2.15 (2.25)	2.72 (2.83)	2.45 (2.54)
C_{trough} (ng/mL)[d]	5.55 (4.16)	4.79 (2.93)	5.16 (3.53)
$C_{trough}N$ (ng/mL/mg)[c,d]	0.12 (0.08)	0.16 (0.14)	0.14 (0.12)

Source. Reviewer's analysis based on adpc.xpt and adpk.xpt for Study MEDI-MM36-206
[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Reported as predicted difamilast dose administered per application (mg); Calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength (1%)
[c] Normalized according to the predicted difamilast dose (mg) per application
[d] Pre-dose trough concentration on Day 15
Abbreviations: AD, atopic dermatitis; AUC_{0-8h}, area under the plasma concentration-time curve from 0 to 8 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

Overall, based on the totality of data, large PK differences are not expected between male and female subjects with AD, assuming topical administration of similar doses and similar BSA involvement. The 2- to 3-fold higher steady-state exposure observed in females compared to males is not expected to have a clinically meaningful impact on safety, particularly given the favorable safety findings observed at substantially higher exposures in the maximal use PK trial MEDI-MM36-206 (refer to Section 17.4.1.1).

6.3.2.3.1.3. Race

To assess the impact of race on difamilast PK, this reviewer compared steady-state PK parameters (C_{max}, AUC, and C_{trough}) between White, Asian, and Black adult subjects with mild-to-moderate AD, following receipt of difamilast ointment, 1%, BID (Table 14, Table 15). This cross-study analysis included PK data derived from four clinical pharmacology trials, including US trials MEDI-MM36-302, 271-12-205, and 271-12-204, and Japanese trial 271-15-001. Note that due to limited PK sampling in Trials 271-12-205, 271-12-204 (Part 2), and 271-15-001, steady-state AUC_{0-12h} was estimated for these studies as previously described in Section 6.3.2.1 in order to facilitate cross-study PK comparison with Study MEDI-MM36-302.

Table 14: Cross-Study Comparison of Mean (SD) Steady-State Difamilast C_{max} and AUC_{0-12h} Values at Week 4 Following BID Topical Administration of Difamilast Ointment, 1%, in Adult Subjects With AD, Stratified by Subject Race

	Subject Race[b]			
PK Parameter[a]	**White**	**Black**	**Asian**	**Overall**
No. of subjects	37	11	8	56
BSA treated (%)	8.5 (12.0)	5.9 (1.6)	12.0 (6.3)	8.5 (10.1)
Predicted dose (mg)[c]	15.7 (24.3)	10.9 (7.9)	34.6 (13.9)	17.5 (21.8)
C_{max} (ng/mL)	3.25 (6.83)	1.81 (2.10)	7.91 (5.52)	3.63 (6.22)
$C_{max}N$ (ng/mL/mg)[d]	0.21 (0.27)	0.17 (0.18)	0.23 (0.16)	0.20 (0.24)
AUC_{0-12h} (ng*h/mL)[e]	25.0 (61.0)	15.0 (17.9)	70.3 (51.9)	29.7 (55.8)
$AUC_{0-12h}N$ (ng*h/mL/mg)[d,e]	1.43 (1.40)	1.39 (1.57)	2.03 (1.54)	1.51 (1.44)

Source. Reviewer's analysis based on CSRs for Study 271-12-205 (PKT-3 [pg. 576]; PKT-12 [pg. 585]), Study 271-12-204 (PKT-2 [pg. 557]; PKT-4, [pg. 559]; PKT-22 [pg. 578-580]; PKT-24 [pg. 581] PKT-26 [pg. 583]), and Study 271-15-001 (PKT 1.2 [pg. 486]; PKT-2.2 [pg. 490-492]; PKT-3 [pg. 496], and pc.xpt and adpk.xpt for Study MEDI-MM36-302

[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All post-baseline samples below the assay LLOQ (0.200 ng/mL for Studies 271-12-205 and 271-12-204; 0.050 ng/mL for Studies 271-15-001 and MEDI-MM36-302) were imputed to 0 for calculation of PK parameters and descriptive statistics

[b] All subjects were adults with AD who received difamilast ointment, 1% BID for 28 days and had evaluable PK data

[c] Reported as predicted dose of difamilast administered per application (mg); In Studies 271-12-205, MEDI-MM36-302, and 271-12-204 (Part 2), this was calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength (1%); In Study 271-12-204 (Part 1), predicted dose was calculated based on assumption of approximately 1 g ointment per 5% BSA; In Study 271-15-001, predicted dose was calculated based on pre-specified ointment application instructions according to the subject's BSA (0.1 g for BSA <1.0 m^2, 0.15 g for BSA 1 to <1.3 m^2, 0.2 g for BSA 1.3 to <1.6 m^2, 0.25 g for BSA 1.6 to <1.9 m^2, and 0.3 g for BSA ≥1.9 m^2)

[d] Normalized according to the predicted topical dose of difamilast (mg) per application

[e] Steady-state AUC_{0-12h} estimated for Studies 271-12-205, 271-12-204 (Part 2), and 271-15-001 based on extrapolation of pre-dose concentration at Day 28 to the plasma concentration at 12 hours post-dose

Abbreviations: AD, atopic dermatitis; AUC_{0-12h}, area under the plasma concentration-time curve from 0 to 12 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

Table 15: Cross-Study Comparison of Mean (SD) Steady-State Difamilast Trough Concentrations at Week 4 Following BID Topical Administration of Difamilast Ointment, 1%, in Adult Subjects With AD, Stratified by Subject Race

	Subject Race[b]			
PK Parameter[a]	**White**	**Black**	**Asian**	**Overall**
No. of subjects	39	12	52	103
BSA treated (%)	8.3 (11.7)	5.8 (1.6)	18.5 (8.9)	13.1 (11.0)
Predicted dose (mg)[c]	15.2 (23.7)	10.8 (7.5)	45.3 (22.8)	29.9 (26.9)
C_{trough} (ng/mL)	1.92 (4.23)	1.20 (1.70)	5.04 (4.70)	3.41 (4.56)
$C_{trough}N$ (ng/mL/mg)[d]	0.14 (0.23)	0.09 (0.12)	0.12 (0.12)	0.12 (0.17)

Source. Reviewer's analysis based on CSRs for Study 271-12-205 (PKT-3 [pg. 576]; PKT-12 [pg. 585]), 271-12-204 (PKT-2 [pg. 557]; PKT-4 [pg. 559]; PKT-22 [pg. 578-579]; PKT-26 [pg. 583]), and Study 271-15-001 (PKT-2.2 [pg. 490-492]; PKT-5.2 [pg. 502-504]), and pc.xpt and adpk.xpt for Study MEDI-MM36-302

[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All post-baseline samples below the assay LLOQ (0.200 ng/mL for Studies 271-12-205 and 271-12-204; 0.050 ng/mL for Studies 271-15-001 and MEDI-MM36-302) were imputed to 0 for calculation of PK parameters and descriptive statistics

[b] All subjects were adults with AD who received difamilast ointment, 1% BID for 28 days and had evaluable PK data

[c] Reported as predicted dose of difamilast administered per application (mg); In Studies 271-12-205, MEDI-MM36-302, and 271-12-204 (Part 2), this was calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength (1%); In Study 271-12-204 (Part 1), predicted dose was calculated based on assumption of approximately 1 g ointment per 5% BSA; In Study 271-15-001, predicted dose was calculated based on pre-specified ointment application instructions according to the subject's BSA (0.1 g for BSA <1.0 m^2, 0.15 g for BSA 1 to <1.3 m^2, 0.2 g for BSA 1.3 to <1.6 m^2, 0.25 g for BSA 1.6 to <1.9 m^2, and 0.3 g for BSA ≥1.9 m^2)

[d] Normalized according to the predicted topical dose of difamilast (mg) per application

Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA, body surface area; CSR, clinical study report; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

The highest mean nominal systemic exposure was observed in Asian subjects; however, these subjects also had the greatest mean BSA involvement and received the highest topical doses.

Following dose-normalization, C_{max}, $AUC_{0\text{-}12h}$, and C_{trough} were slightly higher in Asians compared to White and Black subjects, but generally comparable to the overall population. Conversely, exposure in Black subjects appeared slightly lower than in Whites, Asians, and the overall population. However, these findings should be interpreted with caution given the relatively low number of Black and Asian subjects with sufficient intensive PK data available for the calculation of C_{max} and AUC. Overall, no clinically meaningful differences in PK are anticipated between White, Black, and Asian subjects.

6.3.2.3.1.4. Renal/Hepatic Impairment

No dedicated studies have been conducted to assess the impact of renal or hepatic impairment on the PK of difamilast and its metabolites. Therefore, an information request was issued to the Applicant to perform cross-study PK analyses of difamilast and metabolites MAP-15484, MAP-15485, and MAP-15497 as a function of baseline renal and hepatic function status, defined according to markers of renal impairment (i.e., SCr, CrCl, and eGFR) and hepatic impairment (i.e., AST, ALT, albumin, ALP), respectively (refer to Clinical Information Amendment submitted by the Applicant, dated September 18, 2025). Per the Applicant, the clinical pharmacology program included a total of six studies from which baseline laboratory assessments of hepatic function (AST, ALT, ALP, and albumin [3 studies]) and renal function (SCr, CrCl, eGFR) were available for these analyses, including Trials MEDI-MM36-206, MEDI-MM36-302, 271-14-001, 271-15-001, 271-12-204 and 271-12-205.

Renal Impairment:

Across the pooled PK population, there were a total of twenty-six subjects with mild (i.e., Grade 1) renal impairment (defined as eGFR 60 to <90 mL/min/1.73m^2) and one subject with moderate (i.e., Grade 2) renal impairment (defined as eGFR 30 to <60 mL/min/1.73m^2) at baseline. Boxplots depicting dose-normalized steady-state PK parameters for difamilast, MAP-15484, MAP-15485, and MAP-15497 according to renal impairment category are depicted below in Figure 1.

According to the limited available data, dose-normalized PK of difamilast and its metabolites appeared to be comparable between renally impaired subjects and those with normal renal function (defined as eGFR ≥90 mL/min/1.73m^2) at baseline. Overall, based on the totality of available data, clinically meaningful differences in PK are not expected in subjects with renal impairment and no dosage adjustment or restrictions are recommended in this population. This conclusion is supported by urine PK data derived from Study 271-14-001, in which urinary concentrations of difamilast and its metabolites were either very low (i.e., f_e <0.1%) or undetectable at all timepoints, suggesting very low fraction of renal elimination (refer to Section 17.4.1.7).

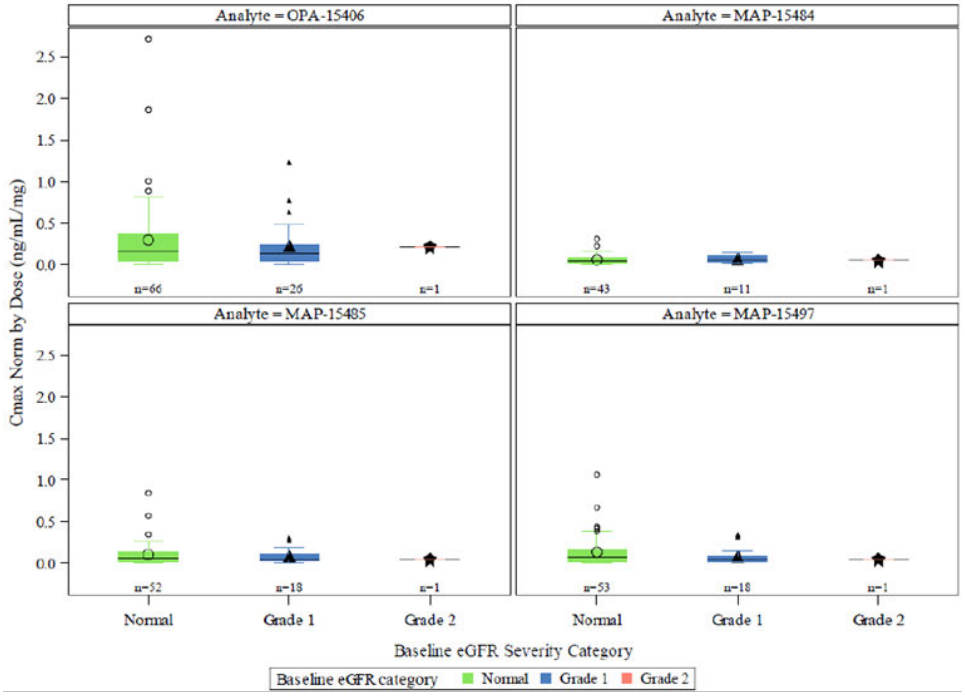
Hepatic Impairment:

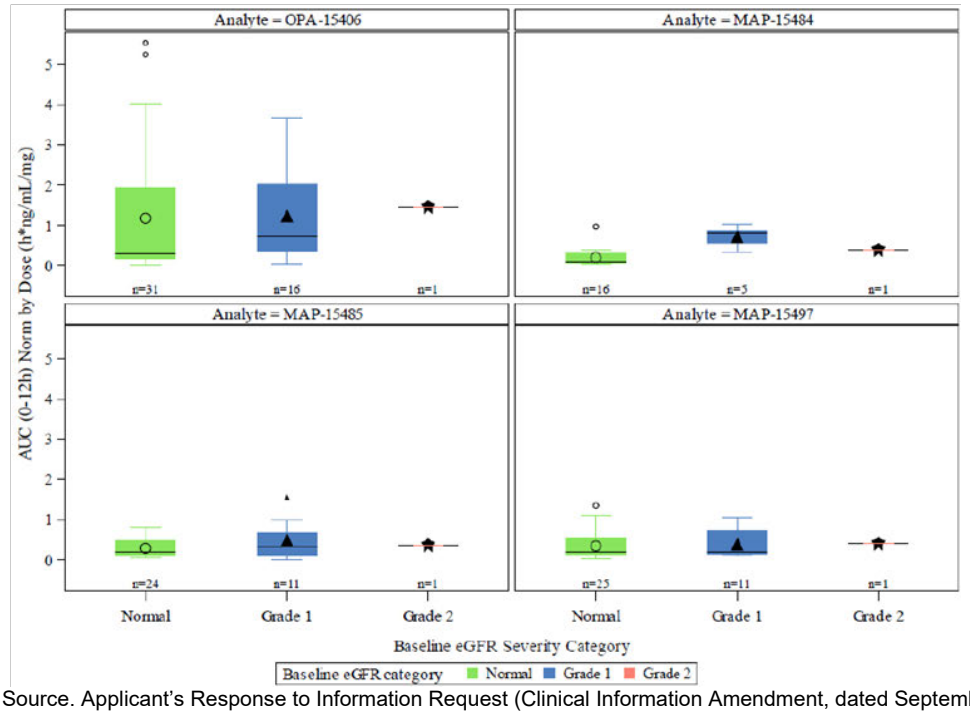
Across the pooled PK population, there were a total of eleven, five, and four subjects with baseline Grade 1 elevations in ALT (defined as >1- to 3-times the upper limit of normal [ULN]),

AST (defined as >1- to 3-times ULN), and ALP (defined as >1- to 2.5-times ULN), respectively, according to Common Terminology Criteria for Adverse Event (CTCAE) scoring. Additionally, a single subject had a Grade 2 elevation in ALT at baseline (defined as >3- to 5-times ULN). No subjects in the pooled analysis dataset had hypoalbuminemia, so the association between albumin and difamilast PK could not be evaluated. Boxplots depicting dose-normalized steady-state PK parameters for difamilast, MAP-15484, MAP-15485, and MAP-15497 according to baseline ALT and AST CTCAE category are depicted below in Figure 2 and Figure 3, respectively.

According to the limited available data, were no notable differences in the dose-normalized PK of difamilast and its metabolites as a function of baseline ALP or ALT. There appeared to be a slight trend of higher difamilast exposure in subjects with Grade 1 increases in AST at baseline, although metabolite exposure was comparable between those with elevated AST to those with normal baseline values. Overall, given the low sample size of subjects with abnormal baseline liver function tests (LFTs), no clear conclusions can be drawn. However, no clinically meaningful increases in difamilast systemic exposure are expected in the setting of hepatic impairment and no dosage adjustment or restrictions are recommended in this population. This is further supported by the totality of available systemic safety data derived from the phase 3 trials, which have demonstrated a generally favorable safety profile for difamilast.

Figure 1: Boxplots of Dose-Normalized $C_{max,ss}$ (Top) and $AUC_{0-12h,ss}$ (Bottom) of Difamilast [OPA-15406], MAP-15484, MAP-15485, and MAP-15497 Versus Baseline eGFR Category[a,b]





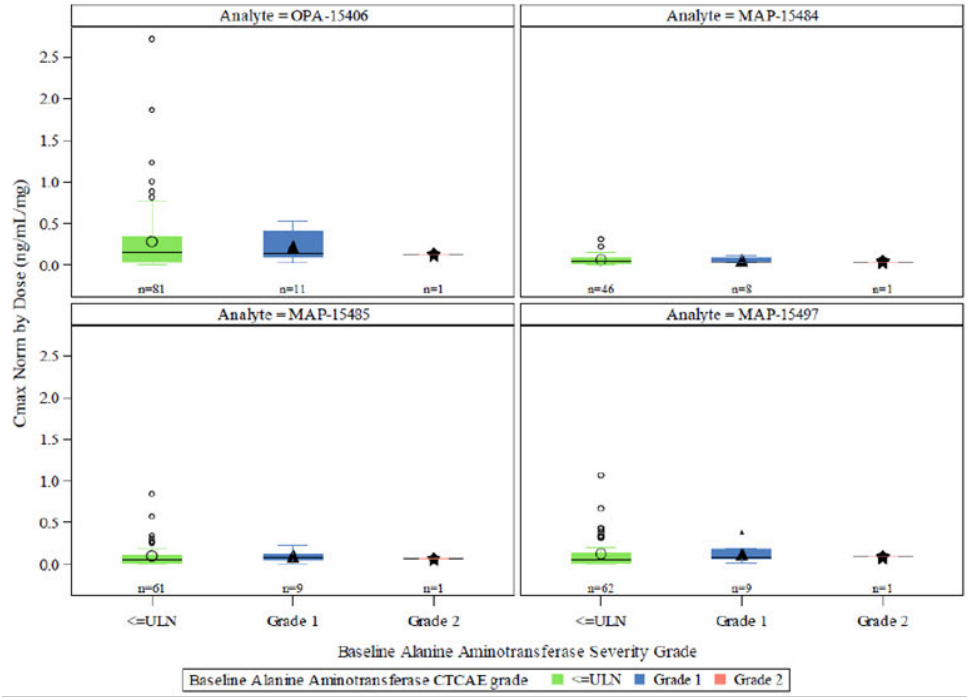
Source. Applicant's Response to Information Request (Clinical Information Amendment, dated September 18, 2025; Figure 3 [pg. 8-9])

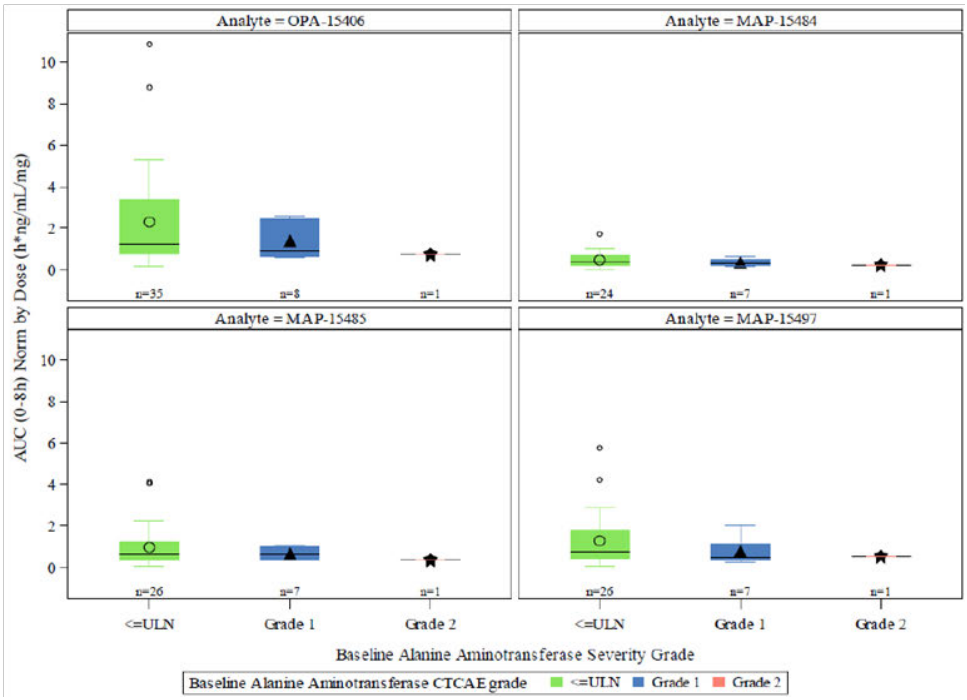
[a] Analyses conducted based on pooled data derived from Studies MEDI-MM36-206, MEDI-MM36-302, 271-14-001, 271-15-001, 271-12-204 and 271-12-205

[b] Normal = eGFR ≥90 mL/min/1.73 m^2; Grade 1 = eGFR 60 to <90 mL/min/1.73 m^2; Grade 2 = eGFR 30 to <60 mL/min/1.73 m^2

Abbreviations: $AUC_{0-12h,ss}$, area under the plasma concentration-time curve from 0 to 12 hours at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; eGFR, estimated glomerular filtration rate; N, number of subjects; OPA-15406, Difamilast

Figure 2: Boxplots of Dose-Normalized $C_{max,ss}$ (Top) and $AUC_{0\text{-}8h,ss}$ (Bottom) of Difamilast [OPA-15406], MAP-15484, MAP-15485, and MAP-15497 Versus Baseline ALT[a,b]





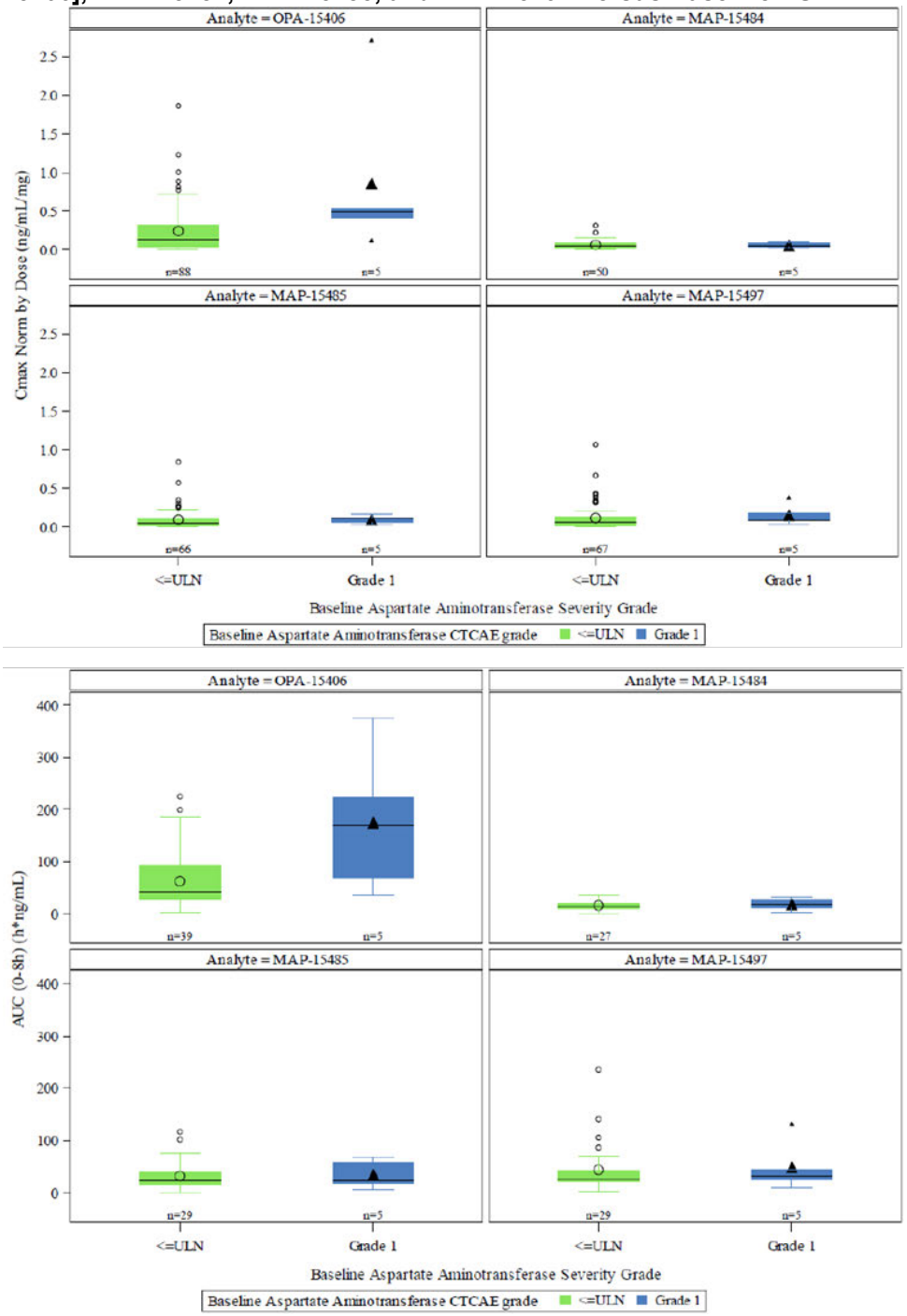
Source. Applicant's Response to Information Request (Clinical Information Amendment, dated September 18, 2025; Figure 1 [pg. 6])

[a] Analyses conducted based on pooled data derived from Studies MEDI-MM36-206, MEDI-MM36-302, 271-14-001, 271-15-001, 271-12-204 and 271-12-205

[b] Grade 1 = ALT >1- to 3-times ULN; Grade 2 = ALT >3- to 5-times ULN

Abbreviations: ALT, alanine aminotransferase; $AUC_{0\text{-}8h,ss}$, area under the plasma concentration-time curve from 0 to 8 hours at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; CTCAE, common terminology criteria for adverse events; eGFR, estimated glomerular filtration rate; N, number of subjects; OPA-15406, Difamilast; ULN, upper limit of normal

Figure 3: Boxplots of Dose-Normalized $C_{max,ss}$ (Top) and $AUC_{0\text{-}8h,ss}$ (Bottom) of Difamilast [OPA-15406], MAP-15484, MAP-15485, and MAP-15497 Versus Baseline AST[a,b]



Source. Applicant's Response to Information Request (Clinical Information Amendment, dated September 18, 2025; Figure 2 [pg. 7])

[a] Analyses conducted based on pooled data derived from Studies MEDI-MM36-206, MEDI-MM36-302, 271-14-001, 271-15-001, 271-12-204 and 271-12-205

[b] Grade 1 = AST >1- to 3-times ULN

Abbreviations: AST, aspartate aminotransferase; $AUC_{0\text{-}8h,ss}$, area under the plasma concentration-time curve from 0 to 8 hours at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; CTCAE, common terminology criteria for adverse events; eGFR, estimated glomerular filtration rate; N, number of subjects; OPA-15406, Difamilast; ULN, upper limit of normal

6.3.2.3.2. Extrinsic Factors

6.3.2.3.2.1. Drug-Drug Interactions

Effects of Difamilast and Major Metabolites on the PK of Other Drugs:

The Applicant conducted a series of in vitro studies to evaluate the potential of difamilast and its major metabolites MAP-15484, MAP-15485, and MAP-15497 to inhibit/induce CYP metabolic enzymes and human uptake and efflux transporters. Clinical DDI risk assessments were performed according to recommendations outlined the M12 Drug Interaction Studies – Guidance for Industry (August 2024). The general criteria for determination of in vivo DDI risk based on in vitro data are summarized below for reversible CYP enzyme inhibition, CYP induction, and transporter inhibition (Table 16).

Table 16: Recommended Criteria and Cutoff Values for Clinical DDI Risk Assessment

In Vitro DDI Evaluation	Guidance-Recommended Criteria and Cutoff Values
Reversible CYP inhibition (basic method)	In vivo DDI risk can be excluded based on in vitro data if: $K_{i,u}$ >50 × $C_{max,u}$ (i.e., $C_{max,u}$/ $K_{i,u}$ <0.02)
CYP induction (basic mRNA fold-change method)	In vivo induction potential cannot be excluded if the drug in hepatocytes from at least one donor meets both of the following criteria: Increases mRNA expression of a CYP enzyme in a concentration-dependent manner; and The fold-change of CYP mRNA expression is greater than or equal to 2-fold at concentrations less than or equal to 50 × $C_{max,u}$
Transporter inhibition	In vivo DDI risk can be excluded based on in vitro data if: P-gp or BCRP: $IC_{50,u}$ >50 × $C_{max,u}$ (i.e., $C_{max,u}$/ $IC_{50,u}$ <0.02)[a] OATP1B1 or OATP1B3: $IC_{50,u}$ >10 × $C_{max,inlet,u}$ (i.e., $C_{max,inlet,u}$/ $IC_{50,u}$ <0.1) OAT1, OAT3, OCT2: $IC_{50,u}$ >10 × $C_{max,u}$ (i.e., $C_{max,u}$/ $IC_{50,u}$ <0.1) MATE1/MATE2-K: $IC_{50,u}$ >50 × $C_{max,u}$ (i.e., $C_{max,u}$/ $IC_{50,u}$ <0.02)

Source. Compiled by reviewer based on M12 Drug Interaction Studies – Guidance for Industry (August 2024)
[a] Note that the cutoff value listed above for inhibition of p-gp/BCRP is indicated for parenterally administered drugs and metabolites formed post-absorption, which differs from the cutoff value recommended for orally administered drugs
Abbreviations: BCRP, breast cancer resistance protein; $C_{max,u}$, unbound C_{max} (maximum plasma concentration) at the highest recommended dose at steady state; $C_{max,inlet,u}$, estimated $C_{max,u}$ of an inhibitor at the liver inlet; CYP, cytochrome P450; DDI, drug-drug interaction; $IC_{50,u}$, unbound half-maximal inhibitor concentration; $K_{i,u}$, unbound inhibition constant; MATE, multidrug and toxin extrusion protein; mRNA, messenger ribonucleic acid; OAT, organic anion transporter; OATP, organic anion transporter polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein

Determination of Worst-Case Scenario for Clinical DDI Risk Assessment

For the purposes of estimating the DDI risk of difamilast as a potential inhibitor of CYP enzymes or transporters, the unbound C_{max} at the highest recommended dose at steady state was used. Since the highest systemic exposure of difamilast and its metabolites was observed in the adolescent sub-population from the maximal use trial MEDI-MM36-206, steady-state PK data from these subjects were used in all subsequent DDI calculations to characterize DDI risk under the potential worst-case scenario.

As previously discussed, significant deficiencies were identified with the validation and performance of the bioanalytical assay used in Study 206 to determine plasma concentrations of MAP-15484, MAP-15485, and MAP-15497. As a result, these metabolite PK data were

considered unreliable to provide an accurate assessment of DDI liability (refer to Section 17.4.4 for additional details related to assessment of bioanalytical methods and performance).

Therefore, to estimate total mean C_{max} for each metabolite in Study 206, the previously determined metabolite: parent molar C_{max} ratios for MAP-15484 (48.5%), MAP-15485 (67.4%), and MAP-15497 (67.8%) to difamilast, which were calculated based on PK data derived from the difamilast ointment, 1%, treatment arm in Study 271-14-001, were applied to the observed steady-state difamilast C_{max} (28.2 ng/mL) in the adolescent sub-population in the maximal use trial. A summary of the estimated total and unbound C_{max} values for difamilast and its metabolites, which were used for all subsequent clinical DDI assessments for this NDA, is provided below in Table 17.

Table 17: Summary of Estimated PK Exposures of Difamilast, MAP-15484, MAP-15485, and MAP-15497 Used to Determine Potential Clinical DDI Risk Under Worst-Case Scenario

Analyte	MW (g/mol)	Fraction Unbound ($f_{u,p}$)	Total Mean C_{max} (ng/mL)	Mean Unbound $C_{max,u}$ (nM)
Difamilast	446.4	0.01	28.2	0.631
MAP-15484	313.2	0.02	9.58	0.611
MAP-15485	418.4	0.01	17.8	0.426
MAP-15497	462.4	0.01	19.8	0.428

Source. Reviewer's analysis based adpk.xpt for Study MEDI-MM36-206 and CSR for Study 271-14-001 (Table 14.1.2.1-5, pg. 387); Protein binding ratios compiled by reviewer based on study reports for in vitro Studies 023081 and 038197
Abbreviations: C_{max}, maximum plasma concentration; $C_{max,u}$, unbound C_{max}; DDI, drug-drug interaction; $f_{u,p}$, fraction unbound in plasma; MW, molecular weight; PK, pharmacokinetic

Inhibition of CYP Enzymes by Difamilast and its Metabolites

The potential for difamilast, MAP-15484, MAP-15485, and MAP-15497 to inhibit various CYP metabolic enzymes, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, was assessed in human hepatic microsomes (Table 18). Additionally, time-dependent inhibition (TDI) of difamilast was evaluated through assessment of percent CYP activity loss with and without pre-incubation with nicotinamide adenine dinucleotide phosphate (NADPH).

Based on the available in vitro data, no risk for reversible inhibition of any of the tested CYP isozymes is anticipated at the expected systemic exposures of difamilast, MAP-15484, MAP-15485, and MAP-15497 following administration of the proposed dosing regimen. Regarding TDI, preliminary data suggested potential for difamilast to exhibit TDI of CYP3A4 and CYP2B6. However, further analysis using the dilution method (i.e., 10-fold) demonstrated no IC_{50} shift, suggesting low probability of difamilast to act as a TDI of these enzymes. Refer to 17.4.2.3 for additional details of the in vitro studies conducted to assess inhibition of CYP enzymes.

Table 18: Summary of In Vitro Inhibition of CYP Enzymes by Difamilast and its Metabolites in Human Hepatic Microsomes

		K_i (µM)	IC_{50} (µM)			
CYP Isozyme	Reaction/CYP Assay	Difamilast	Difamilast	MAP-15484	MAP-15485	MAP-15497
CYP1A2	Phenacetin O-deethylation	1.438	1.888	>30[a]	16.71	>30[a]
CYP2A6	Coumarin 7-hydroxylation	>30[a]	>30[a]	>30[a]	>30[a]	>30[a]
CYP2B6	Bupropion hydroxylation	7.11	5.977	>30[a]	5.737	5.64
CYP2C8	Paclitaxel 6α-hydroxylation	1.284	2.514	>30[a]	1.688	4.656
CYP2C9	Diclofenac 4'-hydroxylation	1.421	2.748	>30[a]	1.233	8.027
CYP2C19	S-Mephenytoin 4'-hydroxylation	2.792	5.438	>30[a]	2.823	12.67
CYP2D6	(±)-Bufuralol 1'-hydroxylation	8.833	15.67	>30[a]	10.07	23.5
CYP2E1	Chlorzoxazone 6-hydroxylation	>30[a]	>30[a]	>30[a]	>30[a]	>30[a]
CYP3A4	Testosterone 6β-hydroxylation	>30[a]	>30[a]	>30[a]	5.197	7.046
CYP3A4	Midazolam 1'-hydroxylation	>30[a]	>30[a]	>30[a]	22.81	27.1

Source. Adapted from Summary of Clinical Pharmacology Studies (Table 2, pg. 14)
[a] Denotes inhibition of <50% at the highest tested concentration of 30 µM
Abbreviations: CYP, cytochrome P450; IC_{50}, half-maximal inhibitor concentration; K_i, inhibition constant

Induction of CYP Enzymes by Difamilast and its Metabolites

The induction potential of difamilast, MAP-15484, MAP-15485, and MAP-15497 on messenger ribonucleic acid (mRNA) expression of CYP1A2, CYP2B6, and CYP3A4 enzymes was assessed in three lots of cryopreserved human hepatocytes. The Applicant also calculated induction parameters (i.e., EC_{50} and E_{max}) for difamilast to further characterize induction profile. Based on these data, clinical risk for induction of CYP enzymes is low at expected systemic exposures of difamilast and its metabolites following administration of the proposed dosing regimen. Refer to Section 17.4.2.3 for additional details of the in vitro studies conducted to assess induction of CYP enzymes.

Inhibition of Human Update and Efflux Transporters by Difamilast and its Metabolites

The potential of difamilast, MAP-15484, MAP-15485, and MAP-15497 to inhibit the transport of known substrates of human uptake and efflux transporters was assessed in cells expressing each human transporter (Table 19).

Based on the available in vitro data, there appears to be low risk for inhibition of any human uptake and efflux transporters at expected systemic exposures of difamilast, MAP-15484, MAP-15485, and MAP-15497 following administration of the proposed dosing regimen. Refer to 17.4.2.5 for additional details of the in vitro studies conducted to assess inhibition of CYP enzymes.

Table 19: Summary of In Vitro Inhibition of Human Update and Efflux Transporters by Difamilast and its Metabolites

		IC_{50} (µM)			
Transporter	**Probe Substrate**	**Difamilast**	**MAP-15484**	**MAP-15485**	**MAP-15497**
P-gp	Quinidine	0.8048	>30[a]	1.139	3.668
BCRP	Prazosin	0.2176	>30[a]	0.2764	0.2579
OATP1B1	Estradiol 17β-D-glucuronide	1.838	22.07	3.256	>30[a]
OATP1B3	Estradiol 17β-D-glucuronide	1.22	17.97	2.544	2.734
OAT1	Aminohippuric acid	>30[a]	1.608	>30	>30[a]
OAT3	Estrone-3-sulfate	6.133	4.882	9.632	>30[a]
OCT1	Metformin	1.443	>30[a]	3.688	>30[a]
OCT2	Metformin	1.032	>30[a]	>30[a]	>30[a]
MATE1	Metformin	1	>30[a]	2.27	0.774
MATE2-K	Metformin	6.433	>30[a]	>30[a]	2.658

Source. Adapted from Summary of Clinical Pharmacology Studies (Table 4, pg. 16)
[a] Denotes inhibition of <50% at the highest tested concentration of 30 µM
Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; IC_{50}, half-maximal inhibitor concentration; K_i, inhibition constant; MATE, multidrug and toxin extrusion protein; OAT, organic anion transporter; OATP, organic anion transporter polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein

Effects of Other Drugs on the PK of Difamilast:

Two CYP enzymes, including CYP3A4 and CYP1A2, are involved in the metabolism of difamilast to form MAP-15485 and MAP-15497, respectively. No dedicated clinical DDI studies were conducted to evaluate the potential impact of coadministration of inhibitors of these enzymes on the PK of difamilast. Instead, the Applicant attempted to characterize the clinical DDI liability of difamilast as a victim drug using a physiologically based pharmacokinetic (PBPK) modeling approach. The PBPK review team concluded that the model was inadequate and, as such, there remained residual uncertainty regarding the clinical significance of these potential interactions (refer to Section 17.4.3). Therefore, a totality of evidence approach was undertaken to provide a comprehensive assessment of potential risks associated with DDI-mediated increases in systemic exposure of difamilast, while minimizing the implementation of unnecessary labeling restrictions.

Systemic Safety in Maximal Use Trial (Study 206)

As discussed in Section 6.3.2.1, nominal systemic exposure of difamilast was substantially higher in the maximal use trial (Study 206) relative to the phase 3 PK sub-study (Study 302), with approximately 22-, 20-, and 11-fold higher mean steady-state C_{max}, $AUC_{0\text{-}12h}$, and C_{trough} values, respectively, in the former compared to the latter. No accumulation was noted following BID dosing in either trial. Additionally, based on safety data derived from Study 206, administration of difamilast ointment, 1%, under maximal use conditions appeared to be generally well-tolerated, with few TEAEs and no significant systemic safety concerns. Since the disease severity, average daily dose, and percent BSA involvement in the target population (i.e., mild-to-moderate AD) are expected to align more closely with those of Study 302 rather than Study 206, the demonstration of safety at the much higher systemic exposure in Study 206 supports the maintenance of safety in a typical patient who may experience elevated difamilast PK due to CYP-mediated DDIs with concomitantly administered medications.

Safety Assessment in Subjects Receiving Strong CYP3A4/1A2 Inhibitors (Phase 2/3 Trials)

The safety profile of subjects who received concomitant administration of difamilast ointment (0.3% or 1%) with strong CYP3A4/1A2 inhibitors was evaluated in comparison to that of the overall population for those randomized to receive difamilast across all completed phase 2 and phase 3 trials, including Studies 271-12-205, MEDI-MM36-206, 271-102-00002, 271-102-00007, 271-102-00008, MEDI-MM36-301, 271-102-320, and MEDI-MM36-302. In total, 49 difamilast-treated subjects were identified as having received treatment with a strong inhibitor of CYP3A4, CYP1A2, or both (Table 20).

Table 20: Summary of Concomitant Use of Strong CYP3A4/1A2 Inhibitors Across Phase 2 and Phase 3 Trials

CYP3A4/1A2 Inhibitor	N	Indication/Reason for Concomitant Use
Clarithromycin	29[a]	To treat infections in 28 subjects (e.g., cold, bronchitis) To treat skin conditions in 3 subjects (e.g., acne, AD)
Ketoconazole	19[a,b]	To treat skin conditions in 18 subjects (e.g., scalp dermatitis) To treat a skin infection, 1 subject (i.e., Paronychia)
Fluvoxamine	3[c]	To treat psychiatric conditions (e.g., adjustment disorder)
Viloxazine	1	Attention-deficit/Hyperactivity Disorder
Fluconazole	1	Reason for use not documented

Source. Adapted from Applicant's Response to Information Request (Information Amendment: Clinical, dated November 24, 2025; Table 5 [pg. 11])
[a] 3 subjects used Ketoconazole and Clarithromycin (Study 271-102- 00007 [Subject (b) (6)]; Study 271-102-00006 [Subjects (b) (6)])
[b] 18 of the 19 subjects used a topical formulation of ketoconazole
[c] 1 subject used Ketoconazole and Fluvoxamine (Study 271-102-00006 [Subject (b) (6)])
Abbreviations: AD, atopic dermatitis; CYP, cytochrome P450; N, number of subjects

Based on these analyses, there was no apparent trend in the type, severity, or incidence of TEAEs for subjects who received inhibitors of these enzymes, nor were there any identified instances of clinically significant changes in laboratory parameters, drug-induced liver injury, or significant organ toxicity. However, it should be noted that concomitant use of clarithromycin (CYP3A4 inhibitor), which is an antibiotic indicated for short-term use, comprised more than half of the DDIs identified. Many of the remaining identified DDIs were due to concomitant treatment with topical ketoconazole (CYP3A4 inhibitor), which is considered unlikely to precipitate interactions due to low systemic absorption. Furthermore, only four subjects had concomitant administration of a strong CYP1A2 inhibitor (3 fluvoxamine, 1 viloxazine). Therefore, these data should be interpreted cautiously and a definitive conclusion regarding safety of difamilast ointment, 1%, in the setting of long-term coadministration of strong CYP3A4/1A2 inhibitors cannot be made.

Safety Assessment According to BSA Involvement and Average Daily Dose

Further safety assessment was conducted to evaluate the frequency and severity of TEAEs according to the extent of drug exposure, which included both average daily dose (grams of ointment) and percent BSA involvement. These safety analyses were conducted based on the pooled safety populations derived from controlled (i.e., 271-12-205, 271-12-00002, 271-12-00007, 271-12-00008, and MEDI-MM36-301) and uncontrolled (i.e., MEDI-MM36-302 and 271-201-00006) phase 2 and phase 3 trials. Both average daily dose and BSA involvement were

stratified by quartiles for the purpose of identifying potential exposure-response relationship(s) for safety signals based on the amount of drug applied. Summary tables of TEAEs according to average daily dose and BSA involvement are provided below in Table 21 and Table 22, respectively, for difamilast- and vehicle-treated subjects enrolled in controlled studies. Additionally, the same analyses for subjects receiving difamilast ointment, 1%, in uncontrolled studies MEDI-MM36-302 and 271-201-00006 is depicted in Table 23.

Table 21: Exposure-Response Analysis for Safety, Stratified by Quartiles of Average Daily Dose (g Ointment; Controlled Studies, Pooled)[a,b]

	Average Daily Dose (g) Quartile			
Treatment Arm TEAE Severity, n (%)	**Q1 (0.11 to <2.72 g)**	**Q2 (2.72 to <4.53 g)**	**Q3 (4.53 to <7.57 g)**	**Q4 (7.57 to ≤35.87 g)**
Difamilast (no. of subj.)[c]	113	107	110	96
Mild	25 (22.1)	17 (15.9)	18 (16.4)	18 (18.8)
Moderate	6 (5.3)	7 (6.5)	6 (5.5)	7 (7.3)
Severe	0	0	2 (1.8)	1 (1.0)
Life-threatening/disabling[d]	1 (0.9)	0	0	0
Total	32 (28.3)	24 (22.4)	26 (23.6)	26 (27.1)
Vehicle (no. of subj.)	89	95	92	106
Mild	16 (18.0)	20 (21.1)	19 (20.7)	25 (23.6)
Moderate	6 (6.7)	5 (5.3)	12 (13.0)	13 (12.3)
Severe	1 (1.1)	1 (1.1)	0	3 (2.8)
Life-threatening/disabling	0	0	0	0
Total	23 (25.8)	26 (27.4)	31 (33.7)	41 (38.7)

Source. Adapted from Applicant's Response to Information Request (Information Amendment: Clinical, dated December 2, 2025; Table 1 [pg. 2])

[a] Safety analysis based on pooled data derived from subjects included in controlled trials (271-12-205, 271-12-00002, 271-12-00007, 271-12-00008, and MEDI-MM36-301)

[b] Participants with missing tube weights were excluded from these safety analyses, as average daily dose could not be calculated for these subjects

[c] Difamilast treatment arm only includes subjects who received the 1% ointment strength

[d] Subject (b) (6) (Study 271-12-205) was diagnosed with a serious TEAE of depression, which resulted in hospitalization for evaluation and treatment. The investigator assessed the event as CTCAE Grade 4 (life-threatening, disabling) and not related to IMP.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; IMP, investigational medicinal product; n, number of subjects reporting a TEAE per quartile; Q, quartile; TEAE, treatment-emergent adverse event

Table 22: Exposure-Response Analysis for Safety, Stratified by Quartiles of Percent BSA Involvement (Controlled Studies, Pooled)[a,b]

Treatment Arm	BSA Involvement (%) Quartile			
TEAE Severity, n (%)	Q1 (5 to <10%)	Q2 (10 to <25%)	Q3 (16 to <25%)	Q4 (25 to ≤40%)
Difamilast (no. of subj.)[b]	107	108	119	95
Mild	12 (11.2)	22 (20.4)	24 (20.2)	20 (21.1)
Moderate	9 (8.4)	5 (4.6)	5 (4.2)	7 (7.4)
Severe	0	1 (0.9)	1 (0.8)	1 (1.1)
Life-threatening/disabling[c]	0	1 (0.9)	0	0
Total	21 (19.6)	29 (26.9)	30 (25.2)	28 (29.5)
Vehicle (no. of subj.)	87	94	93	111
Mild	15 (17.2)	16 (17.0)	24 (25.8)	25 (22.5)
Moderate	6 (6.9)	7 (7.4)	8 (8.6)	16 (14.4)
Severe	1 (1.1)	1 (1.1)	2 (2.2)	1 (0.9)
Life-Threatening/Disabling	0	0	0	0
Total	22 (25.3)	24 (25.5)	34 (36.6)	42 (37.8)

Source. Adapted from Applicant's Response to Information Request (Information Amendment: Clinical, dated December 2, 2025; Table 1 [pg. 2])
[a] Safety analysis based on pooled data derived from subjects included in controlled trials 271-12-205, 271-12-00002, 271-12-00007, 271-12-00008, and MEDI-MM36-301
[b] Difamilast treatment arm only includes subjects who received the 1% ointment strength
[c] Subject (b) (6) (Study 271-12-205) was diagnosed with a serious TEAE of depression, which resulted in hospitalization for evaluation and treatment. The investigator assessed the event as CTCAE Grade 4 (life-threatening, disabling) and not related to IMP.
Abbreviations: BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; IMP, investigational medicinal product; n, number of subjects reporting a TEAE per quartile; Q, quartile; TEAE, treatment-emergent adverse event

Table 23: Exposure-Response Analysis for Safety, Stratified by Quartiles of Average Daily Dose (g Ointment) and Percent BSA Involvement (Uncontrolled Studies, Pooled)[a,b]

Exposure Parameter	Average Daily Dose/BSA Involvement Quartile			
TEAE Severity, n(%)	Q1	Q2	Q3	Q4
Average daily dose (g)[c]	0.14 to <1.31 g	1.31 to <2.45 g	2.45 to <5.29 g	5.29 to ≤31.15 g
No. of Subj.	151	152	153	152
Mild	38 (25.2)	50 (32.9)	52 (34.0)	58 (38.2)
Moderate	25 (16.6)	25 (16.4)	33 (21.6)	38 (25.0)
Severe	1 (0.7)	3 (2.0)	5 (3.3)	2 (1.3)
Total	64 (42.4)	78 (51.3)	90 (58.8)	98 (64.5)
BSA involvement (%)	0 to <4.5%	4.5 to <9%	9 to <21.75%	21.75 to ≤96%
No. of subj.	178	193	202	191
Mild	33 (18.5)	52 (26.9)	69 (34.2)	82 (42.9)
Moderate	33 (18.5)	21 (10.9)	41 (20.3)	51 (26.7)
Severe	1 (0.6)	4 (2.1)	3 (1.5)	5 (2.6)
Total	67 (37.6)	77 (39.9)	113 (55.9)	138 (72.3)

Source. Adapted from Applicant's Response to Information Request (Information Amendment: Clinical, dated December 2, 2025; Table 2 [pg. 3])
[a] Safety analysis based on pooled data derived from subjects included in uncontrolled trials MEDI-MM36-302 and 271-201-00006
[b] All subjects included in these analyses received difamilast ointment, 1% - a total of 98 subjects who initiated treatment with difamilast ointment, 0.3% in Study 271-102-00006 were excluded
[c] A total of 156 subjects were missing average daily dose and were therefore excluded from these safety analyses
Abbreviations: BSA, body surface area; n, number of subjects reporting a TEAE per quartile; Q, quartile; TEAE, treatment-emergent adverse event

Based on evaluation of the controlled trials, there does not appear to be a clear trend in the frequency or severity of TEAEs across quartiles of average daily dose and BSA involvement for difamilast-treated subjects. Within each quartile, the majority of TEAEs were mild or moderate in severity, with few SAEs. Additionally, TEAE incidence for vehicle-treated subjects was comparable to or higher relative to that for subjects receiving difamilast, supporting the

conclusion that safety profile was comparable across the studied range of drug application and BSA involvement.

However, based on analysis of the uncontrolled trials, there was a notable increase in the frequency of TEAEs with higher quartiles of average daily dose and BSA involvement. Of note, this finding appears to have been primarily driven by an increased reporting of TEAEs of dermatitis (atopic), suggesting that many subjects in the upper quartiles experienced a worsening of their underlying disease rather than a true adverse event. Additionally, the average daily dose was calculated based on the summed difference in medication tube weight when dispensed to the subject and later returned to the site over the subject's entire treatment period, whereas actual dose applied may vary over time. Additionally, BSA quartiles were defined according to baseline BSA assessment, which likely fluctuated over the course of these long-term trials. Considering these factors, establishing a definitive correlation between these drug application parameters and safety events is challenging and these data should be interpreted with caution.

Overall Conclusions Regarding Coadministration with CYP3A4/1A2 Inhibitors

Overall, analysis of the safety data generated across the clinical development program did not reveal systemic safety concerns for difamilast ointment, 1%. The absence of effects associated with other approved systemic PDE-4 inhibitors, including psychiatric adverse reactions and weight loss, in both the pediatric and adult patient populations supports a favorable benefit-risk profile. There appears to be a large safety margin associated with topical treatment with difamilast ointment, 1%, such that any potential DDI-mediated increases in difamilast exposure are unlikely to result in a clinically significant increase in safety events. Therefore, based on the totality of evidence, no specific dosing adjustments or restrictions are warranted for subjects receiving inhibitors of CYP3A4 and/or CYP1A2. Refer to Section 8.2 for additional discussion of safety data of difamilast across the broader clinical program.

6.3.2.4. Difamilast Presentations and Formulations

Summary of Formulations Use in Clinical Trials:

The to-be-marketed formulation of difamilast is a 1% topical ointment. Throughout the clinical development program, difamilast was administered as 0.1%, 0.3%, 1%, and 3% topical ointment strengths, although only the 0.3% and 1% ointment strengths were evaluated in phase 3 pivotal efficacy and safety trials. Additionally, difamilast exists as two solid crystalline forms, including (b) (4), the latter of which was developed as a (b) (4) stable polymorphic crystalline form of the former. In general, (b) (4) was used throughout the phase 1 and phase 2 trials, whereas (b) (4) was used in the phase 3 program. Of note, (b) (4) is the intended to-be-marketed commercial drug product, which will be supported by the same manufacturing site, manufacturing method, and equipment used to support the products used in clinical trials ((b) (4)). A summary of the difamilast ointment formulations and strengths used throughout the clinical program is provided below in Table 24.

Table 24: Difamilast Ointment Strengths and Formulations Used Throughout the Clinical Development Program

Development Phase	Study ID	Difamilast Ointment Strength(s)	Crystalline Form
1	271-11-202[a]	0.1%, 0.3%, 1%, 3%	
	271-14-001[a]	0.3%, 1%, 3%	
	271-12-204 (Part 1)[a]		
2	271-12-204 (Part 2)	1%, 3%	(b) (4)
	271-15-001	0.3%, 1%	
	271-12-205		
	271-102-00002		
	MEDI-MM36-206	1%	
3	271-102-00006	0.3%, 1%	
	271-102-00008		
	271-102-00007	1%	(b) (4)
	MEDI-MM36-301		
	MEDI-MM36-302		

Source. Adapted from Summary of Biopharmaceutic Studies (Table 1, pg. 4-5)
[a] All difamilast ointment products used in Studies 271-11-202, 271-14-001, and 271-12-204 (Part 1), were manufactured by Otsuka Pharmaceutical Co., Ltd., whereas drug products in the remaining phase 2 and 3 trials were manufactured by (b) (4) (b) (4).

Bridging Difamilast Formulations: (b) (4) Versus (b) (4):

The Applicant conducted and submitted comparative in vitro dissolution data which demonstrated equivalent drug release between (b) (4) and (b) (4) difamilast ointment, 1%, drug products that were manufactured under identical processing conditions. The dissolution profiles were comparable across all tested lots, supporting that the different crystalline form did not impact drug release characteristics. Furthermore, additional polymorph characterization studies confirmed that (b) (4) is present under the proposed manufacturing conditions, indicating that (b) (4). Collectively, these data were considered sufficient to establish a formulation bridge between (b) (4) and (b) (4) and the risk of impact on product quality or performance is considered low. Refer to the Office of Pharmaceutical Quality (OPQ) review in Panorama, dated February 9, 2026, for additional details regarding the biopharmaceutic and chemistry, manufacturing, and controls (CMC) data submitted to support formulation bridging.

6.3.2.5. Mass Balance Study

The Applicant did not conduct a mass balance study in humans. An information request was issued in the 74-day letter to the Applicant to provide justification that the absorption, distribution, metabolism, and excretion (ADME) of difamilast ointment, 1%, were adequately characterized without conducting this study (refer to Filing Issues Identified Letter dated April 28, 2025 [DARRTS Reference ID: 5579876]). In the Applicant's response to the 74-day letter dated June 5, 2025, they included the requested justifications based on clinical data, as described below.

In Study 271-14-001, plasma and urinary concentrations of difamilast and five metabolites, including MAP-15484, MAP-15485, MAP-15497, MAP-15583, and MAP-15585, were evaluated in healthy Japanese adult subjects following topical administration of difamilast ointment (0.3%, 1%, and 3% strengths) BID for 14 days. Based on the resulting molar $AUC_{0\text{-}12h}$ ratios of each individual analyte to the total AUC of all quantifiable analytes, the major metabolites in the plasma were MAP-15484, MAP-15485, and MAP-15497, all of which accounted for greater than 10% of the total drug-related exposure. Furthermore, relative to the parent drug, molar $AUC_{0\text{-}12h}$ ratios for MAP-15484, MAP-15485, and MAP-15497 were 41.9%, 63.5%, and 66.3%, respectively. Regarding the minor metabolites, MAP-15583 accounted for less than 6% of the AUC of all compounds detected, while MAP-15585 was undetectable in all plasma samples analyzed (lower limit of quantitation [LLOQ] of 0.500 ng/mL).

Regarding urine PK findings, difamilast and MAP-15485 were undetectable in urine samples at all timepoints (LLOQ 0.200 ng/mL). Additionally, urinary excretion of all other metabolites was less than 0.1% of the administered dose for all subjects following both single- and multiple-dose administration, supporting the Applicant's claim of minimal renal elimination of difamilast and its metabolites following topical administration. Refer to Section 17.4.1.7 for additional details regarding the study design and PK results from Study 271-14-001.

Based on these data, the Applicant contended that (1) the major metabolites of difamilast (i.e., MAP-15484, MAP-15485, and MAP-15497) could be inferred, and that (2) it could be concluded that excretion occurred primarily via metabolism and fecal elimination with minimal contribution by renal pathways, without the completion of a dedicated clinical mass balance study. Overall, these justifications are reasonable from a clinical pharmacology perspective.

7 Sources of Clinical Data and Review Strategy

7.1.Table of Clinical Studies

Table 25: Listing of Clinical Trials Relevant to This NDA

Trial Identity	NCT No.	Trial Design	Regimen/Schedule	Study Endpoints	Treatment Duration	No. of Subjects	Study Population	Countries, No. Sites
Controlled trials to support efficacy and safety								
271-12-205	02068352	MC, R, DB, VC, PG	0.3%, 1%, or vehicle twice daily	Efficacy, safety, tolerability, PK	8 weeks	121	≥10 to ≤70 years of age with AD	United States, Australia, Poland, 30
271-15-001	02914548	MC, R, DB, VC	0.3%, 1%, or vehicle twice daily for	Efficacy, safety, PK	8 weeks	200	≥15 to ≤70 years of age with AD	Japan, 3
271-102-00002	03018691	MC, R, DB, VC	0.3%, 1%, or vehicle twice daily	Safety, efficacy, PK	4 weeks	73	≥2 to ≤14 years of age with AD	Japan, 8
271-102-00007	03908970	MC, R, DB, VC	1% or vehicle twice daily	Efficacy, safety	4 weeks	364	≥15 to ≤70 years of age with AD	Japan, 30
271-102-00008	03911401	MC, R, DB, VC	0.3%, 1%, or vehicle twice daily	Efficacy, safety, dose response	4 weeks	251	≥2 to ≤14 years of age with AD	Japan, 30
Long term open-label trials to support safety								
271-102-00006	03961529	OL, UC, LTS	0.3% or 1% or vehicle twice daily	Efficacy, safety, tolerability	52 weeks	366	≥2 to ≤71 years of age with AD	Japan, 37
MEDI-MM36-302	05571943	OL, UC, LTS	1% twice daily	Efficacy, safety, tolerability	52 weeks	542	≥2 years of age with AD	United States, 63
Other trial pertinent to the review of treatment effect								
US-MEDI-MM36-301	05571943	MC, R, DB, VC	1% or vehicle twice daily	Efficacy, safety, tolerability	4 weeks	153	≥2 years of age with AD	United States, 35

Abbreviations: AD, atopic dermatitis; DB, double-blind; LTS, long-term safety; MC, multicenter; OL, open-label; PG, parallel-group; R, randomized; UC, uncontrolled; VC, vehicle-controlled

7.2.Review Strategy

Refer to Section 8.1 for statistical review approach and Section 8.2.1 for the safety review approach.

8 Statistical and Clinical and Evaluation

8.1.Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Phase 2 Trials (Trials 271-12-205, 271-15-001, and 271-102-00002)

8.1.1.1.Trial Design and Endpoints

Three phase 2 trials (271-12-205, 271-15-001, and 271-102-00002) were conducted to evaluate the efficacy of difamilast ointment (also known as OPA-15406). Trial 271-12-205 was a multinational trial that enrolled subjects from Australia, Poland, and the United States. Trials 271-15-001 and 271-102-00002 were conducted exclusively in Japan. The key inclusion criteria that defined the study populations were as follows:

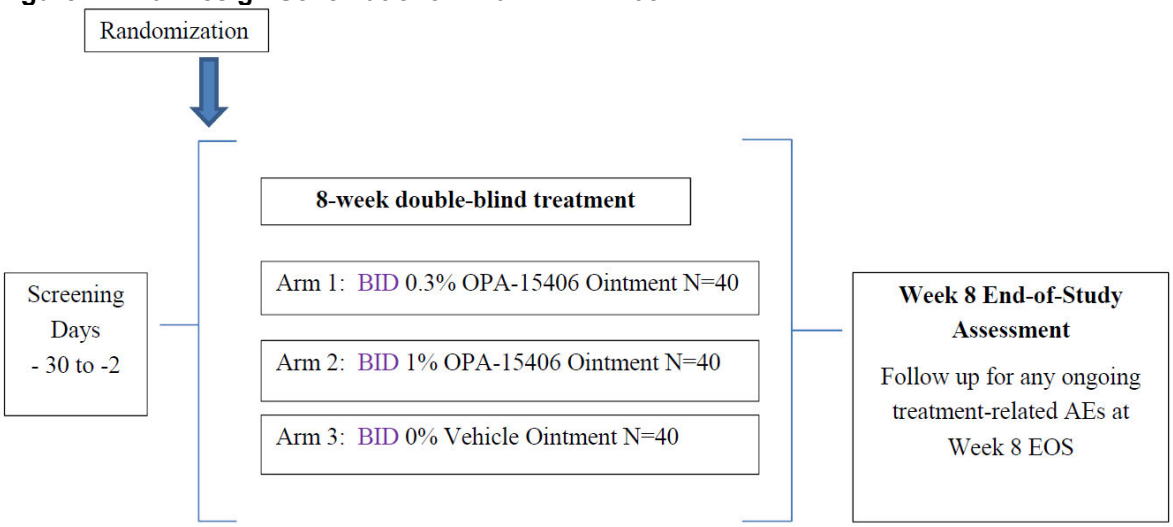
- Male or female
- Age:
  - Trial 271-12-205: 10 to 70 years
  - Trial 271-15-001: 15 to 70 years
  - Trial 271-102-00002: 2 to 14 years
- Diagnosis of atopic dermatitis based upon the criteria of Hanifin and Rajka
- History of AD:
  - Trial 271-12-205: 3 years
  - Trial 271-15-001: 3 years
  - Trial 271-102-00002: not specified
- AD affecting ≥5% to ≤40% of BSA. The protocol for Trial 271-12-205 specified excluding the face, neck, and head from the BSA calculation for enrollment.
- IGA score of 2 (mild) or 3 (moderate)

Figure 4, Figure 5, and Figure 6 present the trial design schematics for Trials 271-12-205, 271-15-001, and 271-102-00002, respectively. All three trials were randomized, multicenter, double-blind, vehicle-controlled, parallel-group, phase 2 trials.

For all three phase 2 trials, subjects were enrolled and randomized in a 1:1:1 ratio to receive either difamilast ointment, 0.3%, difamilast ointment, 1% or vehicle ointment. The randomization for Trial 271-12-205 was stratified by region (North America, Europe, and Australia) and age group (<18 years and ≥18 years). The planned total sample sizes were 120 subjects (Trial 271-12-205), 180 subjects (Trial 271-15-001), and 60 subjects (Trial 271-102-00002).

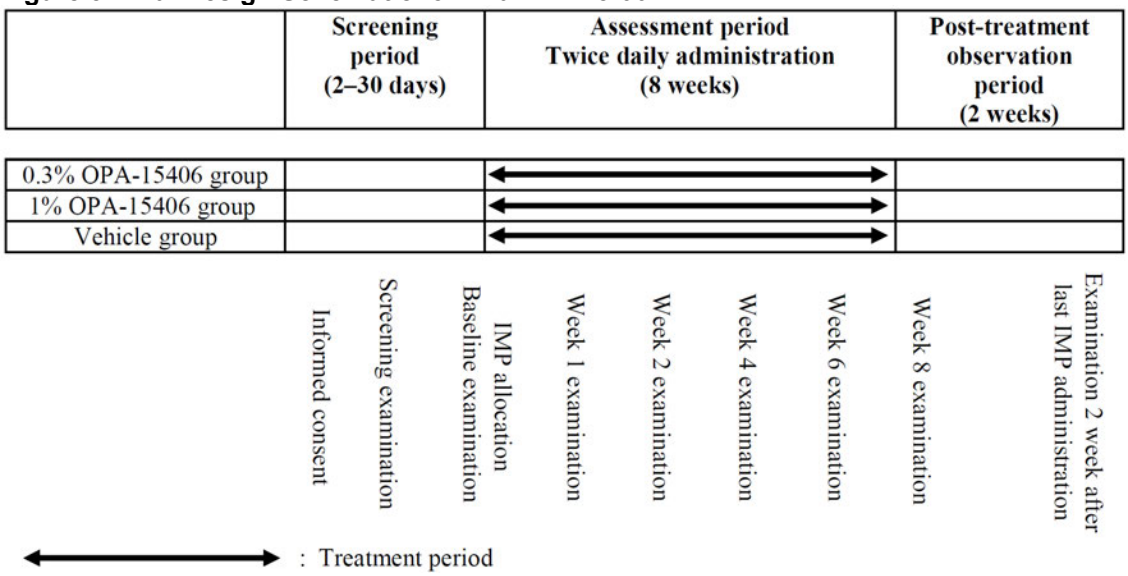
For all three trials, a thin layer of study drug was applied to affected areas twice daily (morning and night, approximately 12 hours apart). The treatment duration was 8 weeks for Trials 271-12-205 and 271-15-001, and 4 weeks for Trial 271-102-00002. For 271-12-205 and 271-15-001, subjects were scheduled to have the following study visits: screening, baseline (Day 1), and Weeks 1, 2, 4, 6, and 8. For Trial 271-102-00002, subjects were scheduled to have the following study visits: screening, baseline, and Weeks 1, 2, and 4.

Figure 4: Trial Design Schematic for Trial 271-12-205



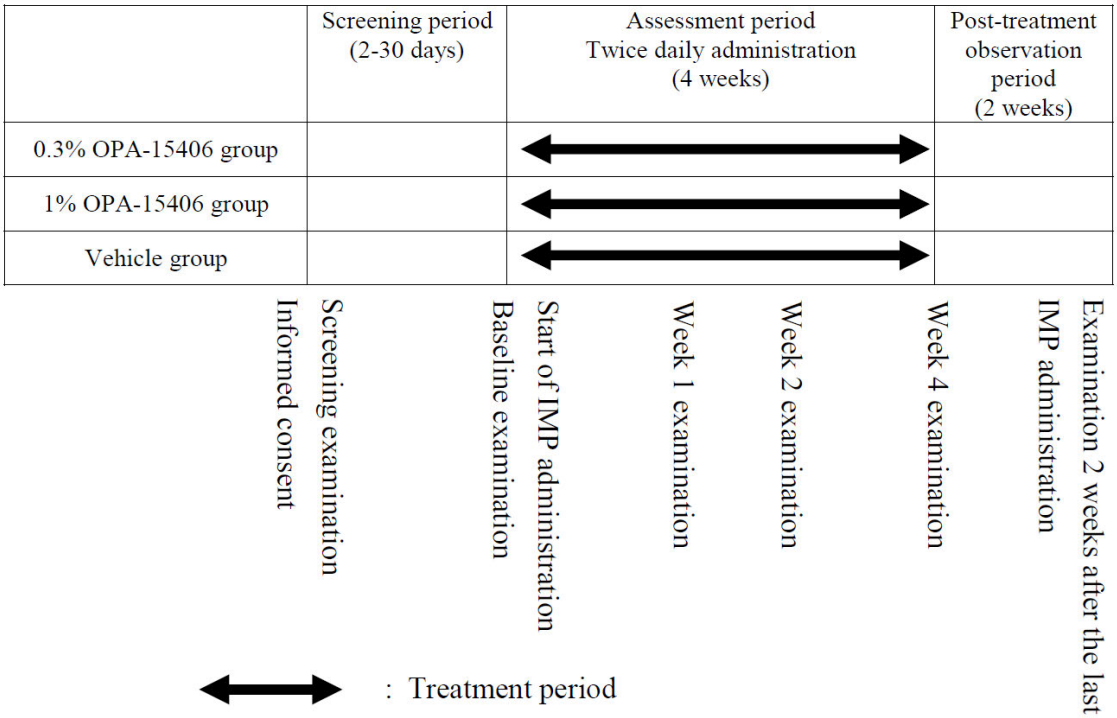
Source: page 33 of the protocol for Trial 271-12-205.
Abbreviations: AE, adverse event; BID, twice daily; EOS, end-of-study

Figure 5: Trial Design Schematic for Trial 271-15-001



Source: page 29 of the protocol for Trial 271-15-001.
Abbreviations: IMP, investigational medicinal product

Figure 6: Trial Design Schematic for Trial 271-102-00002



Source: page 32 of the protocol for Trial 271-102-00002.
Abbreviations: IMP, investigational medicinal product

For Trials 271-12-205 and 271-15-001, the protocol-specified primary efficacy endpoint was the proportion of subjects that achieved IGA success at Week 4, where success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The protocols for Trials 271-12-205 and 271-15-001 specified secondary efficacy endpoints; however, the analyses of these endpoints were not controlled for multiplicity. Therefore, the results of these endpoints are considered exploratory and are not included in this review.

For Trial 271-102-00002, the primary objective was to evaluate the safety of difamilast ointment; therefore, the protocol did not specify a primary efficacy endpoint (i.e., the primary endpoint was based on assessing adverse events). The proportion of subjects that achieved IGA success at Week 4 was specified as a secondary efficacy endpoint in Trial 271-102-00002. The analyses of the secondary efficacy endpoints for the secondary efficacy endpoints were not controlled for multiplicity in Trial 271-102-00002; therefore, only the results for IGA success at Week 4 with nominal p-values are presented in this review.

Table 26 presents the IGA scale used in Trial 271-12-205. Table 27 presents the IGA scale used in Trials 271-15-001 and 271-102-00002.

Table 26: Investigator's Global Assessment Scale for Trial 271-12-205

Score	Definition
0 = Clear	No inflammatory signs of AD
1 = Almost clear	Just perceptible erythema, and Just perceptible papulation/infiltration
2 = Mild disease	Mild erythema, and mild papulation/infiltration
3 = Moderate disease	Moderate erythema, and Moderate papulation/infiltration
4 = Severe disease	Severe erythema, and severe papulation/infiltration
5 = Very severe disease	Severe erythema, and severe crusting papulation/infiltration with oozing

Source: page 101 of the protocol for Trial 271-12-205.
Abbreviations: AD, atopic dermatitis

Table 27: Investigator's Global Assessment Scale for Trials 271-15-001 and 271-102-00002

Symptoms	Severity Score
No inflammatory signs of AD	0 = Clear
Just perceptible erythema and just perceptible papulation/infiltration	1 = Almost clear
Mild erythema and mild papulation/infiltration	2 = Mild
Moderate erythema and moderate papulation/infiltration	3 = Moderate
Severe erythema and severe papulation/infiltration with oozing/crusting	4 = Severe/very severe

Source: page 48 of the protocol for Trial 271-15-001 and page 49 of the protocol for Trial 271-102-00002.
Abbreviations: AD, atopic dermatitis

8.1.1.2. Statistical Analysis Plan

Analysis Populations

For all three phase 2 trials, the statistical analysis plans (SAPs) specified the following analysis populations:

- Full Analysis Set (FAS): all randomized subjects who received at least one dose of study product.
- Safety Set (SS): all subjects who received at least one dose of study product.

Estimands

The phase 2 trials were conducted prior to the finalization of the ICH *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*. Therefore, the protocols and SAPs did not specify any estimands.

Analysis Methods

The SAPs specified analyzing the proportion of subjects that achieved IGA success at Week 4 using a Cochran-Mantel-Haenszel (CMH) test. For Trial 271-12-205, the CMH was specified to be stratified by region (North America, Europe, or Australia) and age group (<18 years or ≥18 years). For Trials 271-15-001 and 271-102-00002, the CMH was specified to be stratified by baseline IGA score (2 or 3).

For Trials 271-12-205 and 271-15-001, the SAPs specified a sequential testing procedure to control the Type I error rate for testing each dose of difamilast against vehicle for the primary efficacy endpoint (i.e., IGA success at Week 4). The difamilast ointment, 1.0% was specified to be tested first. If significant at the two-sided 0.05 level, then difamilast ointment, 0.3% was

tested against vehicle. The SAPs for Trials 271-12-205 and 271-15-001 did not specify a method to control the Type I error rate for the testing of the secondary efficacy endpoints.

The SAP for Trial 271-102-00002 did not specify any method to control for multiplicity.

For all three phase 2 trials, missing data for IGA success at Week 4 were specified to be imputed using non-responder imputation (NRI).

8.1.1.3. Results

Subject Disposition

Trial 271-12-205 enrolled and randomized a total of 121 subjects (43 to difamilast ointment, 1%, 41 to difamilast ointment, 0.3%, and 37 to vehicle) from 29 sites (5 in Australia, 5 in Poland, and 19 in the United States). Trial 271-15-001 enrolled and randomized a total of 200 subjects (67 to difamilast ointment, 1%, 67 to difamilast ointment, 0.3%, and 66 to vehicle) from 14 sites in Japan. Trial 271-15-001 enrolled and randomized a total of 73 subjects (25 to difamilast ointment, 1%, 24 to difamilast ointment, 0.3%, and 24 to vehicle) from 8 sites in Japan.

Table 28, Table 29, and Table 30 present the subject disposition for Trials 271-12-205, 271-15-001, and 271-102-00002, respectively. The trial discontinuation rate was higher in Trials 271-12-205 and 271-15-001 compared to Trial 271-102-00002; however, this may be attributed to the longer treatment duration (i.e., 8 weeks for Trials 271-12-205 and 271-15-001 vs. 4 weeks for Trial 271-102-00002).

Table 28: Subject Disposition – Trial 271-12-205

Disposition	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Randomized subjects	43	41	37
Treated subjects	43	41	37
Discontinued from trial, n (%)[1]	8 (18.6)	10 (24.4)	9 (24.3)
Adverse event	2 (4.7)	4 (9.8)	7 (18.9)
Lost to follow-up	2 (4.7)	0	0
Protocol deviation	0	0	1 (2.7)
Protocol specified withdrawal criteria	1 (2.3)	0	0
Withdrawal by subject	3 (7.0)	6 (14.6)	1 (2.7)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt.
[1] The percentages were calculated based on the number of subjects that were randomized.

Table 29: Subject Disposition – Trial 271-15-001

Disposition	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Randomized subjects	67	67	66
Treated subjects	67	67	66
Discontinued from trial, n (%)[1]	14 (20.9)	21 (31.3)	20 (30.3)
Adverse event	7 (10.4)	15 (22.4)	15 (22.7)
Physician decision	2 (3.0)	2 (3.0)	0
Protocol deviation	0	1 (1.5)	0
Protocol specified withdrawal criteria	1 (1.5)	0	1 (1.5)
Withdrawal by subject	4 (6.0)	3 (4.5)	4 (6.1)

Source: Table 10.1-1 in clinical study report for Trial 271-15-001.
[1] The percentages were calculated based on the number of subjects that were randomized.

Table 30: Subject Disposition – Trial 271-102-00002

Disposition	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Randomized subjects	25	24	24
Treated subjects	25	24	24
Discontinued from trial, n (%)[1]	1 (4.0)	2 (8.3)	7 (29.2)
Adverse event	1 (4.0)	1 (4.2)	4 (16.7)
Lack of efficacy	0	0	1 (4.2)
Withdrawal by parent/guardian	0	1 (4.2)	1 (4.2)
Withdrawal by subject	0	0	1 (4.2)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt.
[1] The percentages were calculated based on the number of subjects that were randomized.

Demographics and Baseline Disease Characteristics

The demographics and baseline disease characteristics for Trials 271-12-205, 271-15-001, and 271-102-00002 are presented in Table 31, Table 32, and Table 33 respectively. The demographics and baseline disease characteristics were generally balanced across the treatment groups in each trial. The proportion of subjects with mild disease (i.e., IGA score of 2) at baseline was higher in Trials 271-12-205 and 271-15-001 compared to Trial 271-102-00002.

Table 31: Demographics and Baseline Disease Characteristics – Trial 271-12-205 (FAS[1])

Characteristic	Difamilast Ointment, 1% (N=43)	Difamilast Ointment, 0.3% (N=41)	Vehicle (N=37)
Age (years)			
Mean (SD)	34.1 (16.5)	36.4 (15.2)	32.2 (15.6)
Median	31.0	38.0	29.0
Min, max	10, 67	10, 59	10, 64
Categories, n (%)			
2 to <6	0	0	0
6<12	2 (4.7)	1 (2.4)	4 (10.8)
12 to <18	7 (16.3)	6 (14.6)	4 (10.8)
≥18	34 (79.1)	34 (82.9)	29 (78.4)
Sex, n (%)			
Female	22 (51.2)	27 (65.9)	23 (62.2)
Male	21 (48.8)	14 (34.1)	14 (37.8)

Characteristic	Difamilast Ointment, 1% (N=43)	Difamilast Ointment, 0.3% (N=41)	Vehicle (N=37)
Race, n (%)			
White	30 (69.8)	24 (58.5)	28 (75.7)
Black or African American	11 (25.6)	14 (34.1)	5 (13.5)
Asian	1 (2.3)	1 (2.4)	2 (5.4)
Native Hawaiian or Other Pacific Islander	0	1 (2.4)	2 (5.4)
Other	1 (2.3)	1 (2.4)	0
Ethnicity, n (%)			
Hispanic or Latino	7 (16.3)	4 (9.8)	7 (18.9)
Not Hispanic or Latino	36 (83.7)	37 (90.2)	30 (81.1)
Country, n (%)			
Australia	8 (18.6)	8 (19.5)	8 (21.6)
Poland	5 (11.6)	4 (9.8)	3 (8.1)
United States	30 (69.8)	29 (70.7)	26 (70.3)
Baseline IGA Score, n (%)			
2 = Mild	13 (30.2)	14 (34.1)	10 (27.0)
3 = Moderate	30 (69.8)	27 (65.9)	27 (73.0)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt and ADOIGA.xpt.
[1] FAS: all randomized subjects who received at least one dose of study product.
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment; SD, standard deviation

Table 32: Demographics and Baseline Disease Characteristics – Trial 271-15-001 (FAS[1])

Characteristic	Difamilast Ointment, 1% (N=67)	Difamilast Ointment, 0.3% (N=67)	Vehicle (N=66)
Age (years)			
Mean (SD)	31.0 (10.8)	30.2 (9.0)	31.6 (10.0)
Median	29.0	29.0	29.0
Min, max	18, 59	15, 50	15, 55
Categories, n (%)			
2 to <6	0	0	0
6<12	0	0	0
12 to <18	0	2 (3.0)	1 (1.5)
≥18	67 (100.0)	65 (97.0)	65 (98.5)
Sex, n (%)			
Female	25 (37.3)	22 (32.8)	23 (34.8)
Male	42 (62.7)	45 (67.2)	43 (65.2)
Race, n (%)			
Asian	67 (100.0)	67 (100.0)	66 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	67 (100.0)	67 (100.0)	66 (100.0)
Country, n (%)			
Japan	67 (100.0)	67 (100.0)	66 (100.0)
Baseline IGA Score, n (%)			
2 = Mild	19 (28.4)	19 (28.4)	19 (28.8)
3 = Moderate	48 (71.6)	48 (71.6)	47 (71.2)

Source: Table 10.1-1 in clinical study report for Trial 271-15-001.
[1] FAS: all randomized subjects who received at least one dose of study product.
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment; SD, standard deviation

Table 33: Demographics and Baseline Disease Characteristics – Trial 271-102-00002 (FAS1)

Characteristic	Difamilast Ointment, 1% (N=25)	Difamilast Ointment, 0.3% (N=24)	Vehicle (N=24)
Age (years)			
Mean (SD)	7.9 (3.5)	8.5 (3.8)	8.5 (3.1)
Median	8.0	9.0	9.0
Min, max	2, 14	2, 14	2, 14
Categories, n (%)			
2 to <6	6 (24.0)	6 (25.0)	4 (16.7)
6<12	14 (56.0)	13 (54.2)	17 (70.8)
12 to <18	5 (20.0)	5 (20.8)	3 (12.5)
≥18	0	0	0
Sex, n (%)			
Female	10 (40.0)	6 (25.0)	5 (20.8)
Male	15 (60.0)	18 (75.0)	19 (79.2)
Race, n (%)			
Asian	25 (100.0)	24 (100.0)	24 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	25 (100.0)	24 (100.0)	24 (100.0)
Not Hispanic or Latino			
Country, n (%)			
Japan	25 (100.0)	24 (100.0)	24 (100.0)
Baseline IGA Score, n (%)			
2 = Mild	5 (20.0)	4 (16.7)	3 (12.5)
3 = Moderate	20 (80.0)	20 (83.3)	21 (87.5)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt and ADOIGA.xpt.
[1] FAS: all randomized subjects who received at least one dose of study product.
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment; SD, standard deviation

Efficacy Results

Table 34 presents the results of IGA success at Week 4 in the phase 2 trials. For all three trials., a dose-response was observed where the difamilast ointment, 1% group had a higher response rate than the difamilast ointment, 0.3% group, and both active treatment groups had higher response rates than vehicle. The proportion of subjects with missing data was higher in the vehicle group compared to the difamilast groups in all three trials. In addition, the difamilast ointment, 1% group had the smallest proportion of subjects with missing data in all three trials. Subjects with missing data were imputed as non-responders.

Table 34: Results of IGA Success[1] at Week 4 for the Phase 2 Trials (FAS[2])

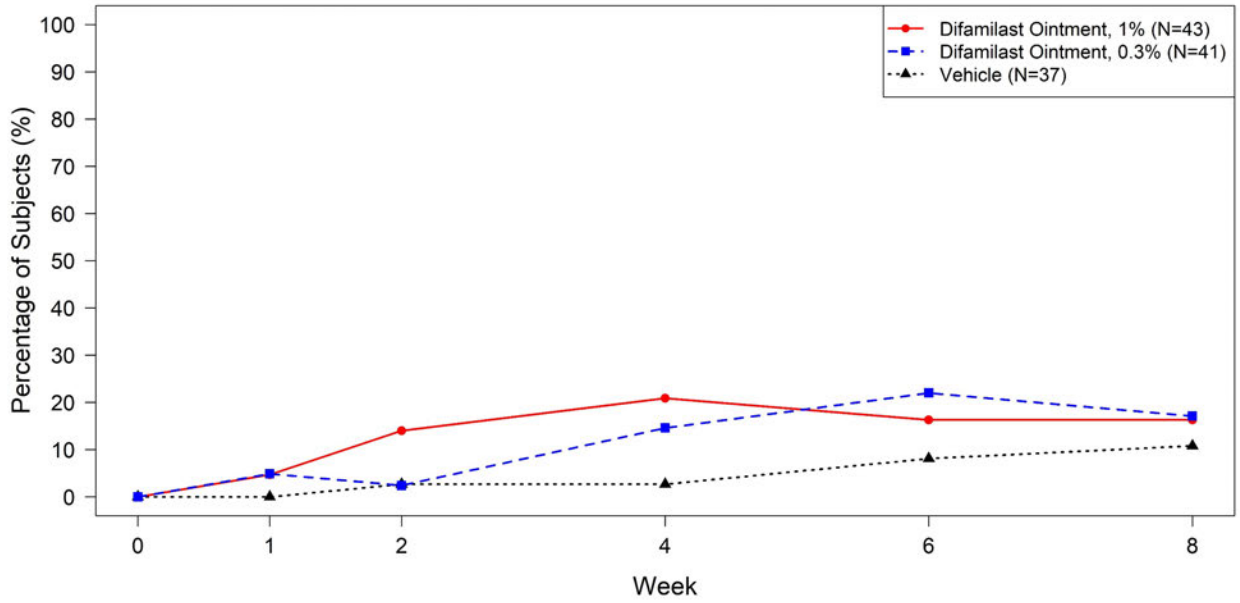
Trial Result	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Trial 271-12-205	N=43	N=41	N=37
Missing, n (%)	3 (7.0)	6 (14.6)	8 (21.6)
Responders, n (%)	9 (20.9)	6 (14.6)	1 (2.7)
Difference from vehicle (95% CI)[3]	18.2 (5.0, 31.5)	11.9 (−0.1, 24.0)	-
p-value[3]	0.017	0.069	-
Trial 271-15-001	N=67	N=67	N=66
Missing, n (%)	9 (13.4)	10 (14.9)	13 (19.7)
Responders, n (%)	15 (22.4)	10 (14.9)	6 (9.1)
Difference from vehicle (95% CI)[4]	13.2 (1.4, 25.1)	5.8 (−5.0, 16.6)	-
p-value[4]	0.033	0.300	-

Trial Result	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Trial 271-102-00002	N=25	N=24	N=24
Missing, n (%)	1 (4.0)	1 (4.2)	6 (25.0)
Responders, n (%)	10 (40.0)	9 (37.5)	2 (8.3)
Difference from vehicle (95% CI)[4]	32.0 (9.8, 54.1)	30.4 (8.5, 52.3)	-
p-value[4]	0.011	0.011	-

Source: Statistical Reviewer's Analysis and Table 11.4.1.1.1-1 in clinical study report for Trial 271-15-001; ADSL.xpt and ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Two-sided 95% CI is calculated based on the Wald confidence interval. P-value is based on the Cochran-Mantel-Haenszel (CMH) test stratified by region (North America, Europe, or Australia) and age group (<18 years or ≥18 years).
[4] Difference in proportions and 95% CI are based on the Mantel-Haenszel (MH) method stratified by baseline IGA score (2 or 3). Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by baseline IGA score (2 or 3).
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

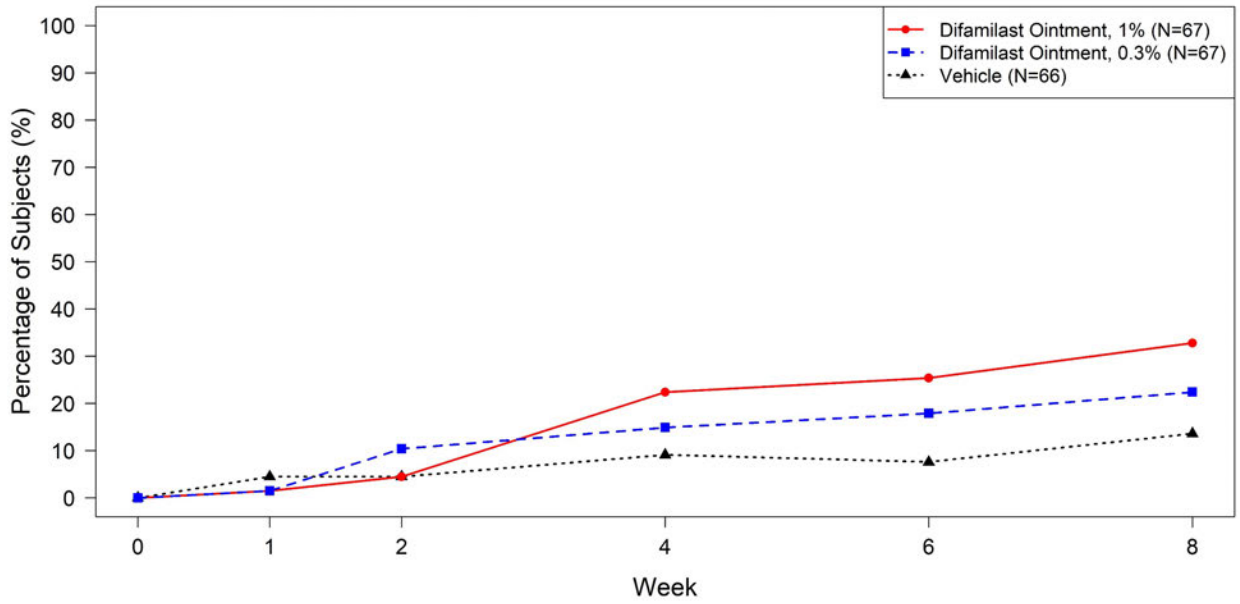
Figure 7, Figure 8, and Figure 9 presents the results of IGA success over time for Trials 271-12-205, 271-15-001, and 271-102-00002, respectively.

Figure 7: Results for IGA Success[1] Over Time – Trial 271-12-205 (FAS[2])



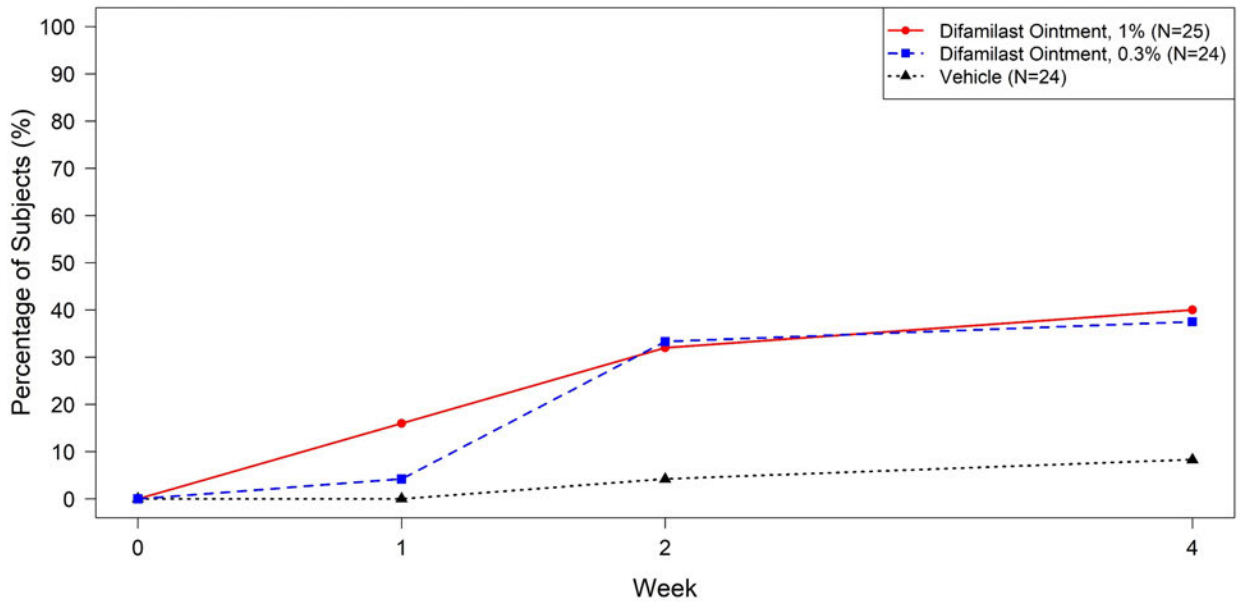
Source: Statistical Reviewer's Analysis; ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment

Figure 8: Results for IGA Success[1] Over Time – Trial 271-15-001 (FAS[2])



Source: Adapted from Table 11.4.1.1.1-1 in clinical study report for Trial 271-15-001.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment

Figure 9: Results for IGA Success[1] Over Time – Trial 271-102-00002 (FAS[2])



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment

Table 35 presents the results of IGA success at Week 4 by age, sex, race, ethnicity, country, and baseline IGA score for Trial 271-12-205. The treatment effect for difamilast ointment, 1% was

generally consistent across the subgroups for age, sex, race, ethnicity, and country. The sample sizes in some of the subgroups for age and race were relatively small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements. The treatment effect for difamilast ointment, 1% was smaller in subject with baseline IGA score of 2 (mild) compared to subjects with baseline IGA score of 3 (moderate).

Table 35, Table 36, and Table 37present the results of IGA success at Week 4 by age, sex, and baseline IGA score for Trials 271-15-001 and 271-102-00002, respectively. Because Trials 271-15-001 and 271-102-00002 were conduct exclusively in Japan, their tables do not include race, ethnicity, and country. The treatment effect for difamilast ointment, 1% was higher in females compared to males in both of these trials. The sample sizes in some of the subgroups for age were relatively small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements. The treatment effect of difamilast ointment, 1% was smaller in subjects with baseline IGA score of 2 (mild) compared to subjects with baseline IGA score of 3 (moderate) in Trial 271-15-001. The reverse was seen in Trial 271-102-00002; however, the sample size of the subgroup with baseline IGA score of 2 (mild) was very small in this trial.

Table 35: Results for IGA Success[1] at Week 4 by Age, Sex, Race, Ethnicity, Country, and Baseline IGA Score – Trial 271-12-205 (FAS[2])

Subgroup	Difamilast Ointment, 1% (N=43)	Difamilast Ointment, 0.3% (N=41)	Vehicle (N=37)	Difference 1% vs. Vehicle (95% CI)[3]	Difference 0.3% vs. Vehicle (95% CI)[3]
Age (years)					
<12	1/2 (5.00%)	0/1 (0%)	0/4 (0%)	50.0% (−19.3%, 100%)	Not estimable
12 to <18	1/7 (14.3%)	1/6 (16.7%)	0/4 (0%)	14.3% (−11.6%, 40.2%)	16.7% (−13.2%, 46.5%)
18 to <65	7/33 (21.1%)	5/34 (14.7%)	1/29 (3.4%)	17.8% (2.3%, 33.2%)	11.3% (−2.4%, 24.9%)
≥65	0/1 (0%)			Not estimable	Not estimable
Sex					
Female	5/22 (22.7%)	4/27 (14.8%)	1/23 (4.3%)	18.4% (−1.0%, 37.8%)	10.5% (−5.3%, 26.3%)
Male	4/21 (19.0%)	2/14 (14.3%)	0/14 (0%)	19.0% (2.3%, 35.8%)	14.3% (−4.0%, 32.6%)
Race					
White	7/30 (23.3%)	3/24 (12.5%)	1/28 (3.6%)	19.8% (3.1%, 36.4%)	8.9% (−6.0%, 23.8%)
Black or African American	2/11 (18.2%)	2/14 (14.3%)	0/5 (0%)	18.2% (−4.6%, 41.0%)	14.3% (−4.0%, 32.6%)
Asian	0/1 (0%)	1/1 (100%)	0/2 (0%)	Not estimable	Not estimable
Other	0/1 (0%)	0/2 (0%)	0/2 (0%)	Not estimable	Not estimable
Ethnicity					
Hispanic or Latino	2/7 (28.6%)	1/4 (25.0%)	1/7 (14.3%)	14.3% (−28.1%, 56.6%)	10.7% (−39.0%, 60.4%)
Not Hispanic or Latino	7/36 (19.4%)	5/37 (13.5%)	0/30 (0%)	19.4% (6.5%, 32.4%)	13.5% (2.5%, 24.5%)
Country					
Australia	1/8 (12.5%)	0/8 (0%)	0/8 (0%)	12.5% (−10.4%, 35.4%)	Not estimable
Poland	1/5 (20.0%)	0/4 (0%)	0/3 (0%)	20.0% (−15.1%, 55.1%)	Not estimable
United States	7/30 (23.3%)	6/29 (20.7%)	1/26 (3.8%)	19.5% (2.6%, 36.3%)	16.8% (0.4%, 33.3%)
Baseline IGA Score					
2 = Mild	1/13 (7.7%)	2/14 (14.3%)	0/10 (0%)	7.7% (−6.8%, 22.2%)	14.3% (−4.0%. 32.6%)
3 = Moderate	8/30 (26.7%)	4/27 (14.8%)	1/27 (3.7%)	23.0% (5.6%, 40.3%)	11.1% (−4.1%, 26.3%)

Source: Statistical Reviewer's Analysis; ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Two-sided 95% CI is calculated based on the Wald confidence interval.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

Table 36: Results for IGA Success[1] at Week 4 by Age, Sex, and Baseline IGA Score – Trial 271-15-001 (FAS[2])

Subgroup	Difamilast Ointment, 1% (N=67)	Difamilast Ointment, 0.3% (N=67)	Vehicle (N=66)	Difference 1% vs. Vehicle (95% CI)[3]	Difference 0.3% vs. Vehicle (95% CI)[3]
Age (years)					
12 to <18		0/2 (0%)	0/1 (0%)	Not estimable	Not estimable
18 to <65	15/67 (22.4%)	10/65 (15.4%)	6/65 (9.2%)	13.0% (1.1%, 24.9%)	6.0% (−5.1%, 17.0%)
Sex					
Female	6/25 (24.0%)	2/22 (9.1%)	0/23 (0%)	24.3% (7.5%, 41.1%)	9.2% (−2.9%, 21.2%)
Male	9/42 (21.4%)	8/45 (17.8%)	6/43 (14.0%)	7.2% (−8.7%, 23.0%)	3.6% (−11.3%, 18.6%)
Baseline IGA Score					
2 = Mild	1/19 (5.3%)	1/19 (5.3%)	0/19 (0%)	5.3% (−4.8%, 15.3%)	5.3% (−4.8%, 15.3%)
3 = Moderate	14/48 (29.2%)	9/48 (18.8%)	6/47 (12.8%)	16.4% (0.4%, 32.4%)	6.0% (−8.6%, 20.6%)

Source: Adapted from Table CT-5.9.1 in clinical study report for Trial 271-15-001.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] For age and sex, the difference and two-sided 95% CI is based on the CMH test stratified by baseline IGA score (2 or 3). For baseline IGA score, the two-sided 95% CI is calculated based on the Wald confidence interval.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IGA, Investigator's Global Assessment

Table 37: Results for IGA Success[1] at Week 4 by Age, Sex, and Baseline IGA Score – Trial 271-102-00002 (FAS[2])

Subgroup	Difamilast Ointment, 1% (N=25)	Difamilast Ointment, 0.3% (N=24)	Vehicle (N=24)	Difference 1% vs. Vehicle (95% CI)[3]	Difference 0.3% vs. Vehicle (95% CI)[3]
Age (years)					
2 to <6	3/6 (50.0%)	2/6 (33.3%)	0/4 (0%)	50.0% (10.0%, 90.0%)	33.3% (−4.4%, 71.1%)
6<12	5/14 (35.7%)	6/13 (46.2%)	2/17 (11.8%)	23.9% (−5.5%, 53.4%)	34.4% (3.3%, 65.5%)
12 to <18	2/5 (40.0%)	1/5 (20.0%)	0/3 (0%)	40.0% (−2.9%, 82.9%)	20.0% (−15.1%, 55.1%)
Sex					
Female	4/10 (40.0%)	2/6 (33.3%)	0/5 (0%)	40.0% (9.6%, 70.4%)	33.3% (−4.4%, 71.1%)
Male	6/15 (40.0%)	7/18 (38.9%)	2/19 (10.5%)	29.5% (1.1%, 57.9%)	28.4% (2.0%, 54.8%)
Baseline IGA Score					
2 = Mild	2/5 (40.0%)	0/4 (0%)	0/3 (0%)	40.0% (−2.9%, 82.9%)	Not estimable
3 = Moderate	8/20 (40.0%)	9/20 (45.0%)	2/21 (9.5%)	30.5% (5.6%, 55.4%)	35.5% (10.3%, 60.6%)

Source: Statistical Reviewer's Analysis; ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Two-sided 95% CI is calculated based on the Wald confidence interval.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

8.1.2. Phase 3 Trials (Trials 271-102-00007, 271-102-00008, and MEDI-MM36-301)

8.1.2.1. Trial Design and Endpoints

Three phase 3 trials (271-102-00007, 271-102-00008, and MEDI-MM36-301) were conducted to evaluate the efficacy of difamilast ointment. Trials 271-102-00007 and 271-102-00008 were conducted exclusively in Japan, and Trial MEDI-MM36-301 was conducted exclusively in the United States. The Applicant stated that Trial MEDI-MM36-301 was terminated early for "business reasons and not for reasons related to safety." The key inclusion criteria that defined the study populations were as follows:

- Male or female
- Age:
  - Trial 271-102-00007: 15 to 70 years
  - Trial 271-102-00008: 2 to 14 years
  - Trial MEDI-MM36-301: ≥2 years
- Diagnosis of AD
  - Trials 271-102-00007 and 271-102-00008: based on the Japanese Dermatological Association's criteria
  - Trial MEDI-MM36-301: American Academy of Dermatology AD diagnostic criteria
- History of AD:
  - Trial 271-102-00007: 3 years
  - Trial 271-102-00008: not specified
  - Trial MEDI-MM36-301: 6 months
- AD affecting ≥5% to ≤40% of BSA. The protocols for all three trials specified excluding scalp from BSA calculation for enrollment.
- IGA score of 2 (mild) or 3 (moderate)

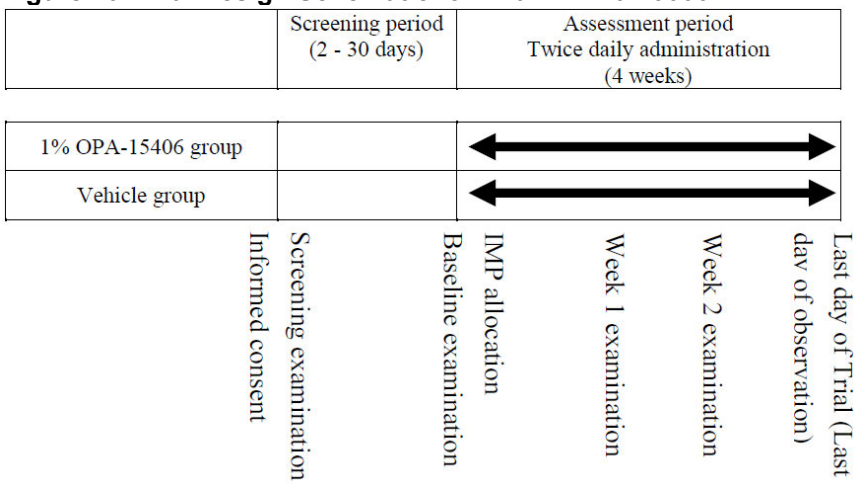
Figure 10, Figure 11, and Figure 12present the trial design schematics for Trials 271-102-00007, 271-102-00008, and MEDI-MM36-301, respectively. All three trials were randomized, multicenter, double-blind, vehicle-controlled, parallel-group, phase 3 trials.

Trial 271-102-00007 was designed to enroll and randomize approximately 340 subjects in a 1:1 ratio to receive either difamilast ointment, 1% (N=170) or vehicle ointment (N=170). Trial 271-102-00008 was designed to enroll and randomize approximately 240 subjects in a 1:1:1 ratio to receive either difamilast ointment, 0.3% (N=80), difamilast ointment, 1% (N=80) or vehicle ointment (N=80). Trial MEDI-MM36-301 was designed to enroll and randomize approximately 336 subjects in a 2:1 to receive either difamilast ointment, 1% (N=224) or vehicle ointment (N=112). The randomization for Trial MEDI-MM36-301 was stratified by study center.

For all three trials, a thin layer of study drug was applied to affected areas twice daily (morning and night, approximately 12 hours apart) for 4 weeks. For Trials 271-102-00007 and 271-102-00008, subjects were scheduled to have the following study visits: screening, baseline (Day 1),

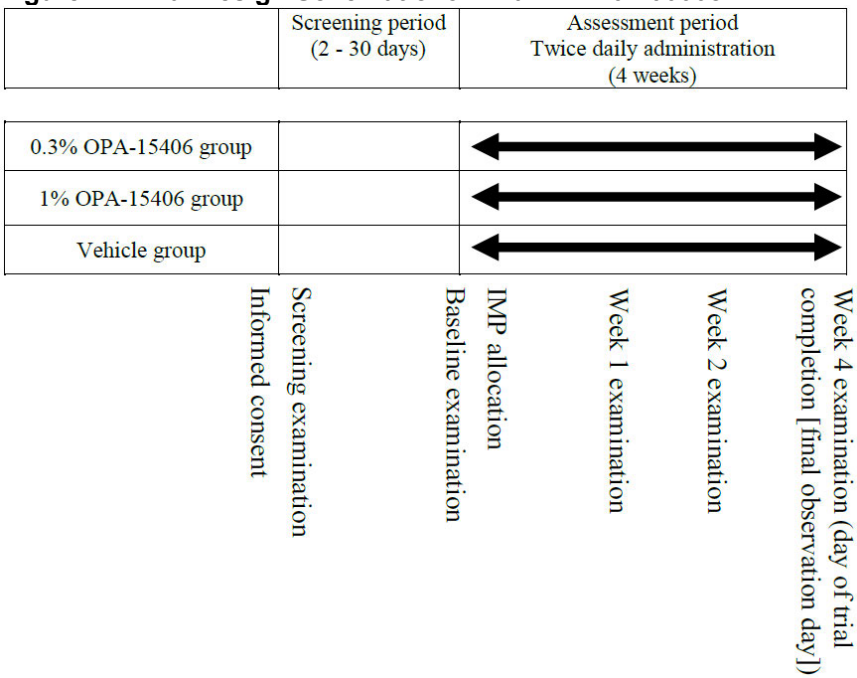
and Weeks 1, 2, and 4. For Trial MEDI-MM36-301, subjects were scheduled to have the following study visits: screening, baseline, and Weeks 1, 2, 3, and 4.

Figure 10: Trial Design Schematic for Trial 271-102-00007



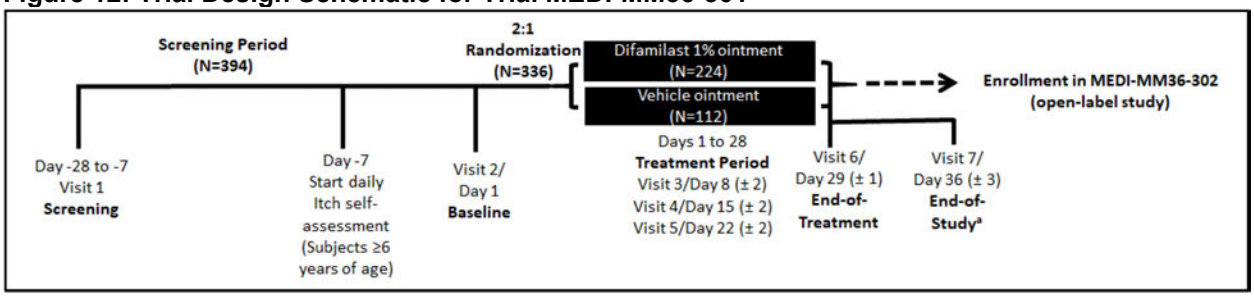
Source: page 31 of the protocol for Trial 271-102-00007.
Abbreviations: IMP, Investigational Medicinal Product

Figure 11: Trial Design Schematic for Trial 271-102-00008



Source: page 31 of the protocol for Trial 271-102-00008.
Abbreviations: IMP, Investigational Medicinal Product

Figure 12: Trial Design Schematic for Trial MEDI-MM36-301



Source: page 34 of the protocol for Trial MEDI-MM36-301.
[a] The End-of-Study visit was conducted via phone for the final evaluation of safety only for those not entering the open-label safety study, MEDI-MM36-302.
Abbreviations: N, number of subjects

For all three trials, the protocol-specified primary efficacy endpoint was the proportion of subjects that achieved an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 4.

For Trials 271-102-00007 and 271-102-00008, the protocols specified several secondary efficacy endpoints; however, the analyses of these endpoints were not controlled for multiplicity. Therefore, the results of these endpoints are considered exploratory and are not included in this review.

For Trial MEDI-MM36-301, the protocol specified the endpoints listed below as the secondary efficacy endpoints. These endpoints were specified in the protocol to be analyzed via a sequential testing procedure to control for multiplicity; however, the SAP did not specify any efficacy analyses (see Section 8.1.2.2).

Proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) at Week 4

- Proportion of subjects with IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 3 (Day 22)
- Proportion of subjects with IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 2 (Day 15)
- Proportion of subjects with IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 1 (Day 8)
- Proportion of subjects ≥6 years of age (capable of self-reporting and with a baseline Peak Pruritus Numeric Rating Scale [PP-NRS] ≥4) achieving a 4-point improvement from Baseline in PP-NRS at Week 4

Table 38 presents the IGA scale used in Trials 271-102-00007 and 271-102-00008. Table 39 presents the IGA scale used in Trial MEDI-MM36-301.

Table 38: Investigator's Global Assessment Scale in Trials 271-102-00007 and 271-102-00008

Symptoms	Severity Score
No inflammatory signs of AD	0 = Clear
Just perceptible erythema and just perceptible papulation/infiltration	1 = Almost clear
Mild erythema and mild papulation/infiltration	2 = Mild disease
Moderate erythema and moderate papulation/infiltration	3 = Moderate disease
Severe erythema, and severe papulation/infiltration Severe erythema, and severe crusting papulation/infiltration with oozing	4 = Severe disease/Very severe disease

Source: page 48 of the protocol for Trial 271-102-00007 and page 49 of the protocol for Trial 271-102-00008.
Abbreviations: AD, atopic dermatitis

Table 39: Investigator's Global Assessment Scale in Trial MEDI-MM36-301

Scale	Grade	Definition
0	Clear	No inflammatory signs of AD.
1	Almost Clear	Barely perceptible erythema.
2	Mild disease	Slight but definite erythema (pink) and slightly perceptible papulation/induration (infiltration).
3	Moderate disease	Clearly perceptible erythema (dull red) and clearly perceptible papulation/induration (infiltration).
4	Severe disease/very severe disease	Marked erythema (deep, dark, or bright red) and marked papulation/induration (infiltration). Crusting or oozing may be present.

Source: page 58 of the protocol for Trial MEDI-MM36-301.
Abbreviations: AD, atopic dermatitis

8.1.2.2. Statistical Analysis Plan

Analysis Populations

The SAPs for the phase 3 trials specified the following analysis populations:

- FAS [Trials 271-102-00007 and 271-102-00008] / Intent-to-Treat [Trial MEDI-MM36-301]: all randomized subjects who received at least one dose of study product.
- Safety Set (SS): all subjects who received at least one dose of study product.

Estimands

Trials 271-102-00007 and 271-102-00008 were conducted prior to the finalization of the ICH *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*. Therefore, the protocols and SAPs did not specify any estimands.

For Trial MEDI-MM36-301, the protocol specified the estimands for the primary and key secondary efficacy endpoints. The protocol specified using the composite variable strategy (i.e., subjects treated as non-responders) to handle intercurrent events of use of prohibited medication, discontinuation of study due to related adverse event, or discontinuation of study due to lack of efficacy. However, the finalized SAP did not specify the estimands. The SAP states:

> "Given that this trial has been discontinued early for business reasons and will not be used to support efficacy, all efficacy analyses defined in the protocol, including statistical testing, sub-group analyses, and per protocol population analysis will not be performed. Listings of the efficacy data will be provided."

For this review, a treatment policy strategy was used for Trial MEDI-MM36-301 to be consistent with the other phase 3 trials as well as the phase 2 trials.

Analysis Methods

The SAPs for Trials 271-102-00007 and 271-102-00008 specified analyzing the primary efficacy endpoint (i.e., the proportion of subjects that achieved IGA success at Week 4) using a CMH test. For Trial 271-102-00007, the CMH was specified to be stratified by baseline IGA score (2 or 3). For Trial 271-102-00008, the CMH was specified to be stratified by baseline IGA score (2 or 3) and age (2 to 6 years or 7 to 14 years).

As noted above, the SAP for Trial MEDI-MM36-301 did not specify any efficacy analyses. The protocol for MEDI-MM36-301 specified using a CMH test stratified by analysis centers to analyze the primary efficacy endpoint. This approach was used for this review.

The SAP for Trial 271-102-00007 did not specify any method to control for multiplicity. For Trial 271-102-00008, the SAP specified a sequential testing procedure to control the Type I error rate for testing each dose of difamilast against vehicle for the primary efficacy endpoint (i.e., IGA success at Week 4). The difamilast ointment, 1.0% was specified to be tested first. If significant at the two-sided 0.05 level, then difamilast ointment, 0.3% was tested against vehicle. The SAP for Trial 271-102-00008 did not a method to control the Type I error rate for the testing of the secondary efficacy endpoints.

For Trial MEDI-MM36-301, the protocol specified a sequential testing procedure to control the Type I error rate for testing the secondary efficacy endpoints. The endpoints were specified to be tested in the order listed in Section 8.1.2.1, with testing of each endpoint proceeding only if the preceding endpoint reaches statistical significance.

For all three phase 3 trials, missing data for IGA success at Week 4 were imputed using NRI.

8.1.2.3. Results

Subject Disposition

Trial 271-102-00007 enrolled and randomized a total of 364 subjects (182 to difamilast ointment, 1% and 182 to vehicle) from 30 sites in Japan. Trial 271-102-00008 enrolled and randomized a total of 251 subjects (85 to difamilast ointment, 1%, 83 to difamilast ointment, 0.3%, and 83 to vehicle) from 30 sites in Japan. Trial MEDI-MM36-301 enrolled and randomized a total of 153 subjects (94 to difamilast ointment, 1% and 59 to vehicle) from 32 sites in the United States.

Table 40, Table 41, and Table 42 present the subject disposition for Trials 271-102-00007, 271-102-00008, and MEDI-MM36-301, respectively. The trial discontinuation rate was higher in Trials 271-102-00007 and 271-102-00008 compared to Trial MEDI-MM36-301. In all three trials, the trial discontinuation rate was higher in the vehicle group compared to the difamilast groups.

Table 40: Subject Disposition – Trial 271-102-00007

Disposition	Difamilast Ointment, 1%	Vehicle
Randomized subjects	182	182
Treated subjects	182	182
Discontinued from trial, n (%)[1]	17 (9.3)	47 (25.8)
Adverse event	7 (3.8)	21 (11.5)
Physician decision	1 (0.5)	4 (2.2)
Withdrawal by subject	9 (4.9)	22 (12.1)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt.
[1] The percentages were calculated based on the number of subjects that were randomized.

Table 41: Subject Disposition – Trial 271-102-00008

Disposition	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Randomized subjects	85	83	83
Treated subjects	85	83	83
Discontinued from trial, n (%)[1]	9 (10.6)	7 (8.4)	25 (30.1)
Adverse event	2 (2.4)	1 (1.2)	5 (6.0)
Lack of efficacy	1 (1.2)	1 (1.2)	8 (9.6)
Physician decision	0	0	1 (1.2)
Withdrawal by parent/guardian	4 (4.7)	4 (4.8)	11 (13.3)
Withdrawal by subject	2 (2.4)	1 (1.2)	0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt.
[1] The percentages were calculated based on the number of subjects that were randomized.

Table 42: Subject Disposition – Trial MEDI-MM36-301

Disposition	Difamilast Ointment, 1%	Vehicle
Randomized subjects	94	59
Treated subjects	94	59
Discontinued from trial, n (%)[1]	4 (4.3)	4 (6.8)
Adverse event	1 (1.1)	1 (1.7)
Lost to follow-up	1 (1.1)	1 (1.7)
Withdrawal by subject	2 (2.1)	2 (3.4)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt.
[1] The percentages were calculated based on the number of subjects that were randomized.

Demographics and Baseline Disease Characteristics

The demographics and baseline disease characteristics for Trials 271-102-00007, 271-102-00008, and MEDI-MM36-301 are presented in Table 43, Table 44, and Table 45, respectively. The demographics and baseline disease characteristics were generally balanced across the treatment groups in each trial. The proportion of subjects with mild disease (i.e., IGA score of 2) at baseline was higher in Trial MEDI-MM36-301 compared to Trials 271-102-00007 and 271-102-00008.

Table 43: Demographics and Baseline Disease Characteristics – Trial 271-102-00007 (FAS[1])

Characteristic	Difamilast Ointment, 1% (N=182)	Vehicle (N=182)
Age (years)		
Mean (SD)	31.7 (10.9)	32.1 (10.6)
Median	29.0	30.0
Min, Max	17.0, 65.0	15.0, 57.0
Categories, n (%)		
2 to <6	0	0
6<12	0	0
12 to <18	1 (0.5)	1 (0.5)
≥18	181 (99.5)	181 (99.5)
Sex, n (%)		
Female	86 (47.3)	81 (44.5)
Male	96 (52.7)	101 (55.5)
Race, n (%)		
Asian	182 (100.0)	182 (100.0)
Ethnicity, n (%)		
Hispanic or Latino	0	0
Not Hispanic or Latino	182 (100.0)	182 (100.0)
Country, n (%)		
Japan	182 (100.0)	182 (100.0)
Baseline IGA Score, n (%)		
2 = Mild	27 (14.8)	26 (14.3)
3 = Moderate	155 (85.2)	156 (85.7)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt and ADOIGA.xpt.
[1] FAS: all randomized subjects who received at least one dose of study product.
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment; SD, standard deviation

Table 44: Demographics and Baseline Disease Characteristics – Trial 271-102-00008 (FAS[1])

Characteristic	Difamilast Ointment, 1% (N=85)	Difamilast Ointment, 0.3% (N=83)	Vehicle (N=83)
Age (years)			
Mean (SD)	7.2 (3.2)	7.1 (3.3)	7.1 (2.8)
Median	7.0	7.0	6.0
Min, max	2.0, 14.0	2.0, 13.0	2.0, 13.0
Categories, n (%)			
2 to <6	30 (35.3)	32 (38.6)	28 (33.7)
6<12	46 (54.1)	39 (47.0)	49 (59.0)
12 to <18	9 (10.6)	12 (14.5)	6 (7.2)
≥18	0	0	0
Sex, n (%)			
Female	37 (43.5)	45 (54.2)	34 (41.0)
Male	48 (56.5)	38 (45.8)	49 (59.0)
Race, n (%)			
Asian	85 (100.0)	83 (100.0)	83 (100.0)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	85 (100.0)	83 (100.0)	83 (100.0)
Country, n (%)			
Japan	85 (100.0)	83 (100.0)	83 (100.0)

Characteristic	Difamilast Ointment, 1% (N=85)	Difamilast Ointment, 0.3% (N=83)	Vehicle (N=83)
Baseline IGA Score, n (%)			
2 = Mild	14 (16.5)	13 (15.7)	12 (14.5)
3 = Moderate	71 (83.5)	70 (84.3)	71 (85.5)

Source: Table 10.1-1 in clinical study report for Trial 271-15-001.
[1] FAS: all randomized subjects who received at least one dose of study product.
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment; SD, standard deviation

Table 45: Demographics and Baseline Disease Characteristics – Trial MEDI-MM36-301 (FAS[1])

Characteristic	Difamilast Ointment, 1% (N=94)	Vehicle (N=59)
Age (years)		
Mean (SD)	38.0 (21.7)	39.0 (22.4)
Median	37.5	41.0
Min, max	2.0, 78.0	2.0, 80.0
Categories, n (%)		
2 to <6	5 (5.3)	4 (6.8)
6<12	6 (6.4)	2 (3.4)
12 to <18	12 (12.8)	8 (13.6)
≥18	71 (75.5)	45 (76.3)
Sex, n (%)		
Female	59 (62.8)	36 (61.0)
Male	35 (37.2)	23 (39.0)
Race, n (%)		
White	55 (58.5)	37 (62.7)
Black or African American	27 (28.7)	14 (23.7)
Asian	4 (4.3)	6 (10.2)
American Indian or Alaska Native	2 (2.1)	2 (3.4)
Multiple	6 (6.4)	0
Ethnicity, n (%)		
Hispanic or Latino	6 (6.4)	6 (10.2)
Not Hispanic or Latino	88 (93.6)	53 (89.8)
Country, n (%)		
United States	94 (100.0)	59 (100.0)
Baseline IGA Score, n (%)		
2 = Mild	29 (30.9)	22 (37.3)
3 = Moderate	65 (69.1)	37 (62.7)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt and ADQS.xpt.
[1] FAS: all randomized subjects who received at least one dose of study product.
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment; SD, standard deviation

Efficacy Results

Table 46 presents the results for IGA success at Week 4 in the phase 3 trials. For Trials 271-102-00007 and 271-102-00008, difamilast ointment, 1% was statistically superior to vehicle (p-values <0.001). Difamilast ointment, 0.3% was also statistically superior to vehicle (p-value<0.001) in Trial 271-102-00008. Difamilast ointment, 1% was not statistically superior to vehicle (p-value=0.702) in Trial MEDI-MM36-301. Note that Trial MEDI-MM36-301 was terminated early for "business reasons." The proportion of subjects with missing data was higher in the vehicle group compared to the difamilast group(s) in all three trials.

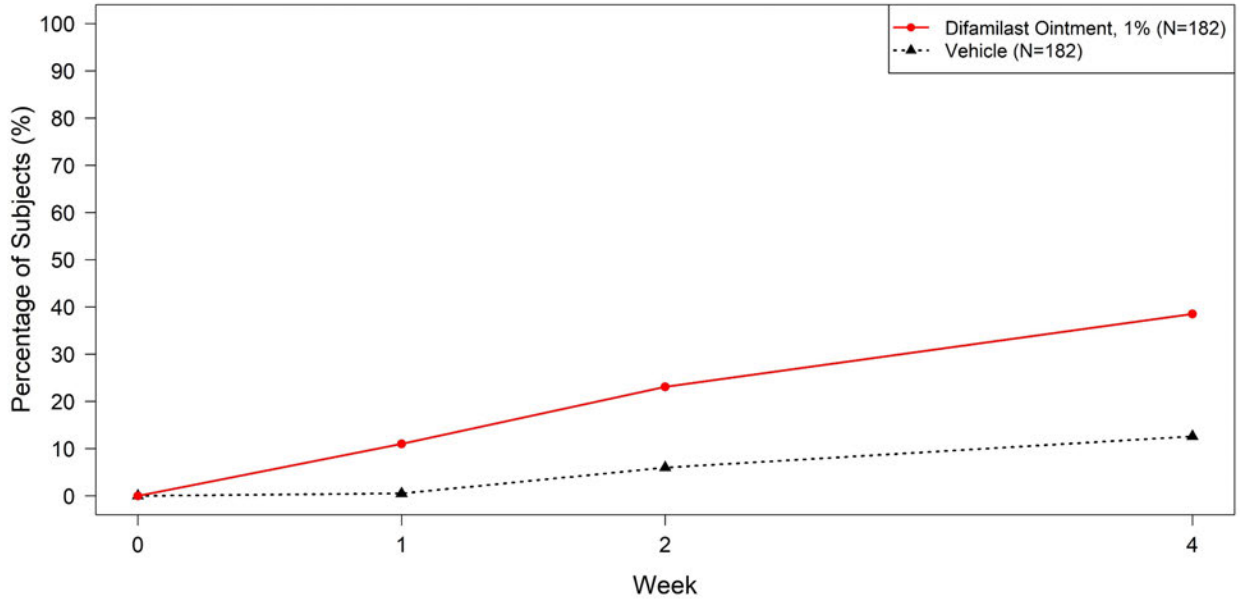
Table 46: Results of IGA Success[1] at Week 4 for the Phase 3 Trials (FAS[2])

Trial Results	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Trial 271-102-00007	N=182	-	N=182
Missing, n (%)	16 (8.8)		48 (26.4)
Responders, n (%)	70 (38.5)	-	23 (12.6)
Difference from vehicle (95% CI)[3]	25.9 (17.5, 34.4)	-	-
p-value[3]	<0.001	-	-
Trial 271-102-00008	N=85	N=83	N=83
Missing, n (%)	8 (9.4)	6 (7.2)	24 (28.9)
Responders, n (%)	40 (47.1)	37 (44.6)	15 (18.1)
Difference from vehicle (95% CI)[4]	28.7 (15.0, 42.5)	24.7 (11.3, 38.0)	-
p-value[4]	<0.001	<0.001	-
Trial MEDI-MM36-301	N=94	-	N=59
Missing, n (%)	4 (4.3)		4 (6.8)
Responders, n (%)	11 (11.7)	-	7 (11.9)
Difference from vehicle (95% CI)[5]	−0.2 (−13.2, 9.0)	-	-
p-value[5]	0.702	-	-

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis except Trial MEDI-MM36-301); ADSL.xpt, ADOIGA.xpt, and ADQS.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] Full Analysis Set (FAS): all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Difference in proportions and 95% CI are based on the Mantel-Haenszel (MH) method stratified by baseline IGA score (2 or 3). P-value is based on the Cochran-Mantel-Haenszel (CMH) test stratified by baseline IGA score (2 or 3).
[4] Difference in proportions and 95% CI are based on the MH method stratified by baseline IGA score (2 or 3) and age (2 to 6 years or 7 to 14 years). P-value is based on the CMH test stratified by baseline IGA score (2 or 3) and age (2 to 6 years or 7 to 14 years).
[5] Difference in proportions and 95% CI are based on the MH method stratified by analysis centers. P-value is based on the CMH test stratified by analysis centers.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

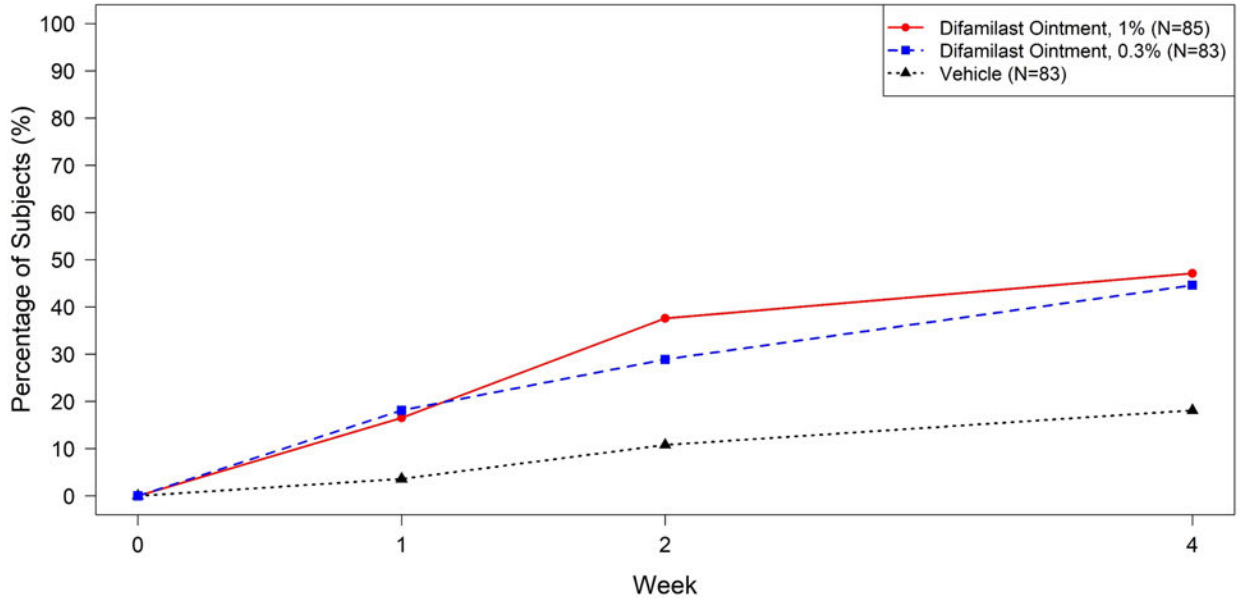
Figure 13, Figure 14, and Figure 15 present the results of IGA success over time for Trials 271-102-00007, 271-102-00008, and MEDI-MM36-301, respectively.

Figure 13: Results for IGA Success[1] Over Time – Trial 271-102-00007 (FAS[2])



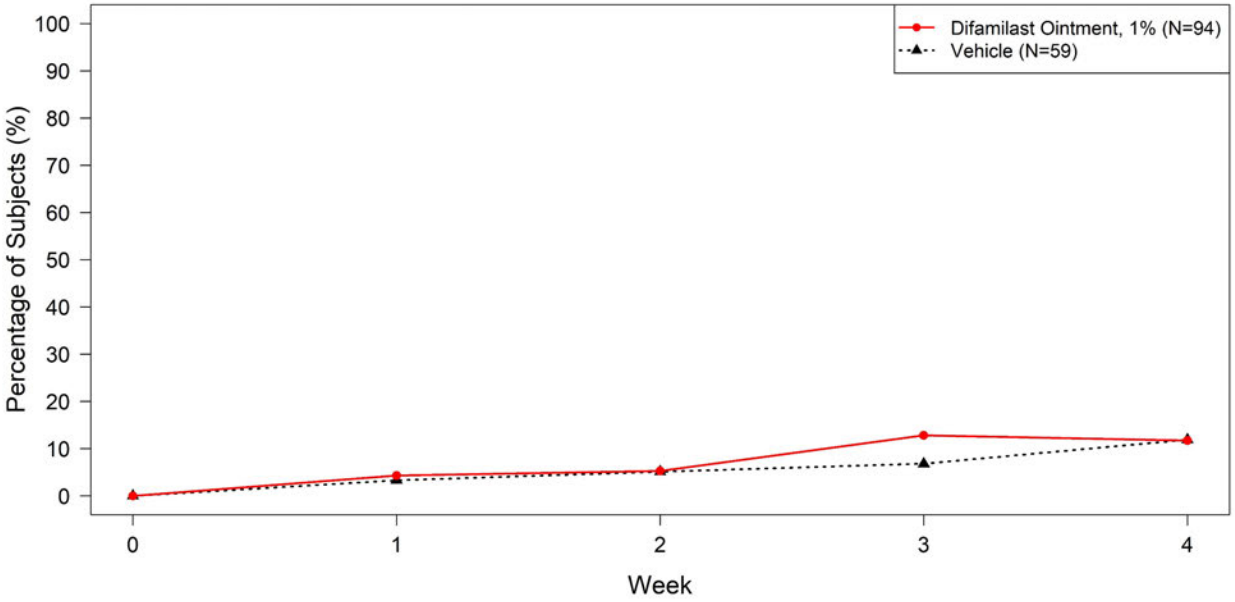
Source: Statistical Reviewer's Analysis; ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment

Figure 14: Results for IGA Success[1] Over Time – Trial 271-102-00008 (FAS[2])



Source: Statistical Reviewer's Analysis; ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment

Figure 15: Results for IGA Success[1] Over Time – Trial MEDI-MM36-301 (FAS[2])



Source: Statistical Reviewer's Analysis; ADQS.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment

Table 47 and Table 48 present the results of IGA success at Week 4 by age, sex, and baseline IGA score for Trials 271-102-00007 and 271-102-00008, respectively. Because Trials 271-102-00007 and 271-102-00008 were conduct exclusively in Japan, their tables do not include race, ethnicity, and country. The treatment effect for difamilast ointment, 1% was similar between males and females in both trials. Trial 271-102-00007 only randomized 2 adolescent subjects; therefore, differences in treatment effect between adults and adolescents cannot be determined. For Trial 271-102-00008, the treatment effect for difamilast ointment, 1% was smaller in subjects 2 to <6 years of age compared to subjects 6 to <12 years of age. In both trials, the treatment effect for difamilast ointment, 1% was smaller for subjects with a baseline IGA score =2 (mild) compared to subjects with a baseline IGA score of 3 (moderate).

Table 49 presents the results of IGA success at Week 4 by age, sex, race, ethnicity, and baseline IGA score.

Table 47: Results for IGA Success[1] at Week 4 by Age, Sex, and Baseline IGA Score – Trial 271-102-00007 (FAS[2])

Subgroup	Difamilast Ointment, 1% (N=182)	Vehicle (N=182)	Difference (95% CI)[3]
Age (years)			
12 to <18	0/1 (0%)	0/1 (0%)	Not estimable
18 to <65	70/180 (38.9%)	23/181 (12.7%)	26.2% (17.6%, 34.8%)
≥65	0/1 (0%)		Not estimable
Sex			
Female	36/86 (41.9%)	11/81 (13.6%)	28.3% (15.5%, 41.1%)
Male	34/96 (35.4%)	12/101 (11.9%)	23.5% (12.1%, 35.0%)
Baseline IGA Score			
2 = Mild	4/27 (14.8%)	1/26 (3.8%)	11.0% (−4.3%, 26.3%)
3 = Moderate	66/155 (42.6%)	22/156 (14.1%)	28.5% (19.0%, 38.0%)

Source: Statistical Reviewer's Analysis; ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Two-sided 95% CI is calculated based on the Wald confidence interval.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

Table 48: Results for IGA Success[1] at Week 4 by Age, Sex, and Baseline IGA Score – Trial 271-102-00008 (FAS[2])

Subgroup	Difamilast Ointment, 1% (N=85)	Difamilast Ointment, 0.3% (N=83)	Vehicle (N=83)	Difference 1% vs. Vehicle (95% CI)[3]	Difference 0.3% vs. Vehicle (95% CI)[3]
Age (years)					
2 to <6	14/30 (46.7%)	16/32 (50.0%)	7/28 (25.0%)	21.7% (−2.3%, 45.7%)	25.0% (1.4%, 48.6%)
6<12	24/46 (52.2%)	18/39 (46.2%)	7/49 (14.3%)	37.9% (20.4%, 55.3%)	31.9% (13.4%, 50.3%)
12 to <18	2/9 (22.2%)	3/12 (25.0%)	1/6 (16.7%)	5.6% (−34.8%, 45.9%)	8.3% (−30.3%, 46.9%)
Sex					
Female	19/37 (51.4%)	20/45 (44.4%)	7/34 (20.6%)	30.8% (9.7%, 51.8%)	23.9% (4.0%, 43.7%)
Male	21/48 (43.8%)	17/38 (44.7%)	8/49 (16.3%)	27.4% (10.0%, 44.9%)	28.4% (9.5%, 47.3%)
Baseline IGA Score					
2 = Mild	4/14 (28.6%)	7/13 (53.8%)	2/12 (16.7%)	11.9% (−19.8%, 43.6%)	37.2% (2.8%, 71.5%)
3 = Moderate	36/71 (50.7%)	30/70 (42.9%)	13/71 (18.3%)	32.4% (17.7%, 47.1%)	24.6% (9.9%, 39.2%)

Source: Statistical Reviewer's Analysis; ADOIGA.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Two-sided 95% CI is calculated based on the Wald confidence interval.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

Table 49: Results for IGA Success[1] at Week 4 by Age, Sex, Race, Ethnicity, and Baseline IGA Score – Trial MEDI-MM36-301 (FAS[2])

Subgroup	Difamilast Ointment, 1% (N=94)	Vehicle (N=59)	Difference (95% CI)[3]
Age (years)			
2 to <6	1/5 (20.0%)	0/4 (0%)	20.0% (−15.1%, 55.1%)
6 to <12	1/6 (16.7%)	0/2 (0%)	16.7% (−13.2%, 46.5%)
12 to <18	1/12 (8.3%)	2/8 (25.0%)	−16.7% (−50.5%, 17.2%)
18 to <65	6/54 (11.1%)	4/36 (11.1%)	0% (−13.3%, 13.3%)
≥65	2/17 (11.8%)	1/9 (11.1%)	0.7% (−25.0%, 26.3%)
Sex			
Female	5/59 (8.5%)	2/36 (5.6%)	2.9% (−7.4%, 13.2%)
Male	6/35 (17.1%)	5/23 (21.7%)	−4.6% (−25.6%, 16.4%)
Race			
White	8/55 (14.5%)	4/37 (10.8%)	3.7% (−9.9%, 17.4%)
Black or African American	3/27 (11.1%)	1/14 (7.1%)	4.0% (−14.0%, 21.9%)
Asian	0/4 (0%)	2/6 (33.3%)	−33.3% (−71.1%, 4.4%)
Other	0/8 (0%)	0/2 (0%)	Not estimable
Ethnicity			
Hispanic or Latino	1/6 (16.7%)	1/6 (16.7%)	0% (−42.2%, 42.2%)
Not Hispanic or Latino	10/88 (11.4%)	6/53 (11.3%)	0% (−10.8%, 10.9%)
Baseline IGA Score			
2 = Mild	3/29 (10.3%)	0/22 (0%)	10.3% (−0.7%, 21.4%)
3 = Moderate	8/65 (12.3%)	7/37 (18.9%)	−6.7% (−21.6%, 8.3%)

Source: Statistical Reviewer's Analysis; ADQS.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Two-sided 95% CI is calculated based on the Wald confidence interval.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

8.1.3. Assessment of Efficacy Across Trials

The Applicant conducted three phase 2 trials (271-12-205, 271-15-001, and 271-102-00002) and three phase 3 trials (271-102-00007, 271-102-00008, and MEDI-MM36-301). Table 50 presents the results of IGA success at Week 4 for the phase 2 and 3 trials. There was some heterogeneity in treatment effects and response rates across the trials. The later phase 3 trials in Japan (i.e., Trials 271-102-00007 and 271-102-00008) had larger treatment effects and response rates than the multinational phase 2 trial (271-12-205).

Table 50: Results of IGA Success[1] at Week 4 for the Phase 2 and 3 Trials (FAS[2])

Trial IGA Success Parameter	Difamilast Ointment, 1%	Difamilast Ointment, 0.3%	Vehicle
Trial 271-12-205 (Phase 2, Multinational)	N=43	N=41	N=37
Responders, n (%)	9 (20.9)	6 (14.6)	1 (2.7)
Difference from vehicle (95% CI)[3]	18.2 (5.0, 31.5)	11.9 (−0.1, 24.0)	-
p-value[3]	0.017	0.069	-
Trial 271-15-001 (Phase 2, Japan)	N=67	N=67	N=66
Responders, n (%)	15 (22.4)	10 (14.9)	6 (9.1)
Difference from vehicle (95% CI)[4]	13.2 (1.4, 25.1)	5.8 (−5.0, 16.6)	-
p-value[4]	0.033	0.300	-
Trial 271-102-00002 (Phase 2, Japan)	N=25	N=24	N=24
Responders, n (%)	10 (40.0)	9 (37.5)	2 (8.3)
Difference from vehicle (95% CI)[4]	32.0 (9.8, 54.1)	30.4 (8.5, 52.3)	-
p-value[4]	0.011	0.011	-
Trial 271-102-00007 (Phase 3, Japan)	N=182	-	N=182
Responders, n (%)	70 (38.5)	-	23 (12.6)
Difference from vehicle (95% CI)[4]	25.9 (17.5, 34.4)	-	-
p-value[4]	<0.001	-	-
Trial 271-102-00008 (Phase 3, Japan)	N=85	N=83	N=83
Responders, n (%)	40 (47.1)	37 (44.6)	15 (18.1)
Difference from vehicle (95% CI)[5]	28.7 (15.0, 42.5)	24.7 (11.3, 38.0)	-
p-value[5]	<0.001	<0.001	-
Trial MEDI-MM36-301 (Phase 3, United States)	N=94	-	N=59
Responders, n (%)	11 (11.7)	-	7 (11.9)
Difference from vehicle (95% CI)[6]	-0.2 (−13.2, 9.0)	-	-
p-value[6]	0.702	-	-

Source: Statistical Reviewer's Analysis and Table 11.4.1.1.1-1 in clinical study report for Trial 271-15-001; ADSL.xpt, ADOIGA.xpt, and ADQS.xpt.
[1] Success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
[2] FAS: all randomized subjects who received at least one dose of study product. Missing data was imputed using non-responder imputation (NRI).
[3] Two-sided 95% CI is calculated based on the Wald confidence interval. P-value is based on the Cochran-Mantel-Haenszel (CMH) test stratified by region (North America, Europe, or Australia) and age group (<18 years or ≥18 years).
[4] Difference in proportions and 95% CI are based on the Mantel-Haenszel (MH) method stratified by baseline IGA score (2 or 3). P-value is based on the CMH test stratified by baseline IGA score (2 or 3).
[5] Difference in proportions and 95% CI are based on the MH method stratified by baseline IGA score (2 or 3) and age (2 to 6 years or 7 to 14 years). P-value is based on the CMH test stratified by baseline IGA score (2 or 3) and age (2 to 6 years or 7 to 14 years).
[6] Difference in proportions and 95% CI are based on the MH method stratified by analysis centers. P-value is based on the CMH test stratified by analysis centers.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment

8.2.Review of Safety

8.2.1. Safety Review Approach

The Applicant submitted data from five double- blind, randomized, vehicle- controlled trials to support the safety of difamilast ointment, 1% for the treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age and older. The study population included males and females aged ≥2 years with a diagnosis of atopic dermatitis of mild (2) or moderate (3) severity as measured by the IGA with ≥5% to ≤40% involvement of the BSA, excluding scalp.

The review team conducted the primary safety analyses on the following two pools of data:

- Phase 3, 4-week Japanese vehicle-controlled trials
  - 271-102-00007 (≥15 years-70 years) 2 arms: 1% and vehicle
  - 271-102-00008 (ages ≥2 to <15 years) 3 arms: 0.3 and 1% and vehicle
- Phase 2 and phase 3, 4-week vehicle-controlled US and Japanese trials
  - 271-102-00007 (≥15 years to 70 years) phase 3: 1% and vehicle (Japan)
  - 271-102-00008 (ages ≥2 to <15 years) phase 3: 0.3 and 1% and vehicle (Japan)
  - 271-102-00002 (ages 2 to 14 years) phase 2: 0.3 and 1% and vehicle (Japan)
  - US-MEDI-MM36-301 (ages ≥2 years) phase 3: 1% and vehicle (aborted US trial)

The review team also analyzed data from adequate and well-controlled phase 2 multinational trial (271-12-205) that was conducted in the US, Australia and Poland and evaluated subjects ages 10 to 70 years who received one of two concentrations of difamilast ointment (0.3% and 1%) or vehicle for 8 weeks, and also analyzed data from adequate and well-controlled phase 2 trial (271-15-001) that was conducted in Japan and evaluated subjects ages 15 to 70 years who received 0.3%, 1%, or vehicle for 8 weeks.

In addition, the Applicant supported the long-term safety of difamilast ointment, with pooled data from two open-label safety trials that enrolled subjects 2 years of age and older and evaluated the to be marketed concentration(s) of the product in the respective country. Trial 271-102-00006 evaluated difamilast ointment, 0.3% and 1% in subjects from Japan while Trial MEDI-MM36-302 evaluated difamilast ointment, 1% in subjects from the US, both for 52 weeks.

Because the Applicant submitted most of the controlled safety data from trials conducted in Japan, the review team performed a comparative analysis of the safety findings from the Japanese phase 3 trials (007 and 008) and the US aborted phase 3 trial (MEDI-301). Although all subjects had mild to moderate AD as assessed on the IGA scale, there were some differences in the study populations evaluated in the Japanese and US trials. The diagnostic criteria for AD were different in the two populations (Japanese Dermatological Association's Criteria versus American Academy of Dermatology AD diagnostic criteria). In the Japanese trials, subjects had a history of AD for at least 3 years while in the US trial subjects had a history of AD for at least 6 months. In addition, the scale used to define the severity of AD at baseline was different in the "almost clear" category. The category of "almost clear" (1) was not as distinct from the

category of “mild” (2) in the IGA scale used in the Japanese trials. The impact of these differences is difficult to predict.

The review team analyzed the following types of pooled data: exposure, demographics and baseline characteristics, TEAEs, SAEs, and AEs leading to discontinuation. In addition, the review team identified systemic adverse reactions (depression/suicidal ideation and behavior [SI/B], weight loss, and gastrointestinal adverse events) associated with the class of orally administered PDE-4 inhibitors as adverse events of special interest.

Supportive safety information that was reviewed by the team included data from the 120- day safety update report (SUR) and the Pharmaceuticals and Medical Devices Agency (PMDA) Periodic Safety Update Report on a New Prescription Pharmaceutical.

8.2.2. Review of the Safety Database

Overall Exposure

In the vehicle-controlled trials pool, the mean treatment duration was 27.4 days and 24.4 days for the Difamilast 1% and Vehicle groups, respectively. The mean average daily amount of study product used was 5.1 grams and 5.6 grams, respectively. Overall, the majority of subjects (596/734, 81.2%) had moderate AD severity (Grade 3 on IGA) at Baseline. The majority of subjects had ≥10% to <30% (458/734, 62.4%) or ≥5% to <10% (161/734, 21.9%) BSA affected at Baseline

In the long-term uncontrolled trials pool, the mean treatment duration was 225.5 days for Difamilast ointment, 1%. The mean average daily amount used was 4.0 grams. The majority (469, 54.8%) of subjects applied study product for 8 or more 4-week treatment cycles. There were 522 (60.9%) subjects who received treatment for at least 6 months and 257 (30.0%) subjects who received treatment for 1 year. Overall, the majority of subjects had moderate (IGA Grade 3; 533/857, 62.2%) or mild (IGA Grade 2; 288/857, 33.6%) AD at Baseline.

Across all vehicle-controlled trials to support safety, a total of 429 subjects received difamilast ointment, 1%, including 143 subjects under 18 years of age and 286 subjects 18 years of age and older. In the open-label trials, a total of 857 subjects received difamilast ointment, 1%, including 361 subjects under 18 years of age and 496 subjects 18 years of age and older. The number of subjects per each trial to support safety by age ranges are summarized below.

Table 51: Number of Subjects per Arm by Age Range, Vehicle Controlled Trials

Trial Age Range	Difamilast, 0.3%	Difamilast, 1% N=429	Vehicle N=385
Japanese P3 trials 007 and 008	N=83	N=267	N=265
≥2 to <12	71	76	77
≥12 to <18	12	10	7
≥18	0	181	181
US P3 Trial MEDI-301 (aborted early):	NA	N=94	N=59
≥2 to <12	NA	11	6
≥12 to <18	NA	12	8
≥18	NA	71	45
Japanese P2 trial 271-102-00002	NA	N=26	N=24
≥2 to ≤14	NA	25	24
US+ (multinational) P2 Trial 271-12-205	NA	N=43	N=37
≥10 to <18	NA	9	8
≥18 to 70	NA	34	29

Abbreviations: N, number of total subjects in trial/arm; NA, not applicable

Table 52: Number of Subjects per Arm by Age Range, Long-Term Uncontrolled Trials

Trials Age Range	Difamilast, 1% N=857[1]
Japanese open-label LTS trial 006	N=320[2]
≥2 to <12	123
≥12 to <18	45
≥18	152
US open-label LTS trial MEDI-302	N=537[3]
≥2 to <12	120
≥12 to <18	73
≥18	344

[1] In the long-term uncontrolled trials the mean treatment duration was 226 days. 522 (61%) subjects received treatment for at least 6 months and 257 (30%) subjects received treatment for 52 weeks.
[2] There were 98 subjects in this trial who initially received 0.3% and then were escalated to 1%. Subjects with any exposure to 1% [N=320] were analyzed for safety.
[3] 437 Denovo, 100 from aborted trial MEDI-301 [66 previously on difam, 34 previously on vehicle]
Abbreviations: N, number of total subjects in trial/arm; NA, not applicable

Adequacy of the Safety Database:

The total subject exposure to difamilast ointment applied twice daily for the treatment of mild to moderate atopic dermatitis provides adequate data for the evaluation of safety. Although the majority of the subjects in the safety database were from Japan, the overall epidemiological characteristics of AD are comparable between Japan and the United States, with prevalences of approximately 10% in both populations and similar distributions of severity (primarily mild-to-moderate). There is some genetic variability between Japanese patients with AD and other races/ethnicities, and in clinical presentation of AD (e.g., more sharply demarcated lesions with more lichenification in Asian patients.) However, the clinical relevance of these differences is unclear. Therapeutic guidelines recommend identical treatment approaches for AD irrespective of the race and ethnicity, suggesting that such differences do not impact response to treatment. Therefore, the review team concludes that the demographics of the study population are sufficiently representative of the target population in the United States and safety findings from the Japanese trials may be extrapolated to the United States population.

The total exposures for up to one year are sufficient to characterize the safety of the product over longer treatment periods.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no data integrity or submission quality issues.

Categorization of Adverse Events

Definitions

The Applicant defined an adverse event (also referred to as an adverse experience) as "any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality."

Examples of an AE include but are not limited to the following:

- Clinically significant abnormal test findings
- Clinically significant signs and symptoms
- Clinically relevant changes in physical examination findings
- Hypersensitivity
- Progression/worsening of an underlying condition(s) or disease(s)

The Applicant defined an adverse reaction (AR) as " an AE for which there is a reasonable possibility that the drug caused the AE." For the purposes of IND safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE.

An AE or suspected AR is considered "unexpected" if

- it is not listed in the Investigator Brochure (IB), is not listed at the specificity or severity that has been observed, or if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere.
- mentioned in the IB or other applicable documentation as occurring with a class of drug or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

An AE or AR is considered "serious" if it results in any of the following outcomes:

- Death
- Life-threatening AE: its occurrence places the study subject at immediate risk of death.
- Requires hospitalization or prolongation of existing hospitalizations
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

- Other important medical events (events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above)

Documentation

- All observed or volunteered AEs regardless of suspected causal relationship to the study drug were recorded on the appropriate electronic case report form from the time consent/assent is obtained through the end of the trial.
- For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. If related to the study drug, the Investigator is required to follow the subject until the adverse event or its sequelae resolves or stabilizes at a level acceptable

Assessment of Severity

The investigator determined the severity of an AE or SAE according to the following scale:

Table 53: Criteria for Determining Grade/Severity of an Adverse Event and Serious

Grade	Description
1	Mild; discomfort noticed but no disruption to daily activity
2	Moderate; discomfort sufficient to reduce or affect normal daily activity
3	Severe; inability to work or perform normal daily activity; not immediately life threatening; hospitalization or prolongation of hospitalization
4	Life-threatening consequences; urgent intervention indicated
5	Death

Source: Table 6, Protocol MEDI-MM36-301

Assessment of Relationship of an Adverse Event to Study Drug

The investigator determined the relationship to the study drug using the following definitions:

Table 54: Criteria for Determining Relationship of an Adverse Event to the Study

Relationship	Description
Related	There is a reasonable possibility of a temporal and causal relationship between the study drug and the AE.
Not related	There is no temporal or causal relationship between the study drug and the AE.

Source: Table 6, Protocol MEDI-MM36-301
Abbreviations: AE, adverse event

Pregnancy Reporting

If a subject became pregnant during the trial, the Investigator reported the pregnancy to the Applicant or representative within 24 hours of being notified. The investigator followed the pregnancy until completion and documented the outcome. If the outcome met the definition of

serious (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), then reporting procedures for SAE were implemented.

Routine Clinical Tests

In US Trial MEDI-MM36-301, safety monitoring included clinical evaluation of AEs, SAEs, vital signs including height and weight, physical examinations, clinical laboratory evaluation (chemistry, hematology, and urinalysis and pregnancy testing), ECGs, application site assessment by the investigator and local tolerability assessment by the subject/caregiver. Because patients with a chronic disease such as AD are at increased risk of depression and suicidal ideation and behavior (SI/B), and per the agreed upon SPA, investigators actively assessed subjects for these psychiatric AEs. Investigators evaluated subjects for SI/B using the Columbia Suicide Severity Rating Scale (C-SSRS) and depression using the Patients Health Questionnaire 9 (PHQ-9; adults); Center for Epidemiologic Studies Depression Scale for Children (CES-DC: ages 6 to 17 years) and Child Behavior Checklist for Ages 1½ - 5 (CBCL: ages 2 to 5 years.)

In Japanese trials 271-102-00007/271-102-00008, safety monitoring included clinical evaluation of AEs, SAEs, vital signs (body temperature, blood pressure, pulse rate) and body weight, physical examinations, clinical laboratory evaluation (hematology, serum chemistry, qualitative urinalysis, and pregnancy testing for women of childbearing potential). Local tolerability was monitored through adverse event reporting and clinical examination. No formal psychiatric assessment scales (C-SSRS, PHQ-9, CES-DC, or CBCL) were used for systematic evaluation of depression or suicidal ideation/behavior; instead, psychiatric adverse events were captured through routine adverse event monitoring and reporting.

Local Tolerability and Application Site Reactions Assessments

Active local tolerability and application site assessments were conducted only in US vehicle-controlled trial MEDI-MM36-301 (N=153) and US open-label long term safety trial MEDI-MM36-302 (N=542). Local tolerability (burning, stinging, itching) were assessed by subjects/caregivers after the most recent application at Baseline (prior to first application), 15 minutes post-application, and at each trial visit (provided trial drug applied within 7 days prior). Application site assessments (for erythema, papulation/vesiculation, and edema; graded none, mild, moderate, or severe) were performed by investigators.

The Japanese phase 3 trials (vehicle controlled 271-102-00007 and 271-102-00008, N=619; and open-label long term safety Trial 271-102-00006, N=320 received difamilast ointment 1%,) did not include active local tolerability assessments and instead relied on clinical examinations and adverse event reporting.

All Japanese phase 3 trials and US phase 3 trials included patch testing as needed to assess any suspected hypersensitivity reactions within the treatment area. Patch testing was not performed in trials 271-102-00002, 271-102-00007, 271-102-00008, and 271-102-00006.

8.2.4. Safety Results

Deaths

There were no deaths in the development program.

Serious Adverse Events

Serious adverse events were infrequent across the integrated safety analysis and were generally not related to difamilast treatment. No serious TEAEs occurred in the pivotal trials pool (271-102-00007 and 271-102-00008). In the vehicle-controlled trials pool (271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301), 1 serious TEAE occurred in 1 subject - thyroid cancer in a subject receiving Difamilast 1%, which was considered not related to treatment by the investigator nor clinical reviewer and did not result in study discontinuation.

The long-term uncontrolled trials pool (studies 271-102-00006 and MEDI-MM36-302) had 11 serious TEAEs in 11 subjects (1.28%), representing an exposure-adjusted incidence rate of 1.93 per 100 person-years. These events included neoplasms (diffuse large B-cell lymphoma, esophageal carcinoma, spinal cord neoplasm), cardiovascular events (acute myocardial infarction), respiratory events (asthma, pulmonary embolism), and other conditions (cholecystitis acute, chronic kidney disease, procedural pain). None of these were considered related by the investigator nor clinical reviewer. Only one serious TEAE was deemed treatment-related by the Investigator - spontaneous abortion in one subject - however, the Medical Monitor considered this unlikely related to treatment given the subject's concurrent use of phentermine, a medication which is contraindicated during pregnancy. The Division of Maternal Health clinical reviewer determined that the concomitant phentermine exposure confounds the relationship between difamilast exposure and the adverse pregnancy outcome, and details such as the subjects medical and obstetrical history are missing, further contributing to the difficulty in determining a causal relationship (review by Dr. Kerry Shaab dated 1/5/2026).

Dropouts and/or Discontinuations Due to Adverse Effects

Details of discontinuations due to TEAEs are provided below:

Pivotal Trials Pool (007 and 008, N=532):

- Total discontinuations due to TEAEs: 35 subjects (6.58%); Difamilast 1%: 9/267 subjects (3.37%) and vehicle: 26/265 subjects (9.81%). The most common TEAE leading to study discontinuation was atopic dermatitis in 30 subjects (3.37% Difamilast 1%, 7.92% Vehicle). Other TEAEs that led to discontinuation occurred in single subjects (0.38% Vehicle each) and included: dermatitis acneiform, dermatitis contact, drug eruption, application site hypersensitivity, application site pain, herpes simplex, and herpes virus infection.

Vehicle-Controlled Trials Pool (Trials -102-00002, 271-102-00007, 271-102-00008, MEDI-MM36-301, N=734):

- Total discontinuations due to TEAEs: 42 subjects (5.72%); Difamilast 1%: 11/386 subjects (2.85%) and vehicle: 31/348 subjects (8.91%). The most common TEAE leading to discontinuation was atopic dermatitis in 36 subjects (2.59% Difamilast 1%, 7.47% Vehicle). Other TEAEs that led to discontinuation included: dermatitis contact (0.26% Difamilast 1%, 0.29% Vehicle), and in single subjects (0.29% Vehicle each): dermatitis acneiform, drug eruption, application site hypersensitivity, application site pain, herpes simplex, and herpes virus infection.

Long-Term Uncontrolled Trials Pool (Studies 271-102-00006 and MEDI-MM36-302, N=857):

- Total discontinuations due to TEAEs: 33 subjects (3.85%), all subjects received Difamilast 1% in these uncontrolled trials. The most common TEAEs leading to discontinuation included: Atopic dermatitis: 11 subjects (1.28%), Application site pain: 5 subjects (0.58%), Application site pruritus: 4 subjects (0.47%) and contact dermatitis: 4 subjects (0.47%).

Treatment-Emergent Adverse Events and Adverse Reactions

In the vehicle-controlled trials, difamilast ointment, 1% demonstrated an acceptable safety profile across all age groups with no clinically significant safety signals identified.

Among 386 subjects receiving difamilast ointment, 1% compared to 348 receiving vehicle, no TEAEs occurred with an incidence rate difference of ≥1% between the difamilast group and vehicle group. The most frequently reported TEAEs were nasopharyngitis (4.9% versus 4.6% for difamilast ointment, 1% versus vehicle) and viral infections (2.8% versus 2.6%), both occurring at similar rates between treatment groups. While several low-frequency TEAEs (<1%) occurred exclusively in the difamilast ointment, 1% group, including molluscum contagiosum (0.8%) and various infections and systemic adverse events (each in single subjects, 0.3%), these findings did not suggest a concerning safety pattern.

Age-stratified analyses revealed that pediatric subjects (≥2 to <12 years) had the highest incidence rates for common TEAEs, with nasopharyngitis occurring in 7.5% of difamilast-treated subjects versus 6.7% receiving vehicle, while adult subjects (≥18 years) showed lower overall TEAE rates at 4.4% versus 3.5% for nasopharyngitis, respectively. The adolescent population (≥12 to <18 years) showed generally low TEAE frequencies across both treatment groups.

TEAE in All Ages in Vehicle-Controlled Trials:

In the overall study population of the vehicle -controlled trials with 4 weeks of treatment duration (-002, -007, -008, and MEDI-MM36--301), difamilast ointment,1% was administered to 386 subjects compared to 348 subjects receiving vehicle (refer to Table 55 below). There were no incidence rate differences of greater than 1% for TEAEs between difamilast and vehicle groups. The most common TEAE was nasopharyngitis, occurring in 19/386 (4.9%) subjects in the

difamilast 1% group versus 16/348 (4.6%) in the vehicle group. Viral infections occurred in 11/386 (2.8%) subjects receiving difamilast 1% compared to 9/348 (2.6%) receiving vehicle. No other TEAEs occurred at ≥1% frequency in the difamilast 1% group while being higher than vehicle.

TEAEs occurring at <1% frequency in the difamilast 1% group but absent in the vehicle group included: molluscum contagiosum (3/386, 0.8%), and single cases (0.3% each) of eczema herpeticum, herpangina, herpes simplex, oral herpes, abscess limb, cystitis, folliculitis, pharyngitis streptococcal, streptococcal infection, body tinea, tinea pedis, eye contusion, contusion, back pain, bronchospasm/asthma, depression, fatigue, lethargy, malaise, thyroid cancer, peripheral edema, renal and urinary infection/cystitis, somnolence/lethargy, and systemic hypertension.

Refer to "Available Safety Data for Local Tolerability and Application Site Reactions" below for discussion of local tolerability and application site reactions observed in these trials.

Table 55: NDA 219474 ISS Vehicle Controlled Studies 002, 007, 008 and 301: Summary of Subjects With TEAEs by Narrow OCMQ and PT

Narrow OCMQ Term Preferred Term	Difamilast 0.3% N=107 n (%)	Difamilast 1% N=386 n (%)	Vehicle N=348 n (%)
Nasopharyngitis	7 (6.5)	19 (4.9)	16 (4.6)
Nasopharyngitis	6 (5.6)	16 (4.1)	13 (3.7)
Upper respiratory tract infection	0 (0.0)	2 (0.5)	3 (0.9)
Pharyngitis streptococcal	0 (0.0)	1 (0.3)	0 (0.0)
Pharyngitis	1 (0.9)	0 (0.0)	0 (0.0)
Viral Infection	4 (3.7)	11 (2.8)	9 (2.6)
Molluscum contagiosum	0 (0.0)	3 (0.8)	0 (0.0)
Influenza	2 (1.9)	2 (0.5)	2 (0.6)
Skin papilloma	1 (0.9)	2 (0.5)	1 (0.3)
Eczema herpeticum	0 (0.0)	1 (0.3)	0 (0.0)
Herpangina	0 (0.0)	1 (0.3)	0 (0.0)
Herpes simplex	0 (0.0)	1 (0.3)	2 (0.6)
Oral herpes	0 (0.0)	1 (0.3)	1 (0.3)
Adenovirus infection	1 (0.9)	0 (0.0)	0 (0.0)
Conjunctivitis viral	0 (0.0)	0 (0.0)	1 (0.3)
Hand-foot-and-mouth disease	1 (0.9)	0 (0.0)	0 (0.0)
Herpes virus infection	0 (0.0)	0 (0.0)	1 (0.3)
Influenza a virus test positive	0 (0.0)	0 (0.0)	1 (0.3)
Varicella	0 (0.0)	0 (0.0)	1 (0.3)

Narrow OCMQ Term Preferred Term	Difamilast 0.3% N=107 n (%)	Difamilast 1% N=386 n (%)	Vehicle N=348 n (%)
Bacterial Infection	11 (10.3)	9 (2.3)	14 (4.0)
Impetigo	6 (5.6)	3 (0.8)	5 (1.4)
Abscess limb	0 (0.0)	1 (0.3)	0 (0.0)
Application site folliculitis	3 (2.8)	1 (0.3)	2 (0.6)
Cystitis	0 (0.0)	1 (0.3)	0 (0.0)
Folliculitis	0 (0.0)	1 (0.3)	0 (0.0)
Pharyngitis streptococcal	0 (0.0)	1 (0.3)	0 (0.0)
Streptococcal infection	0 (0.0)	1 (0.3)	0 (0.0)
Application site cellulitis	0 (0.0)	0 (0.0)	1 (0.3)
Cellulitis	0 (0.0)	0 (0.0)	1 (0.3)
Furuncle	0 (0.0)	0 (0.0)	1 (0.3)
Paronychia	1 (0.9)	0 (0.0)	2 (0.6)
Purulence	0 (0.0)	0 (0.0)	1 (0.3)
Sinusitis bacterial	1 (0.9)	0 (0.0)	0 (0.0)
Staphylococcal infection	0 (0.0)	0 (0.0)	1 (0.3)
Rash	3 (2.8)	4 (1.0)	7 (2.0)
Dermatitis contact	0 (0.0)	2 (0.5)	2 (0.6)
Application site rash	0 (0.0)	1 (0.3)	0 (0.0)
Urticaria	1 (0.9)	1 (0.3)	0 (0.0)
Acne	0 (0.0)	0 (0.0)	1 (0.3)
Application site acne	0 (0.0)	0 (0.0)	2 (0.6)
Dermatitis	1 (0.9)	0 (0.0)	0 (0.0)
Dermatitis acneiform	0 (0.0)	0 (0.0)	1 (0.3)
Rash	0 (0.0)	0 (0.0)	1 (0.3)
Rash papular	1 (0.9)	0 (0.0)	0 (0.0)
Arthralgia	1 (0.9)	3 (0.8)	0 (0.0)
Arthralgia	1 (0.9)	3 (0.8)	0 (0.0)
Fatigue	0 (0.0)	2 (0.5)	0 (0.0)
Lethargy	0 (0.0)	1 (0.3)	0 (0.0)
Malaise	0 (0.0)	1 (0.3)	0 (0.0)
Fungal Infection	0 (0.0)	2 (0.5)	0 (0.0)
Body tinea	0 (0.0)	1 (0.3)	0 (0.0)
Tinea pedis	0 (0.0)	1 (0.3)	0 (0.0)
Hemorrhage	0 (0.0)	2 (0.5)	0 (0.0)
Contusion	0 (0.0)	1 (0.3)	0 (0.0)
Eye contusion	0 (0.0)	1 (0.3)	0 (0.0)
Back Pain	0 (0.0)	1 (0.3)	0 (0.0)
Back pain	0 (0.0)	1 (0.3)	0 (0.0)
Bronchospasm	0 (0.0)	1 (0.3)	1 (0.3)
Asthma	0 (0.0)	1 (0.3)	1 (0.3)
Depression	0 (0.0)	1 (0.3)	0 (0.0)
Depression	0 (0.0)	1 (0.3)	0 (0.0)
Diarrhea	1 (0.9)	1 (0.3)	1 (0.3)
Diarrhoea	1 (0.9)	1 (0.3)	1 (0.3)

Narrow OCMQ Term Preferred Term	Difamilast 0.3% N=107 n (%)	Difamilast 1% N=386 n (%)	Vehicle N=348 n (%)
Local Administration Reaction	0 (0.0)	1 (0.3)	2 (0.6)
Application site rash	0 (0.0)	1 (0.3)	0 (0.0)
Application site hypersensitivity	0 (0.0)	0 (0.0)	1 (0.3)
Application site pain	0 (0.0)	0 (0.0)	1 (0.3)
Malignancy	0 (0.0)	1 (0.3)	0 (0.0)
Thyroid cancer	0 (0.0)	1 (0.3)	0 (0.0)
Peripheral Edema	0 (0.0)	1 (0.3)	0 (0.0)
Oedema peripheral	0 (0.0)	1 (0.3)	0 (0.0)
Purulent Material	0 (0.0)	1 (0.3)	2 (0.6)
Abscess limb	0 (0.0)	1 (0.3)	0 (0.0)
Furuncle	0 (0.0)	0 (0.0)	1 (0.3)
Purulence	0 (0.0)	0 (0.0)	1 (0.3)
Pyrexia	1 (0.9)	1 (0.3)	1 (0.3)
Pyrexia	1 (0.9)	1 (0.3)	1 (0.3)
Renal and Urinary Infection	0 (0.0)	1 (0.3)	0 (0.0)
Cystitis	0 (0.0)	1 (0.3)	0 (0.0)
Somnolence	0 (0.0)	1 (0.3)	0 (0.0)
Lethargy	0 (0.0)	1 (0.3)	0 (0.0)
Systemic Hypertension	0 (0.0)	1 (0.3)	0 (0.0)
Hypertension	0 (0.0)	1 (0.3)	0 (0.0)
Urticaria	1 (0.9)	1 (0.3)	0 (0.0)
Urticaria	1 (0.9)	1 (0.3)	0 (0.0)
Abdominal Pain	0 (0.0)	0 (0.0)	2 (0.6)
Abdominal pain	0 (0.0)	0 (0.0)	2 (0.6)
Arrhythmia	0 (0.0)	0 (0.0)	1 (0.3)
Bradycardia	0 (0.0)	0 (0.0)	1 (0.3)
Constipation	1 (0.9)	0 (0.0)	0 (0.0)
Constipation	1 (0.9)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	1 (0.3)
Cough	0 (0.0)	0 (0.0)	1 (0.3)
Headache	1 (0.9)	0 (0.0)	0 (0.0)
Headache	1 (0.9)	0 (0.0)	0 (0.0)
Hepatic Injury	0 (0.0)	0 (0.0)	1 (0.3)
Hepatic function abnormal	0 (0.0)	0 (0.0)	1 (0.3)
Hyperglycemia	0 (0.0)	0 (0.0)	1 (0.3)
Blood glucose increased	0 (0.0)	0 (0.0)	1 (0.3)
Hypersensitivity	0 (0.0)	0 (0.0)	3 (0.9)
Allergy to chemicals	0 (0.0)	0 (0.0)	1 (0.3)
Application site hypersensitivity	0 (0.0)	0 (0.0)	1 (0.3)
Drug eruption	0 (0.0)	0 (0.0)	1 (0.3)
Drug hypersensitivity	0 (0.0)	0 (0.0)	1 (0.3)
Pruritus	0 (0.0)	0 (0.0)	2 (0.6)
Application site pruritus	0 (0.0)	0 (0.0)	2 (0.6)

Narrow OCMQ Term Preferred Term	Difamilast 0.3% N=107 n (%)	Difamilast 1% N=386 n (%)	Vehicle N=348 n (%)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.3)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Difamilast 0.3%" and STUDYID = "27110200007" or "27110200008" or "27110200002" or "MEDI-MM36-301" and SAFFL = Y (Difamilast 0.3%); TRT01A = "Difamilast 1%" and STUDYID = "27110200007" or "27110200002" or "27110200008" or "MEDI-MM36-301" and SAFFL = Y (Difamilast 1%); TRT01A = "Vehicle" and STUDYID = "27110200007" or "27110200002" or "27110200008" or "MEDI-MM36-301" and SAFFL = Y (Vehicle); TRTEMFL = "Y" (Adverse Events).
Abbreviations: OCMQ, Office of New Drugs Custom Medical Queries; OCS, Office of Computational Science; PT, preferred term; TEAE, treatment-emergent adverse event

TEAE Stratified by Age in Vehicle-Controlled Trials

TEAE stratified by age group were also analyzed by the review team (refer to Table 56 below).

Nasopharyngitis was consistently the most common adverse event across all age-stratified populations, though it occurred more frequently in children (7.5%) than in adults (4.4%) receiving difamilast. Viral infections also showed an age-related pattern, with higher rates in the pediatric population (6.5%) compared to adults (1.6%) in the difamilast group. These differences likely reflect the natural increased susceptibility of children to respiratory infections such as nasopharyngitis, potential seasonal variations across trials, and typical exposure patterns in pediatric populations rather than a drug-related effect. The safety profile was generally comparable between difamilast and vehicle across all age groups, with no major safety signals identified.

Pediatric Population (2 to under 12 years): This group included 107 children who received difamilast 1% and 104 who received vehicle. Nasopharyngitis occurred in 8/107 children (7.5%) in the difamilast group compared to 7/104 children (6.7%) in the vehicle group. Viral infections affected 7/107 children (6.5%) in the difamilast group compared to 4/104 children (3.8%) in the vehicle group. Bacterial infections occurred in 6/107 children (5.6%) in the difamilast group compared to 6/104 children (5.8%) in the vehicle group.

Adolescent Population (12 to under 18 years): This group included 27 adolescents who received difamilast 1% and 18 who received vehicle. There were no reports of nasopharyngitis in adolescents, and TEAEs that occurred in adolescent subjects on 1% difamilast and none in vehicle included single subjects cases (3.7%) of arthralgia, malaise, and lethargy, all unrelated to the drug product.

Adult Population (18 years and older): This group included 252 adults who received difamilast 1% and 226 who received vehicle. Nasopharyngitis occurred in 11/252 adults (4.4%) in the difamilast group compared to 8/226 adults (3.5%) in the vehicle group. Viral infections affected 4/252 adults (1.6%) in the difamilast group compared to 5/226 adults (2.2%) in the vehicle group. Overall, adverse event rates were generally lower in adults compared to children.

Table 56: NDA 219474 ISS Vehicle Controlled Studies 002, 007, 008 and 301: Summary of Subjects With TEAEs by Narrow OCMQ and PT Stratified by Age

	Difamilast 0.3%						Difamilast 1%						Vehicle					
	≥2 to <12 years (N=90)		≥12 to <18 years (N=17)		≥18 years (N=0)		≥2 to <12 years (N=107)		≥12 to <18 years (N=27)		≥18 years (N=252)		≥2 to <12 years (N=104)		≥12 to <18 years (N=18)		≥18 years (N=226)	
Narrow OCMQ Term **Preferred Term**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Nasopharyngitis	7	(7.8)	0	(0.0)	0	(0.0)	8	(7.5)	0	(0.0)	11	(4.4)	7	(6.7)	1	(5.6)	8	(3.5)
Nasopharyngitis	6	(6.7)	0	(0.0)	0	(0.0)	7	(6.5)	0	(0.0)	9	(3.6)	5	(4.8)	1	(5.6)	7	(3.1)
Pharyngitis streptococcal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Upper respiratory tract infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.4)	2	(1.9)	0	(0.0)	1	(0.4)
Pharyngitis	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Viral Infection	4	(4.4)	0	(0.0)	0	(0.0)	7	(6.5)	0	(0.0)	4	(1.6)	4	(3.8)	0	(0.0)	5	(2.2)
Eczema herpeticum	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes simplex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	2	(0.9)
Oral herpes	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.4)
Skin papilloma	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.4)
Adenovirus infection	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis viral	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Hand-foot-and-mouth disease	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Herpangina	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes virus infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Influenza	2	(2.2)	0	(0.0)	0	(0.0)	2	(1.9)	0	(0.0)	0	(0.0)	2	(1.9)	0	(0.0)	0	(0.0)
Influenza a virus test positive	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Molluscum contagiosum	0	(0.0)	0	(0.0)	0	(0.0)	3	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Varicella	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Fungal Infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)
Body tinea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)

	Difamilast 0.3%						Difamilast 1%						Vehicle					
Narrow OCMQ Term Preferred Term	≥2 to <12 years (N=90)		≥12 to <18 years (N=17)		≥18 years (N=0)		≥2 to <12 years (N=107)		≥12 to <18 years (N=27)		≥18 years (N=252)		≥2 to <12 years (N=104)		≥12 to <18 years (N=18)		≥18 years (N=226)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Rash	3	(3.3)	0	(0.0)	0	(0.0)	2	(1.9)	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	7	(3.1)
Dermatitis contact	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	2	(0.9)
Acne	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Application site acne	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)
Application site rash	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis acneiform	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Rash	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Rash papular	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Arthralgia	0	(0.0)	1	(5.9)	0	(0.0)	1	(0.9)	1	(3.7)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Arthralgia	0	(0.0)	1	(5.9)	0	(0.0)	1	(0.9)	1	(3.7)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Back Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Bacterial Infection	10	(11.1)	1	(5.9)	0	(0.0)	6	(5.6)	2	(7.4)	1	(0.4)	6	(5.8)	0	(0.0)	8	(3.5)
Pharyngitis streptococcal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Abscess limb	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Application site cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Application site folliculitis	2	(2.2)	1	(5.9)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Cystitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Folliculitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Furuncle	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Impetigo	6	(6.7)	0	(0.0)	0	(0.0)	3	(2.8)	0	(0.0)	0	(0.0)	5	(4.8)	0	(0.0)	0	(0.0)
Paronychia	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.4)
Purulence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Sinusitis bacterial	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Staphylococcal infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Streptococcal infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Bronchospasm	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(1.0)	0	(0.0)	0	(0.0)
Asthma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(1.0)	0	(0.0)	0	(0.0)

	Difamilast 0.3%						Difamilast 1%						Vehicle					
Narrow OCMQ Term	**≥2 to <12 years (N=90)**		**≥12 to <18 years (N=17)**		**≥18 years (N=0)**		**≥2 to <12 years (N=107)**		**≥12 to <18 years (N=27)**		**≥18 years (N=252)**		**≥2 to <12 years (N=104)**		**≥12 to <18 years (N=18)**		**≥18 years (N=226)**	
Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Depression	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Depression	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Fatigue	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Lethargy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Malaise	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Eye contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Malignancy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Thyroid cancer	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Peripheral Edema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Lethargy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Systemic Hypertension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.4)
Abdominal pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.4)
Arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Constipation	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Constipation	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Cough	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Diarrhea	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Headache	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Headache	1	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hepatic Injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Hepatic function abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)

	Difamilast 0.3%						Difamilast 1%						Vehicle					
Narrow OCMQ Term **Preferred Term**	**≥2 to <12 years (N=90)**		**≥12 to <18 years (N=17)**		**≥18 years (N=0)**		**≥2 to <12 years (N=107)**		**≥12 to <18 years (N=27)**		**≥18 years (N=252)**		**≥2 to <12 years (N=104)**		**≥12 to <18 years (N=18)**		**≥18 years (N=226)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Hyperglycemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Blood glucose increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)	2	(0.9)
Allergy to chemicals	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Application site hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Drug eruption	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)	0	(0.0)
Drug hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Local Administration Reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)
Application site hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Application site pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Application site rash	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)	1	(0.4)
Application site pruritus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)	1	(0.4)
Purulent Material	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)
Abscess limb	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Furuncle	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Purulence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Pyrexia	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Pyrexia	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)
Renal and Urinary Infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cystitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)

	Difamilast 0.3%						Difamilast 1%						Vehicle					
Narrow OCMQ Term Preferred Term	≥2 to <12 years (N=90) n	(%)	≥12 to <18 years (N=17) n	(%)	≥18 years (N=0) n	(%)	≥2 to <12 years (N=107) n	(%)	≥12 to <18 years (N=27) n	(%)	≥18 years (N=252) n	(%)	≥2 to <12 years (N=104) n	(%)	≥12 to <18 years (N=18) n	(%)	≥18 years (N=226) n	(%)
Urticaria	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(1.1)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Difamilast 0.3%" and STUDYID = "MEDI-MM36-301" or "27110200002" or "27110200007" or "27110200008" and AGEGR1 = "≥2 to <12" and SAFFL = Y (Difamilast 0.3% ≥2 to <12 years); TRT01A = "Difamilast 0.3%" and STUDYID = "27110200002" or "27110200007" or "27110200008" or "MEDI-MM36-301" and AGEGR1 = "≥12 to <18" and SAFFL = Y (Difamilast 0.3% ≥12 to <18 years); TRT01A = "Difamilast 0.3%" and STUDYID = "27110200002" or "27110200007" or "27110200008" or "MEDI-MM36-301" and AGEGR1 = "≥18" and SAFFL = Y (Difamilast 0.3% ≥18 years); TRT01A = "Difamilast 1%" and STUDYID = "27110200007" or "27110200008" or "27110200002" or "MEDI-MM36-301" and AGEGR1 = "≥2 to <12" and SAFFL = Y (Difamilast 1% ≥2 to <12 years); TRT01A = "Difamilast 1%" and STUDYID = "27110200002" or "27110200007" or "27110200008" or "MEDI-MM36-301" and AGEGR1 = "≥12 to <18" and SAFFL = Y (Difamilast 1% ≥12 to <18 years); TRT01A = "Difamilast 1%" and STUDYID = "27110200002" or "27110200007" or "27110200008" or "MEDI-MM36-301" and AGEGR1 = "≥18" and SAFFL = Y (Difamilast 1% ≥18 years); TRT01A = "Vehicle" and STUDYID = "27110200007" or "27110200008" or "27110200002" or "MEDI-MM36-301" and AGEGR1 = "≥2 to <12" and SAFFL = Y (Vehicle ≥2 to <12 years); TRT01A = "Vehicle" and STUDYID = "27110200002" or "27110200007" or "27110200008" or "MEDI-MM36-301" and AGEGR1 = "≥12 to <18" and SAFFL = Y (Vehicle ≥ 12 to <18 years); TRT01A = "Vehicle" and STUDYID = "27110200002" or "27110200007" or "27110200008" or "MEDI-MM36-301" and AGEGR1 = "≥18" and SAFFL = Y (Vehicle ≥18 years); TRTEMFL = "Y" (Adverse Events).
Abbreviations: ISS, integrated summary of safety; OCMQ, Office of New Drugs Custom Medical Queries; OCS, Office of Computational Science; PT, preferred term; TEAE, treatment-emergent adverse event

Long-Term Safety in Open-Label Uncontrolled Trials:

The long-term uncontrolled trials included 857 subjects (320 Japanese subjects in trial -006, 537 USA subjects in trial 302). Results of long-term safety trials, including age-stratified analyses, were generally comparable with those observed in the vehicle-controlled trials, with no new systemic safety signals identified by the review team.

While not observed in the vehicle-controlled trials, application site pain was reported in the long-term safety trials in 10 subjects overall: 7 subjects (1.3%) in US trial MEDI-MM36-301 and 3 subjects (0.9%) in Japanese trial -006, and will therefore be included in labeling section 6.

Refer to "Available Safety Data for Local Tolerability and Application Site Reactions" below for discussion of local tolerability and application site reactions observed in this trial.

Available Safety Data for Local Tolerability and Application Site Reactions:

Active local tolerability assessments (burning, stinging, and itching) and application site reactions (erythema, papulation/vesiculation, and edema were conducted in US trials MEDI-MM36-301 and -302 only. The review team analyzed shift tables from baseline through all study visits to assess for clinically meaningful changes and differences in local tolerability, as well as any trends indicating worsening of burning, stinging, or itching symptoms, and for erythema, papulation/vesiculation, and edema (refer to "Summary of Local Tolerability Findings" for an integrated discussion of all findings).

Trial MEDI-MM36-301: vehicle-Controlled Trial

- Difamilast ointment, 1%: N=94 (pediatric 2-<12 years N=11, adolescent 12-<18 years N=12, adult ≥18 years: N=71);
- Vehicle: N=59 (pediatric N=6, adolescent N=8, adult N=45))

In the 4-week vehicle-controlled trial (Trial MEDI-MM36-301), local tolerability was assessed through both investigator evaluations of application site reactions (erythema, papulation/vesiculation, and edema) and subject/caregiver assessments of local symptoms (burning, stinging, and itching). The difamilast ointment, 1% group (N=94) demonstrated comparable local tolerability to the vehicle group (N=59) throughout the trial duration.

- **Application Site Reactions:** Results in both treatment groups showed similar trends for application site assessments, with most parameters remaining stable or improving from baseline. Erythema improved in both groups, while papulation/vesiculation improved in the difamilast group but remained unchanged from baseline in the vehicle group. Edema assessments remained similar to baseline in both treatment groups throughout the trial.
- **Local Tolerability Symptoms:** Burning and stinging were rare events in both treatment groups. At the final visit, subjects who received difamilast ointment, 1% showed a slightly higher incidence of mild burning (5.3% versus 1.7%) but notably lower rates of

moderate to severe burning (4.3% versus 10.2%) compared to vehicle. Symptoms of stinging improved from baseline in both groups, with moderate and severe cases becoming less frequent over time. Itching showed similar improvement patterns in both treatment groups, with severity decreasing from baseline values.

Trial MEDI-MM36-302: Open-Label Trial

- Difamilast N=542 (pediatric N=120, adolescent N=73, adult N=349)

In the long-term open-label trial (Trial MEDI-MM36-302), local tolerability assessments were conducted in 542 subjects treated with difamilast ointment, 1% for up to 52 weeks, including both rollover subjects from trial MM36-301 and de novo subjects. Overall, local tolerability findings were consistent with those observed in the controlled trials, with no evidence of symptom worsening or cumulative irritant effects over extended treatment duration. However, some application site reactions did lead to study discontinuation including application site pain (7 subjects, 1.3%), application site pruritus (4 subjects, 0.7%), contact dermatitis (4 subjects, 0.7%), application site vesicles, blistering, and application site erythema. These adverse reactions will be included in section 6 of labeling.

The review team also analyzed individual subject narratives for TEAEs relevant to local tolerability and application site adverse reactions:

In the vehicle- controlled Trial MEDI-MM36- -301: one subject ((b) (6)) receiving difamilast ointment, 1% developed contact dermatitis which led to study drug and trial discontinuation (narrative below).

- *Subject #(b) (6), a 55-year-old African American male, received difamilast ointment and developed a TEAE of moderate contact dermatitis on Day 14. The investigator considered the TEAE to be definitely related to study drug. The TEAE led to study discontinuation on Day 29. No patch testing was performed as hypersensitivity was not suspected.*

In open- label Trial -302, there were reports of application site pain, application site pruritus, application site vesicles, blistering, application site erythema, burning and contact dermatitis (without evidence of hypersensitivity). The investigator considered all of these TEAEs to be probably or definitely related to the study drug. Because these TEAEs led to both study drug and study discontinuation, the review team recommended these adverse reactions be included in section 6 of labeling. Select narratives are below:

- *Subject (b) (6), a 16-year-old female, who received DeNovo difamilast ointment developed severe **application site pain** and severe **application site pruritus** that started on Study Day 26 and recovered/resolved on Study Day 35. These TEAEs were deemed definitely related to study drug and led to study discontinuation*
- *Subject (b) (6), a 63-year-old male, who received DeNovo difamilast ointment developed moderate **application site pain** and mild **application site erythema** that started on Study*

Day 2 and recovered/resolved on Study Day 6. These TEAEs were deemed probably related to study drug and led to study discontinuation.

- *Subject (b) (6), a 14-year-old white female who received DeNovo difamilast ointment developed moderate **contact dermatitis** affecting the treated areas of arms, chest, and legs on Day 4. The investigator deemed that the adverse event was definitely related to the study drug and resulted in drug withdrawal after 6 doses. The contact dermatitis resolved by Day 8 without requiring additional treatment. Due to this adverse event, the subject was discontinued from the trial. Patch testing was not performed to further characterize the reaction.*

  - *Reviewer causality assessment -The temporal relationship between study drug initiation and onset of contact dermatitis, localization to treatment areas, resolution upon drug discontinuation, and absence of alternative explanations support causal relationship. While the localized distribution suggests irritant contact dermatitis rather than allergic contact dermatitis or systemic hypersensitivity reaction, the absence of patch testing does not allow a definitive diagnosis.*

- *Subject (b) (6), a 37-year-old female who received 4 weeks of difamilast ointment, 1% in Trial- MEDI-MM36-301 and 12 weeks of difamilast ointment in Trial-302, developed **moderate burning**, **moderate itching**, and **mild blistering** in the treatment area. The investigator assessed these TEAEs as definitely related to study drug. These TEAEs resolved by Week 14 when the investigational product was "used sparingly" per the Applicant. However, the subject elected to terminate her participation in the trial at Week 17 for "personal reasons due to tolerability issues with the investigational product," despite resolution of the application site reactions. No patch testing was performed.*

  - *Reviewer causality assessment- The temporal relationship between drug application and onset of local skin reactions (burning, itching, blistering), combined with resolution upon dose reduction and the Investigator's assessment, supports a clear causal relationship with the investigational product.*

In Japanese vehicle-controlled Trials -007 and -008, 83 subjects received difamilast ointment, 0.3%, 267 subjects received difamilast ointment, 1%, and 265 received vehicle. Two subjects (2.4%) who received difamilast 0.3% and one subject (0.4%) who received difamilast ointment, 1% developed **application site folliculitis**. One subject (0.4%) who received difamilast ointment, 1% developed **Application site rash**. One subject (0.4%) who received difamilast 1% and in 1 subject (0.4%) who received vehicle developed **Contact dermatitis**. **Therefore, these adverse reactions are proposed for inclusion in labeling section 6 as occurring in <1% of subjects.**

In Japanese open- label Trial -006 enrolled 166 adult subjects and 200 pediatric subjects (144 subjects with a starting dose of the difamilast ointment, 0.3% and 56 subjects with a starting dose of the difamilast ointment, 1%). One subject who received difamilast ointment, 0.3% reported a severe adverse event of **application** site pruritus which was assessed as related to

the study product by the investigator; 2 subjects who received difamilast ointment, 1% reported **application site pain**; and 1 subject who received difamilast ointment, 1% reported **skin burning sensation**.

Age-Stratified Analysis Of Local Tolerability

Age-stratified analyses of local tolerability symptoms were conducted for both the vehicle-controlled trial (Trial MEDI-MM36-301) and the long-term open-label trial (Trial MEDI-MM36-302). In the 4-week vehicle-controlled trial, local tolerability assessments demonstrated improvement in symptoms over the treatment period across all age groups.

Throughout the treatment period, local tolerability symptoms of burning, stinging, and itching when present were predominantly mild in severity across age groups, with both pediatric and adult subjects showing decreasing symptom severity from baseline values.

In the long-term trial, local tolerability assessments over 52 weeks showed that symptom profiles remained stable or improved over time in both pediatric and adult populations, with no evidence of cumulative irritant effects with extended use. The overall local tolerability profile was acceptable in all age groups evaluated, supporting the use of difamilast ointment in both pediatric patients 2 years of age and older and adults with mild to moderate atopic dermatitis.

Patch testing and Hypersensitivity:

All Japanese and US phase 3 trials included optional patch testing to assess any suspected hypersensitivity reactions within the treatment area. In vehicle-controlled Trial MEDI-MM36--301, patch testing was performed for a 26-year-old Asian female (Subject # (b) (6)) who received vehicle. All results on patch testing were grade "0" except for one patch which showed an irritant reaction to white petroleum on Day 3 post-application, see narrative below).

Additionally, an investigator in Trial MEDI-MM36--301 requested patch testing for a 55-year-old male (# (b) (6)) on difamilast ointment, 1%, which the subject declined (see narrative below). In open- label Trial MEDI-MM36-302, the investigator performed patch testing for a 10-year-old female (subject # (b) (6)) on difamilast ointment, 1%. All results were grade "0", suggesting no allergic response (see narrative below). **Overall, the review of the limited patch testing data and subject narratives, including analyses of subjects who reported "urticaria" as TEAEs, do not suggest hypersensitivity as a significant safety concern with difamilast ointment.**

- *Subject (b) (6), a 26-year-old Asian female who received vehicle in Trial MEDI-MM36-301, developed moderate **contact dermatitis** on Day 18 that resolved on Day 36 following treatment with Medrol Dosepak and triamcinolone ointment. Patch testing showed no reactions to study drug or vehicle on Days 3, 5, or 8 post-application. The investigator documented mild irritation to the white petroleum control on Day 3.*

  - *Reviewer causality assessment – The temporal relationship between exposure to vehicle and onset of contact dermatitis supports a causal relationship. However, the*

negative patch testing result to vehicle and study drug and mild irritation to white petroleum control suggests irritant rather than allergic contact dermatitis.

- *Subject (b) (6), a 55-year-old male in the Difamilast Ointment, 1% group (protocol MEDI-MM36-301), developed moderate **contact dermatitis** affecting his arms on Day 14. The investigator deemed the TEAE as definitely related to the study drug and interrupted drug administration. The TEAE resolved on Day 29 following treatment with gabapentin 100 mg daily. Due to this TEAE, the subject discontinued the trial. Patch testing was not performed as the subject declined.*

  - *Reviewer causality assessment – The temporal relationship between exposure to the study drug and onset of dermatitis, localized distribution to treatment areas, and resolution following drug interruption support a causal relationship. However, the lack of data from patch testing prevents definitive diagnosis of irritant versus allergic contact dermatitis.*

- *Subject (b) (6), a 10-year-old female in the difamilast ointment, 1% group (protocol MEDI-MM36-302), developed **worsening atopic dermatitis** on Day 45 (Week 6). Initially the investigator attributed the TEAE to the normal fluctuations in underlying atopic dermatitis severity; however, the investigator subsequently suspected that the TEAE was due to allergic contact dermatitis to the study drug. This suspicion prompted discontinuation of difamilast ointment and treatment with triamcinolone. The condition resolved by Week 13, but a secondary folliculitis developed at triamcinolone application sites, requiring treatment with cephalexin and topical benzoyl peroxide. Patch testing performed at Week 18 with readings at 72 hours, Day 3, and Day 7 showed no reactions to study drug, vehicle ointment, or white petroleum control (all graded "0").*
  - *Reviewer causality assessment – The negative patch testing to study drug and vehicle suggests the worsening was likely due to underlying atopic dermatitis progression or irritant contact dermatitis rather than allergic contact dermatitis.*

- *Subject # (b) (6), a 45-year-old Asian female with baseline moderate AD received vehicle for 4 weeks in Trial -007 and then developed a SAE of severe AD on Day 33, seven days after completing treatment with vehicle. The subject's baseline moderate AD worsened in the extremities with exudate development, requiring systemic steroid treatment and impacting daily activities. On Day 35, the subject presented to the emergency department with fever (38.0°C), swelling, heat, redness, and increased pain in the left elbow, where she was diagnosed and treated for cellulitis. The subject was hospitalized for cellulitis treatment, with slight improvement noted at follow-up on Day 41. However, cellulitis recurred on Day 53, requiring additional hospitalization. Although hypersensitivity was suspected and a patch test was planned by the investigator, the subject declined consent for patch testing. Both the investigator and sponsor assessed the event as related to study drug (vehicle).*
  - *Reviewer causality assessment: While hypersensitivity cannot be definitively ruled out due to the subject's refusal to undergo confirmatory patch testing, the subject's*

course could represent natural progression of the subject's underlying atopic dermatitis. Therefore, this case is not considered a hypersensitivity reaction, and hypersensitivity is not recommended for inclusion in labeling neither as a Warning and Precaution nor as an adverse reaction.

Racial Analysis

In Trial MEDI-MM36-301 and long-term safety MEDI-MM36-302, there was limited enrollment of Asian subjects (e.g., MEDI-MM36-301: 10 Asian subjects compared to 143 non-Asian subjects; MEDI-MM36-302: 40 Asian subjects compared to 502 non-Asian subjects).

In the long-term US Trial **MEDI-MM36-302**, no clinically meaningful differences were observed between Asian (N=40) and non-Asian (N=502) populations across all local tolerability parameters, though the Asian representation remained limited.

Summary of Local Tolerability Findings

Based on the available data, the local tolerability profile of difamilast ointment demonstrates acceptable safety across both short-term controlled and long-term open-label treatment period.

- **Short-term tolerability:** In vehicle-controlled trials, difamilast 1% demonstrated similar or improved local tolerability compared to vehicle. Local tolerability symptoms and application site reactions when present were predominantly mild in severity, with improvement observed over the treatment period.
- **Long-term tolerability**: Extended treatment up to 52 weeks generally maintained stable symptom severity with predominantly mild events when present. However, several subjects experienced clinically significant local reactions that led to trial discontinuation. In the vehicle-controlled trials, 1/386 (0.26%) subjects receiving difamilast 1% discontinued due to local reactions (contact dermatitis). In the long-term trials, 13/857 (1.52%) subjects discontinued due to local reactions, including application site pain (5 subjects), application site pruritus (4 subjects), contact dermatitis (4 subjects), with additional cases of application site erythema, application site vesicles, blistering, and burning.
- **Age-related tolerability patterns**: Age-stratified analyses showed some variation in local tolerability symptoms across age groups, though symptoms when present were predominantly mild in severity and showed improvement over time in both pediatric and adult populations.
- **Contact dermatitis and application site reactions:** Multiple cases of contact dermatitis occurred across trials, leading to study discontinuation in affected subjects. These reactions appeared to be primarily irritant contact dermatitis rather than allergic hypersensitivity, based on limited patch testing data and clinical presentation patterns.

- **Limited hypersensitivity evidence:** Patch testing performed in select cases showed predominantly negative results, with no clear pattern suggesting allergic contact dermatitis as a primary concern. The available data do not support hypersensitivity as a significant safety signal.

The overall local tolerability profile supports the safety of difamilast ointment, 1% for both short-term and long-term use across all age groups, with recognition that some patients may develop clinically significant application site reactions requiring treatment discontinuation, which will be reflected in labeling Section 6.

Laboratory Findings

Laboratory evaluations in the pivotal trials pool (271-102-00007 and 271-102-00008) and vehicle-controlled trials pool (studies 271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301) demonstrated that the majority of subjects maintained normal clinical laboratory test values throughout the trials. Few shifts from normal to abnormal (high or low) values or changes from baseline in serum chemistry and hematology parameters were observed, and any shifts or abnormal values did not appear to be clinically relevant. A total of 12 subjects had changes in serum chemistry analytes that were documented as TEAEs, mostly mild in severity. In the Difamilast 1% group, these included: alanine aminotransferase increased (1 subject), blood bilirubin increased (1 subject), gamma-glutamyl transferase increased (1 subject), blood potassium increased (1 subject), and protein urine present (2 subjects). Although isolated abnormal serum chemistry findings were reported as TEAEs, examination of shift tables for these analytes did not identify any trends suggesting a drug effect, and none are considered drug-related by the clinical reviewer. Overall, the laboratory findings support the safety profile of Difamilast 1% with no clinically significant patterns of laboratory abnormalities attributable to treatment.

Vital Signs

No clinically meaningful changes or trends were observed in vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) for subjects treated with Difamilast 1% ointment compared to vehicle in any of the clinical trials. The findings were consistent across all age groups.

QT

Background

The Agency initially agreed that QTc assessment for difamilast ointment (topical PDE-4 inhibitor indicated for treatment for mild to moderate atopic dermatitis in patients >2 years of age) could be based on a substudy within open-label extension trial MEDI-MM36-302 combined with nonclinical risk assessment.

QT-IRT Assessment

The QT-Interdisciplinary Review Team (QT-IRT) determined that the QTc substudy results are not representative of the intended patient population due to:

> **Significantly lower disease severity** - substudy subjects had only 5.5% (±3%) mean body surface area affected compared to 10% (±11%) in the overall phase 3 population
>
> **Substantially lower difamilast exposure** - mean steady-state Cmax of only 0.5 ng/mL compared to 14 ng/mL in the maximum use study that included moderate to severe atopic dermatitis subjects

Based on these findings, the QT-IRT concluded that QTc effects have not been adequately evaluated (QT-IRT review dated July 22, 2025) and recommends that a dedicated QTc study be conducted as a PMR, with labeling statements describing inadequate QTc characterization until study completion.

Interdisciplinary Assessment Supporting PMR Waiver

Clinical Team: In contrast to the QT-IRT team's assessment, the clinical team recommends that a dedicated PMR for QT prolongation is not necessary for this topical product based on the following rationale:

> **Known Drug Class with Established Safety Profile:** Difamilast is a phosphodiesterase 4 (PDE-4) inhibitor, a well-characterized class with multiple approved products: Crisaborole (EUCRISA) - topical PDE-4 inhibitor for atopic dermatitis, Apremilast (OTEZLA) - oral PDE-4 inhibitor for psoriatic arthritis and plaque psoriasis, and Roflumilast (DALIRESP) - oral PDE-4 inhibitor for COPD exacerbations.
>
> **Existing Class Labeling Precedent:** The approved oral PDE-4 inhibitor roflumilast does not have warnings regarding QT concerns in its labeling, despite achieving much higher systemic exposures than expected with topical administration.
>
> **Favorable Nonclinical Data:** The difamilast nonclinical package demonstrated a large hERG safety margin (7,931-fold) and no QTc prolongation in the in vivo dog study at exposures 98x the clinical C_{max}.

Clinical Pharmacology Team: Assessed that no accumulation was observed following multiple dosing in both the maximal use trial and QTc sub-study. Considering this finding along with the clinical team's rationale, they do not object to waiving the PMR for QTc assessment.

Nonclinical Pharmacology-Toxicology Team: Also do not object to the proposal to waive the PMR based on available nonclinical data.

Recommendation:

Given the totality of data, the team recommends a QTc study PMR is not necessary. Labeling will include a statement in section 12.2 Pharmacodynamics, Cardiac Electrophysiology: "ADQUEY ointment is not expected to cause clinically significant QTc interval prolongation at the recommended dosages"

Immunogenicity

Difamilast is not a therapeutic protein and would not be expected to be associated with immunogenicity. This section is not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

While no adverse events of special interest were prespecified in the protocols, the Sponsor and clinical review team reviewed the integrated safety database for events (e.g., effects on growth and weight and psychiatric symptoms) associated with other oral PDE-4 inhibitors (e.g., roflumilast and apremilast).

8.2.5.1. Assessment of the Impact of Difamilast on Weight and Growth

Oral PDE-4 inhibitors are associated with effects on growth and weight through multiple mechanisms including appetite suppression, gastrointestinal side effects leading to reduced caloric intake, and potential effects on growth hormone pathways and bone metabolism. Apremilast (OTEZLA) carries label warnings about weight loss with recommendations for regular weight monitoring. Roflumilast (DALIRESP) includes warnings about weight loss, with label recommendations for regular weight monitoring and treatment discontinuation if unexplained or clinically significant weight loss occurs. Growth monitoring is particularly critical in pediatric populations where development is a key safety consideration. Topical PDE-4 inhibitors are not labeled for this class effect. The review team analyzed the data related to growth and development in collaboration with the Division of Pediatrics and Maternal Health (DPMH). Refer to the Memorandum dated January 14, 2026 by Karen Fratantoni, MD, MPH.

Weight Monitoring in Clinical Trials:

Weight was systematically monitored across all clinical trials as part of routine safety assessments. The monitoring schedule varied by trial design:

Controlled trials: (4-week duration)

- Trials 271-102-00002, 271-102-00007, 271-102-00008, and MEDI-MM36-301
- Weight assessments: Baseline, Week 1, Week 2, and Week 4

Long-term Uncontrolled Trials:

- Trials 271-102-00006 and MEDI-MM36-302
- Weight assessments: Baseline and monthly thereafter

- Average exposure: 225.5 days

The review team analyzed weight changes as change from baseline at each assessment timepoint and categorized as:

- Mild decrease: <5% change from baseline
- Moderate decrease: ≥5% to <10% change from baseline
- Severe decrease: ≥10% change from baseline

Summary of Findings:

Controlled Studies (4-Week Duration)-

Overall Population:

- No subjects experienced severe weight decrease (≥10% from baseline) in any treatment group
- Mild weight decrease (<5% from baseline) occurred in 40.6% of difamilast 1% subjects versus 37.0% of vehicle subjects
- 4 adult subjects (2 in each treatment group) experienced moderate weight decrease (≥5% to <10% from baseline)

Age-Stratified Results:

- Children (2-<12 years): 22.6% of difamilast subjects versus 26.2% of vehicle subjects had mild weight decrease
- Adolescents (12-<18 years): 25.9% of difamilast subjects versus 44.4% of vehicle subjects had mild weight decrease
- Adults (≥18 years): 49.8% of difamilast subjects versus 41.3% of vehicle subjects had mild weight decrease

Racial Differences: A directionally higher trend for mild weight decrease was observed in the difamilast group compared to vehicle, with a somewhat higher trend in non-Asian subjects across all age groups.

Long-term Uncontrolled Studies (Average 225.5 Days Exposure)-

Adult Population (≥18 years):

- 66.8% showed no weight change
- 24.9% had mild weight decrease
- 5.5% had moderate weight decrease
- 2.8% had severe weight decrease

Severe Weight Loss Analysis: Of the 21 subjects with severe weight loss (≥10% decrease), 18 were overweight (n=9) or obese (n=9) at baseline, suggesting these changes may reflect lifestyle modifications rather than drug-related effects.

Pediatric Growth Patterns:

Weight changes in pediatric age groups were similar to or slightly lower than anticipated weight changes over a 1-year period based on CDC growth charts:

- Ages 2-11 years: Expected ~2.9 kg/year (CDC), observed growth rates were comparable
- Ages 12-18 years: Expected ~3 kg/year (CDC), observed growth rates were comparable

The Applicant noted that reduced growth velocity in children with atopic dermatitis is documented in the literature, particularly for children with more severe disease, which may explain the slightly lower than anticipated weight increases compared to CDC averages.

Pediatric Growth Analysis Using Z-Score Methodology:

A specialized pediatric growth analysis was conducted using weight z-score changes of ±0.5 as a screening threshold for potential growth concerns. This threshold represents a clinically reasonable screening tool used by pediatric reviewers to identify populations at risk for potential growth concerns. In a normal distribution, z-scores represent the number of standard deviations a data point is from the population mean.

Key Findings:

- Equal numbers of subjects met the screening z-score threshold for weight loss (n=17) and weight gain (n=17)
- No overall clinical signal for weight loss among those receiving treatment

Detailed Analysis of Weight Loss Cases:

Among the 17 subjects with weight z-score decreases ≥0.5:

- 11/17 subjects had minimal weight loss that was not concerning based on other growth parameters
- 6/17 subjects required further investigation due to magnitude of weight loss (3-10 kg over 52 weeks):
  - 1 subject was extremely underweight at baseline (15-year-old male, 34.1 kg =0.05th percentile), indicating underlying contributors to abnormally low weight
  - 5 subjects had weight loss of 3-10 kg over 12 months:
    - 3 adolescents: 2 had baseline weights in 90th percentile (suggesting intentional weight management), 1 dropped from 63rd to 40th percentile
    - 2 younger children (ages 7.9 and 9.5 years): the 9.5-year-old had baseline obesity with BMI normalization during trial; the 7.9-year-old had concerning weight loss (82nd to 22nd percentile) but maintained normal height velocity

Summary of Weight Changes in Difamilast Program:

The weight monitoring data suggest that topical difamilast 1% does not demonstrate the characteristic weight loss profile associated with systemic PDE-4 inhibitors. No subjects

experienced severe weight loss (≥10% from baseline) during the 4-week controlled trials, and weight decrease patterns were remarkably similar between difamilast and vehicle groups in these studies. Long-term data demonstrated age-appropriate weight gain in pediatric populations, with growth rates comparable to CDC standards. The absence of significant gastrointestinal toxicity typically associated with systemic PDE-4 inhibitors further supports the favorable safety profile of topical administration.

A specialized pediatric growth analysis using weight z-score changes of ±0.5 as a screening threshold for potential growth concerns provided additional reassurance regarding safety profile of difamilast. This analysis identified equal numbers of subjects meeting the screening threshold for weight loss (n=17) and weight gain (n=17), indicating no overall clinical signal for drug-related weight loss. Among the 17 subjects with weight z-score decreases ≥0.5, detailed evaluation revealed that 11 subjects had minimal weight loss that was not concerning based on other growth parameters. Of the 6 subjects requiring further investigation due to magnitude of weight loss (3-10 kg over 52 weeks), most had baseline characteristics suggesting alternative explanations: one subject was extremely underweight at baseline with clear underlying contributors, two adolescents had baseline weights in the 90th percentile suggesting intentional weight management toward healthier ranges, and one child with obesity showed BMI normalization during the trial. Only one subject (7.9 years old) showed concerning weight loss (82nd to 22nd percentile) without obvious alternative explanations but maintained normal height velocity.

Most subjects who experienced severe weight loss in long-term studies were overweight or obese at baseline, suggesting these changes likely reflect intentional weight management rather than drug-related effects. A slightly greater trend for mild weight decrease was observed in non-Asian subjects and these findings warrant continued monitoring with routine post-marketing surveillance. However, the clinical significance appears limited given the overall safety profile and lack of associated gastrointestinal toxicity.

Conclusion:

The comprehensive weight monitoring across the difamilast clinical program, including detailed pediatric growth analysis using z-score methodology, suggests that topical difamilast 1% does not exhibit the weight loss profile characteristic of systemic PDE-4 inhibitors. The observed weight changes appear consistent with normal variation and expected growth patterns in pediatric populations, with no clinically meaningful differences between treatment groups in controlled trials and no overall signal for drug-related growth impairment in the pediatric population. Due to an absence of a safety signal, the review team including colleagues from Division of Pediatrics and Maternal Health (DPMH) does not recommend inclusion of any language regarding risk of weight loss in labeling.

8.2.5.2. Assessment of the Impact of Difamilast on Psychiatric Events

PDE-4 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 PDE-4 a promising therapeutic target for these conditions (Nahid et al. 2025). However, two approved oral PDE-4 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 PDE-4 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 adverse reactions. Safety analyses of these drugs have been consistent with this hypothesis and have shown no significant psychiatric safety signals thus far.

Nonetheless, there is an increased baseline risk of suicide and psychiatric concerns in the AD treatment population that warrants consideration (Ronnstad et al. 2018). Therefore, due to the increased baseline risk of suicide in this treatment population and known psychiatric safety concerns with other approved PDE-4 inhibitors (apremilast and roflumilast), which carry warnings for depression, suicidal ideation/behavior, and other psychiatric symptoms, the review team performed safety analyses focusing on the impact of difamilast on psychiatric events, summarized below (refer to review by Dr. Roberta Rasetti, Division of Psychiatry [DP], dated 8/25/25).

Safety Review Strategy:

The safety review strategy was focused on 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 Trial 271-15-001 and Trial 217-12-205, where only clinical study reports [CSRs] were available)
- Shift tables for psychiatric scales (HPQ-9, C-SSRS, CES-DC, and CBCL) were carefully analyzed, where available (trials MEDI-MM36-301 and MEDI-MM36-302 only).

Psychiatric Inclusion/Exclusion Criteria:

The trials recruited male and female subjects over 2 years of age (with age ranges varying by trial) who had a diagnosis of AD affecting ≥5% to ≤40% BSA. The trials had the following exclusion criteria related to psychiatric issues:

1. Trial 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 trial

2. All Other Double-Blind Trials (Conducted ex-U.S.)

Exclusion criteria

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

Reviewer's comments: The exclusion criteria for psychiatric disorders in Trial MEDI-MM36-301 align with recommendations provided by DP in previous consultations regarding this development program. However, all other trials 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. Trial 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 trials.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 trial drug should have been discontinued. If the subject answered “yes” to question 1 or 2, the mental health professional should have determined whether the trial drug should have been discontinued or not.

- Subject 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 trial 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 trial 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 trial drug and referred for immediate assessment by a mental health professional via referral to psychiatric emergency services. The event was recorded as an AE.
- Center for Epidemiologic Trials 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 trial 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 trial 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 trial 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 trial drug should have been discontinued depending on severity of symptoms.

2. All Other Trials:

No specific psychiatric scales were administered in the trials conducted outside the United States. Those trials 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 Trial MEDI-MM36-301. All other trials 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 Trial MEDI-MM36-301. However, safeguards for managing SI/B events were not incorporated into any of the trials conducted outside the United States that were included in the "Trial-Controlled Trials 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 Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (MedDRA version 25.0) was evaluated by examining adverse event datasets for the Vehicle- Controlled Trials 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.

- Review of TEAEs Related to Psychiatric Disorders:

Table 57: Psychiatric TEAEs in Difamilast Trials (Safety Populations)

	Placebo-Controlled Studies		Uncontrolled Studies
System Organ Class Preferred Term	**Difamilast 1%** N = 386 n (%)	**Vehicle** N = 348 n (%)	**Difamilast 1%** N = 857 n (%)
Psychiatric Disorders	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)
Investigations (Psychiatric)	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 subject reported a TEAE of worsening depression in Trial MEDI-MM36-301 (Subject ID MEDI-MM36-301-(b) (6)) (Table 57 above, Vehicle-Controlled Trials column).

- a 37-year-old White female developed worsening depression 5 weeks after initiating difamilast 1% ointment, 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 trial drug is unlikely.

No other TEAEs related to psychiatric disorders and SI/B were reported in the Vehicle-Controlled Trials Pool analysis

Psychiatric Scale Assessment:

The findings from active assessments for depression and SI/B (C-SSRS, PHQ-9, CES-DC, and CBCL 1½-5) were consistent with the documented TEAEs related to neuropsychiatric conditions in Trial MEDI-MM36-301. Only one subject (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: Comprehensive analysis examined the frequency of TEAEs categorized as "psychiatric disorders" within the SOC across both treatment groups. The analysis revealed no significant difference in psychiatric disorder occurrence between the difamilast and vehicle groups. Psychiatric scale shift analyses yielded consistent findings. However, psychiatric scales were evaluated in only one trial (Trial MEDI-MM36-301), which substantially limits the generalizability of these conclusions due to insufficient psychiatric assessment across the

broader trial program. Additionally, Trial MEDI-MM36-301 was terminated early, further decreasing the size of its database.

Long-Term Uncontrolled Trials Pool:

Although the time of exposure in the open-label long term extension trials appears adequate to detect psychiatric disorders, the absence of vehicle control groups inhibits interpretation of the data. Without a vehicle-controlled comparator, the observation of psychiatric TEAEs due to chance cannot be excluded. Therefore, results from these open-label trials must be interpreted with caution.

- Deaths Related to SI/B: No deaths were reported in the long-term extension trials.
- TEAEs Related to SI/B: No TEAE related to SI/B were reported.

Review of TEAEs Related to Psychiatric Disorders:

A total of 25 TEAEs occurred within the SOC of Psychiatric Disorders and Investigations (Psychiatric) in the TEAE dataset from the long-term extension trials. 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 MEDIMM36-302-(b) (6)). None of the psychiatric TEAEs were SI/B, as shown in Table 57 (Uncontrolled Trials column).

Reviewer's comment: No cases of SI/B were reported in the open-label trials. While psychiatric disorders, including depression, were observed in the open-label trials, the absence of a vehicle-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 Trial Assessment:

For completeness, this reviewer evaluated the CSRs for Trial 271-15-001 and Trial 271-12-205 for TEAEs related to psychiatric disorders and SI/B. These trials were phase 2, double-blind, 8-week dose-finding trials. One case of depression was reported among subjects receiving difamilast 1% compared to no cases in the vehicle group in Trial 271-12-205.

- a 16-year-old subject ((b) (6)) with a history of attention deficit/hyperactivity disorder and depression developed a serious TEAE of worsening depression that resulted in hospitalization. The investigator assessed the event as CTCAE Grade 4 and not related to the investigational medicinal product. Given the participant's past psychiatric history of depression, a causal link with difamilast ointment, 1% 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 trial or in Trial 271-15- 001.

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

Summary of the Impact of Difamilast on Psychiatric events:

The clinical trial data are insufficient to support a causal link between difamilast ointment, 1% 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 vehicle for the vehicle-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.

This conclusion must be interpreted with caution for several reasons. First, two of the three double-blind vehicle-controlled trials did not include an active prospective assessment of suicidal ideation/behavior or depression using validated scales. Results were based solely on adverse event reporting. Second, the only trial that included systematic psychiatric assessments using validated instruments (Subject Health Questionnaire-9, Columbia Suicide Severity Rating Scale, and Center for Epidemiological Trials Depression Scale for Children) was Trial MEDI-MM36-301, that was terminated early for business reasons by the Applicant. Thus, there was limited data available for review.

Nonetheless, the overall results appear reassuring and do not demonstrate a strong signal for psychiatric AEs related to difamilast ointment, 1%. This finding is consistent with its formulation as a topical drug with minimal expected systemic exposures.

Labeling Recommendations

Inclusion in Section 5 of Prescribing Information:

No information about the increased risk of psychiatric disorders or SI/B associated with difamilast is recommended for inclusion in section 5 (Warnings and Precautions) of the prescribing information.

Postmarketing Trials:

At this time, based on the psychiatric safety signal results in the program to date, a dedicated postmarketing trial to assess SI/B is not considered necessary and not recommended by the review team.

8.2.5.3. Applicability of Safety Data in Japanese Subjects to the US Population

The safety assessment for difamilast relies heavily on clinical trial data generated in Japanese populations, as the pivotal phase 3 trials -007 and -008 supporting this NDA were conducted exclusively in Japan. In addition, given that the number of US subjects in the phase 2 multinational Trial 271-12-205 was small and the US phase 3 Trial MEDI-MM36--301 was

aborted early, the review team evaluated whether the safety data from Japanese subjects can be extrapolated to support the safety profile in the intended US patient population.

This cross-population safety assessment is important because atopic dermatitis pathogenesis, immune response patterns, and genetic susceptibility factors are known to vary across ethnic populations, potentially influencing drug safety profiles.

Population Differences in Atopic Dermatitis Pathogenesis

Atopic dermatitis pathogenesis involves complex interactions between genetic, immunological, and environmental factors that can vary across ethnic populations. Research has identified distinct patterns of immune pathway activation and genetic susceptibility between populations that could theoretically impact drug response and safety profiles.

In European Americans, atopic dermatitis is characterized by increased TH2/TH22 activity with decreased TH1/TH17 responses. This population shows mutations in filaggrin (FLG), a key skin barrier protein, in up to 50% of patients. These FLG mutations contribute to impaired skin barrier function and may influence both disease severity and treatment response patterns. Asian populations, including Japanese subjects, demonstrate increased TH22/TH17 activity compared to other ethnic groups. FLG mutations occur in up to 27% of Asian patients, representing an intermediate frequency between European Americans and African Americans. The elevated TH17 activity in Asian populations could theoretically influence inflammatory responses and drug metabolism, though clinical significance remains unclear.

African American populations show decreased TH17/TH1 activity and notably do not exhibit FLG mutations. This distinct immunological profile may contribute to different clinical presentations and potentially different safety considerations (Kaufman et al. 2018; Nomura et al. 2020).

In addition, underlying atopic dermatitis pathophysiological differences among race/ethnicities manifest in distinct clinical presentations that could impact safety assessment. Asian patients typically present with better demarcated lesions and more scaling/lichenification compared to other populations. Additionally, erythema may be more difficult to assess in patients with darker skin tones, potentially affecting the detection of local skin reactions or irritation.

Nonetheless, current clinical guidelines do not propose any differences in the diagnosis and treatment of AD by racial subgroup and no definitive evidence exists to show that treatment should be addressed differentially by racial subgroup (Alexis et al 2019).

Comparison of Safety in the Difamilast Program Between Japanese and US Subjects

Treatment-emergent adverse events observed in Japanese phase 3 trials -007 and -008 were generally compared to those observed in US aborted Trial MEDI-MM36-01 (refer to Table 58 below).

The most common TEAEs in the Japanese phase 3 vehicle-controlled trials (-007 and -008) were nasopharyngitis (6.0% difamilast versus 4.5% vehicle), viral infection (3.4% versus 3.4%), and bacterial infection (1.9% versus 4.9%), and in the US aborted phase 3 vehicle controlled trial (MEDI-MM36-301) were nasopharyngitis (2.1% difamilast ointment versus 3.4% vehicle), bacterial infection (2.1% versus 1.7%), and rash (1.1% versus 3.4%).

In the uncontrolled long-term safety trials, most common TEAEs in the Japanese trial (-006) were bacterial infections (15.6%), nasopharyngitis (14.4%), and viral infections (9.4%), and in the US trial (-302) were nasopharyngitis (13.0%), viral infections (8.8%), and bacterial infections (7.1%). Specific AE imbalances are described in detail below.

Infections:

Vehicle-controlled phase 3 trials: In the Japanese trials, nasopharyngitis was the most common infection, occurring in 6.0% of difamilast subjects versus 4.5% of vehicle subjects. Viral infections occurred at similar rates between difamilast and vehicle groups (3.4% each), while bacterial infections were lower with difamilast (1.9% versus 4.9%). In the US trial, infection rates were generally low, with nasopharyngitis occurring in 2.1% of difamilast subjects versus 3.4% of vehicle subjects, and bacterial infections in 2.1% versus 1.7% respectively.

Long-Term uncontrolled trials: Bacterial Infections showed higher rates in the Japanese population compared to US subjects. Specific bacterial infections more prevalent in Japanese subjects included paronychia (2.8% versus 0%), application site folliculitis (3.1% versus 0.6%), and hordeolum (1.6% versus 0%). Conversely, certain bacterial infections were more common in US subjects, particularly pharyngitis streptococcal (0% versus 2.4%). Viral infection rates were similar between populations (9.4% Japan versus 8.8% US). In the context of this uncontrolled data overall there did not appear to be any meaningful differences in overall bacterial or viral infections between Japanese and US subjects.

Dermatological Adverse Events:

Vehicle-controlled phase 3 trials: There were no meaningful differences in application site reactions between Japanese and US subjects.

Long-Term uncontrolled trials: Japanese subjects showed higher rates of application site urticaria (2.8% versus 0.2%), and application site acne (1.6% versus 0). Application site pain was slightly more common in US subjects (1.3% versus 0.9%).

Systemic Adverse Events

Vehicle controlled phase 3 trials: Systemic adverse events were infrequent in the controlled trials. In Japanese trials, no such events occurred in ≥1% of subjects, and events in <1% of subjects on active and none in vehicle included arthralgia (0.4% difamilast versus 0%), back pain (0.4% versus 0%), and fatigue (0.4% versus 0%). In the US trial, there was an isolate case of depression (1.1% versus 0%), considered unlikely related to drug. Refer to Section 8.2.5.2 of this review for discussion of psychiatric adverse events in the difamilast program. Overall, the

controlled trial data showed no clear pattern of systemic adverse events attributable to difamilast treatment in either the Japan or US trials, with most events occurring at similar or lower rates compared to vehicle.

Long-Term uncontrolled trials: Depression was exclusively observed in US subjects (0% versus 1.7% in long-term studies). Headache was also more common in US subjects (0.3% versus 1.7%). Gastrointestinal events such as vomiting (0.3% versus 1.9%) and nausea were also more prevalent in the US population. In the context of this uncontrolled data overall there did not appear to be any meaningful differences in long-term adverse events between the Japanese and US populations.

Summary of Findings:

Overall, no significant imbalances in adverse events were observed between Japanese and US subjects across the clinical development program. Class effects associated with systemic PDE-4 inhibitors (particularly psychiatric adverse reactions and weight loss) were not observed with topical difamilast in either Japanese or US populations. The safety profiles were comparable between populations, with no population-specific safety signals identified.

The observed regional differences in TEAE patterns should be interpreted with caution given the substantial differences in sample sizes between the Japanese (N=320) and US (N=537) long-term studies, as well as the uncontrolled nature of these trials. Many of the apparent imbalances may reflect underlying population characteristics, environmental factors, genetic predisposition, or differences in study conduct rather than true drug-related safety signals. The controlled phase 3 trial data, which provides the most reliable safety comparison, showed generally similar and low rates of adverse events between difamilast and vehicle in both populations. The higher rates of certain infections and dermatological reactions in Japanese subjects, and systemic events in US subjects, likely represent regional baseline differences rather than clinically significant safety concerns, particularly given the overall favorable benefit-risk profile demonstrated in the controlled trials.

In the controlled phase 2 and phase 3 trials, the most common treatment-emergent adverse events in both Japanese and US populations were nasopharyngitis, representing upper respiratory tract infections that are common in the general population and unlikely to be drug-related. Consistent with the controlled trial experience, in the uncontrolled long-term safety trials nasopharyngitis was the most common treatment-emergent adverse event in both trials.

Pharmacokinetic Considerations

Cross-study pharmacokinetic comparisons at Week 4 in adults with atopic dermatitis, stratified by race, showed that while nominal exposure was highest in Asian subjects, this difference was explained by the 2- to 3-fold higher doses administered in these subjects due to greater body surface area involvement. When normalized for dose, exposure was generally comparable between White and Black subjects, with only slightly higher dose-normalized exposure in Asian subjects (refer to Clinical Pharmacology Section 6.3.2.3 Therapeutic Individualization).

This pharmacokinetic data suggests that population differences in drug metabolism or absorption are minimal and do not result in clinically meaningful exposure differences that would impact safety. The slightly higher dose-normalized exposure in Asian subjects did not translate into increased adverse event rates, supporting the conclusion that these pharmacokinetic differences are not clinically significant from a safety perspective

Conclusion

The totality of safety data from controlled and long-term studies demonstrates a consistent safety profile for difamilast across Japanese and US populations. The absence of population-specific safety signals, combined with comparable adverse event rates and types between populations, supports the applicability of Japanese safety data to the US population for regulatory decision-making.

Comparison of TEAEs observed in vehicle controlled Japanese phase 3 trials versus aborted US phase 3 trial:

Table 58: NDA 219474 ISS Pivotal Studies 007 and 008 vs. Study 301: Summary of Subjects With TEAEs by Narrow OCMQ and PT

	Japan				USA			
	Difamilast 1%		Vehicle		Difamilast 1%		Vehicle	
Narrow OCMQ Term	N=267		N=265		N=94		N=59	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Nasopharyngitis	16	(6.0)	12	(4.5)	2	(2.1)	2	(3.4)
Nasopharyngitis	16	(6.0)	10	(3.8)	0	(0.0)	1	(1.7)
Pharyngitis streptococcal	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Upper respiratory tract infection	0	(0.0)	2	(0.8)	1	(1.1)	1	(1.7)
Viral Infection	9	(3.4)	9	(3.4)	0	(0.0)	0	(0.0)
Molluscum contagiosum	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Skin papilloma	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)
Eczema herpeticum	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Herpangina	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes simplex	1	(0.4)	2	(0.8)	0	(0.0)	0	(0.0)
Influenza	1	(0.4)	2	(0.8)	0	(0.0)	0	(0.0)
Oral herpes	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Conjunctivitis viral	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Herpes virus infection	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Influenza a virus test positive	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Varicella	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)

	Japan				USA			
	Difamilast 1%		Vehicle		Difamilast 1%		Vehicle	
Narrow OCMQ Term	N=267		N=265		N=94		N=59	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Bacterial Infection	5	(1.9)	13	(4.9)	2	(2.1)	1	(1.7)
Impetigo	2	(0.7)	5	(1.9)	0	(0.0)	0	(0.0)
Application site folliculitis	1	(0.4)	2	(0.8)	0	(0.0)	0	(0.0)
Cystitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Folliculitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Abscess limb	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Application site cellulitis	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Cellulitis	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Furuncle	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Paronychia	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)
Pharyngitis streptococcal	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Purulence	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Staphylococcal infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Fungal Infection	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
Body tinea	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea pedis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Rash	2	(0.7)	5	(1.9)	1	(1.1)	2	(3.4)
Application site rash	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Dermatitis contact	1	(0.4)	1	(0.4)	1	(1.1)	1	(1.7)
Acne	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Application site acne	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)
Dermatitis acneiform	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Rash	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Arthralgia	1	(0.4)	0	(0.0)	1	(1.1)	0	(0.0)
Arthralgia	1	(0.4)	0	(0.0)	1	(1.1)	0	(0.0)
Back Pain	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Back pain	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Bronchospasm	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Asthma	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Fatigue	1	(0.4)	0	(0.0)	1	(1.1)	0	(0.0)
Malaise	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Lethargy	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Local Administration Reaction	1	(0.4)	2	(0.8)	0	(0.0)	0	(0.0)
Application site rash	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Application site hypersensitivity	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Application site pain	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Renal and Urinary Infection	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Cystitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal Pain	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)
Abdominal pain	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)
Arrhythmia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Bradycardia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Cough	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Cough	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)

	Japan				USA			
	Difamilast 1%		Vehicle		Difamilast 1%		Vehicle	
Narrow OCMQ Term	N=267		N=265		N=94		N=59	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Depression	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Depression	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Hemorrhage	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Eye contusion	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Hepatic Injury	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Hepatic function abnormal	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Hyperglycemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Blood glucose increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Hypersensitivity	0	(0.0)	2	(0.8)	0	(0.0)	1	(1.7)
Allergy to chemicals	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Application site hypersensitivity	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Drug eruption	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Drug hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Malignancy	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Thyroid cancer	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Peripheral Edema	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Oedema peripheral	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Pruritus	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Application site pruritus	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Purulent Material	0	(0.0)	2	(0.8)	1	(1.1)	0	(0.0)
Abscess limb	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Furuncle	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Purulence	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Pyrexia	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Pyrexia	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Lethargy	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Systemic Hypertension	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)
Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Difamilast 1%" and STUDYID = "27110200007" or "27110200008" and SAFFL = Y (Difamilast 1% (Japan)); TRT01A = "Vehicle" and STUDYID = "27110200007" or "27110200008" and SAFFL = Y (Vehicle (Japan)); TRT01A = "Difamilast 1%" and STUDYID = "MEDI-MM36-301" and SAFFL = Y (Difamilast 1% (USA)); TRT01A = "Vehicle" and STUDYID = "MEDI-MM36-301" and SAFFL = Y (Vehicle (USA)); TRTEMFL = "Y" (Adverse Events).
Abbreviations: ISS, integrated summary of safety; OCMQ, Office of New Drugs Custom Medical Queries; OCS, Office of Computational Science; PT, preferred term; TEAE, treatment-emergent adverse event

8.2.6. COA Analyses Informing Safety/Tolerability

Safety and tolerability were assessed in the difamilast program through the following methods COA measures.

Local Tolerability Assessments: In US trials MEDI-MM36-301 and MEDI-MM36-302, subjects/caregivers actively assessed local tolerability symptoms (burning, stinging, and itching)

after study drug application using severity rating scales. These assessments were conducted at baseline (prior to first application), 15 minutes post-application, and at each trial visit (provided trial drug was applied within 7 days prior). Investigators also performed application site assessments evaluating erythema, papulation/vesiculation, and edema, graded as none, mild, moderate, or severe. Refer to Section 8.2.4 for detailed analysis of local tolerability findings, including shift table analyses and age-stratified comparisons.

Psychiatric Safety Assessments: In US trial MEDI-MM36-301, systematic psychiatric assessments were conducted using instruments to evaluate depression and suicidal ideation/behavior, given the known psychiatric safety concerns with oral PDE-4 inhibitors. These included:

- C-SSRS for subjects ≥6 years of age
- PHQ-9 for subjects ≥18 years of age
- CES-DC for subjects 6 to 17 years of age
- CBCL for Ages 1½-5 for subjects 2 to 5 years of age

Refer to Section 8.2.5.2 for comprehensive analysis of psychiatric safety findings, including shift table analyses for all psychiatric scales and assessment of treatment-emergent psychiatric adverse events.

Japanese Trials: Trials 271-102-00007, 271-102-00008, 271-15-001, and 271-102-00002 conducted in Japan did not include active local tolerability assessments using structured scales or systematic psychiatric assessments using validated instruments. Instead, these trials relied on clinical examinations and adverse event reporting to capture safety and tolerability concerns.

8.2.7. Safety Analyses by Demographic Subgroups

The primary analysis of safety analyses by demographic subgroup focused on the Vehicle-Controlled Trials Pool, as it provided the most robust dataset for comparison.

Analysis by Age

The safety profile of difamilast was evaluated across three distinct age groups: pediatric (≥2 to <12 years), adolescent (≥12 to <18 years), and adult (≥18 years). Overall Incidence: In the vehicle-controlled trials, the overall incidence of TEAEs was generally highest in the pediatric population and lowest in the adult population for both the difamilast and vehicle groups, likely reflecting a higher background rate of common childhood illnesses.

Common TEAEs:

- Pediatric (≥2 to <12 years; N=107 difamilast, N=104 vehicle): The most frequent TEAEs were nasopharyngitis (7.5% difamilast versus 6.7% vehicle) and viral infections (6.5% difamilast versus 3.8% vehicle). No new safety signals specific to this age group were identified.

- Adolescent (≥12 to <18 years; N=27 difamilast, N=18 vehicle): The incidence of TEAEs was low in this small cohort. Arthralgia was reported in one subject in the difamilast group (unrelated to treatment) and none in the vehicle group, but no other notable differences were observed). No new safety signals specific to this age group were identified.
- Adult (≥18 years; N=252 difamilast, N=226 vehicle): TEAE rates were lower than in the pediatric group. Nasopharyngitis occurred in 4.4% of difamilast-treated subjects versus 3.5% of those receiving vehicle.

Conclusion: No clinically significant age-specific safety signals were identified. The types and frequencies of adverse events were consistent with what would be expected for these age populations, with no concerning trends attributable to difamilast treatment.

Analysis by Sex

In the vehicle-controlled trials, the incidence and types of TEAEs were comparable between male and female subjects. No clinically meaningful differences were observed in the safety profile of difamilast based on sex.

Analysis by Race

The safety data were analyzed to identify potential differences between racial groups. This analysis was primarily a comparison between Asian subjects (predominantly from the Japanese pivotal trials) and non-Asian subjects (largely from the US trials).

- Vehicle-Controlled Trials: In the pooled data, there were no significant differences in the overall incidence or types of TEAEs between Asian and non-Asian subjects. The safety profile appeared consistent across these groups.
- Long-Term Uncontrolled Trials: In the long-term open-label studies, some numerical differences were observed. For instance, bacterial skin infections and certain rash-related events were reported more frequently in Japanese subjects, while some systemic events like depression and headache appeared more common in US subjects.
- Local Tolerability: As noted in Section 8.2.4, proactive local tolerability assessments were only conducted in the US trials (MEDI-MM36-301 and MEDI-MM36-302), which had limited enrollment of Asian subjects. In the long-term trial (MEDI-MM36-302), no clinically meaningful differences in burning, stinging, or itching were observed between the 40 Asian and 502 non-Asian subjects, though this comparison is limited by the small sample size of the Asian cohort in this specific analysis.

Conclusion: While some numerical differences were noted in the long-term uncontrolled trials, these are difficult to interpret without a control group and may be influenced by regional differences in medical practice or reporting rather than a true drug effect. Data from the vehicle-controlled trials did not reveal any race-specific safety signals. Overall, the safety profile of difamilast appears to be broadly similar across racial groups.

Summary Conclusion for Demographic Analyses

The comprehensive analysis of safety data by demographic subgroups (age, sex, and race) did not identify any specific population that would be at a higher risk when treated with difamilast 1% ointment. The safety profile was generally consistent across all subgroups evaluated.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant conducted no additional specific safety trials.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a specific clinical trial to evaluate human carcinogenicity or tumor development. During the development program, the trial designs did not include an active assessment to evaluate for carcinogenicity or designate malignancy as an AESI. Labeling for oral roflumilast tablets includes a statement that among the "serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in roflumilast tablets-treated patients" were lung cancer and prostate cancer. However, similar statements are not included in labeling for other oral and topical PDE-4 inhibitors and malignancy is not considered to be a class effect.

While a few subjects were diagnosed with malignancies during the development program, these SAEs were not considered to be related to the study product.

- 271-102-00006: a 40-year-old male (Subject (b) (6)) developed diffuse large B-cell lymphoma on Day 353 of treatment with the study product. Risk factors were not provided. The subject withdrew from the trial.
- MEDI-MM36-301: a 42-year-old Caucasian male ((b) (6)) developed thyroid cancer on study Day 7. The subject received a total thyroidectomy and completed the trial.
- MEDI-MM36-302:
  - a 73-year-old male ((b) (6)) received 232 applications of the study product and developed esophageal carcinoma, a poorly differentiated adenocarcinoma at the gastroesophageal junction. Risk factors were not provided. The subject withdrew from the trial.
  - a 26-year-old female ((b) (6)) received 655 applications of the study product and developed a thoracic epidural spine tumor, hemangioblastoma. The subject complained of bilateral lower extremity paresthesia, weakness, and back pain prior to enrollment in the trial. Her participation in the trial was interrupted but the subject resumed the study product.
  - a 45-year-old male (b) (6) with a history of bilateral chronic nephrolithiasis and renal disease who received 500 applications of the study drug was diagnosed with chronic renal failure and a non-functioning atrophic right kidney. Histologic examination of the nephrectomy specimen showed grade 2 papillary renal cell

carcinoma. His participation in the trial was interrupted but the subject resumed the study product.

In addition, two subjects were diagnosed with a skin cancer (basosquamous carcinoma and squamous cell carcinoma) during the long-term uncontrolled US trial MEDI-MM36-302.

Nonclinical data from 104-week carcinogenicity studies in mice and rats did not identify a significant imbalance in the development of tumors between the vehicle and active treatment groups. Refer to Section 5 of this review for a discussion of these findings and section 13.1 of labeling.

Therefore. the data submitted does not support a safety signal for malignancy.

Human Reproduction and Pregnancy

Pregnancy Exposures During Development Program

Five pregnancy cases were reported during the difamilast ointment clinical development program:

- Case 1: A 22-year-old subject who started difamilast on (b) (6), had a positive pregnancy test at Week 4. Her last menstrual period was (b) (6) (two days prior to starting treatment). Difamilast was discontinued, and she delivered a full-term, normal infant with no complications, malformations, or anomalies.
- Case 2: A 25-year-old subject received difamilast from (b) (6), to (b) (6) (223 applications total). She discontinued due to positive pregnancy test and experienced spontaneous abortion on (b) (6) Notably, she was also taking phentermine from (b) (6), which confounds the relationship between difamilast exposure and the adverse outcome.
- Case 3: A 28-year-old subject received difamilast from (b) (6), to (b) (6) (699 applications total). She discontinued due to positive pregnancy test but was lost to follow-up with unknown outcome.
- Case 4: A 34-year-old subject received difamilast from (b) (6), to (b) (6) . She had a positive pregnancy test and underwent elective abortion on (b) (6) without complications.
- Case 5: One subject had pregnancy identified at baseline visit but did not receive trial drug or participate in the trial.

DPMH Consultation Summary

The review team consulted the Division of Pediatrics and Maternal Health (DPMH) for a Pregnancy and Lactation Labeling Review and recommendations for PMR/PMCs. Refer to

review by Dr. Kerry Shaab dated January 5, 2026 for details. Key findings and recommendations included:

- **Pregnancy:** Animal reproduction studies conducted in rats and rabbits demonstrated no specific safety signals indicating increased risk for embryo-fetal toxicity at clinical exposures. In rat embryo-fetal development studies, adverse effects including increased post-implantation loss, decreased fetal weight, retarded ossification, and increased visceral abnormalities (membranous ventricular septum defects) were observed only at the highest dose of 100 mg/kg/day, while the NOAEL was established at 10 mg/kg/day, providing a 30-fold safety margin compared to MRHD. In rabbit studies, increased skeletal variations were seen at 3 mg/kg/day, with a NOAEL of 1 mg/kg/day providing a 3-fold safety margin. Despite these adequate safety margins, the limited clinical data from pregnancy exposures during development and postmarketing experience are insufficient to assess drug-associated risks for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Given that emollients, topical corticosteroids, and phototherapy represent preferred first-line treatments for atopic dermatitis during pregnancy and considering the lack of specific safety concerns for the topical PDE-4 inhibitor class, DPMH determined that a postmarketing pregnancy safety study was not warranted and recommended routine pharmacovigilance instead.
- **Lactation:** No human lactation data are currently available for difamilast. Nonclinical studies demonstrated that following subcutaneous administration of radiolabeled difamilast to lactating rats, the drug was present in milk at concentrations higher than blood (milk/blood ratios of 13.7 for Cmax and 5.4 for AUC). However, no adverse developmental effects were observed in nursing pups during pre- and postnatal development studies. Due to species-specific differences in lactation physiology, the concentration of difamilast in rat milk does not necessarily predict the concentration of drug in human milk. While no lactational exposures were reported during the clinical development program, nine cases of "exposure via breast milk" were identified in the Japanese postmarketing database with no reported adverse events. Based on the lack of safety concerns for the PDE-4 inhibitor class generally, the low systemic exposure expected from topical administration, and the absence of specific lactational safety signals, DPMH concluded that a clinical lactation study was not necessary and recommended routine pharmacovigilance monitoring.
- **Reproductive Potential:** Fertility and early embryonic development studies in rats showed effects on reproductive function (irregular estrus cycles, sperm abnormalities, increased preimplantation loss, decreased copulation and fertility indexes) only at the highest dose of 100 mg/kg/day, while the NOAEL was established at 10 mg/kg/day, providing safety margins of 20-30 times the MRHD. One postmarketing case reported decreased sperm concentration in a male patient, but insufficient details regarding duration of use, timing, and outcome prevented meaningful causality assessment. Given the absence of fertility effects at clinically relevant exposures and the lack of evidence suggesting embryofetal harm that would necessitate pregnancy testing or contraceptive use during treatment, DPMH recommended omitting labeling subsection 8.3 for Females and Males of Reproductive Potential entirely.

The DPMH concluded that routine drug pharmacovigilance and published literature reviews would be reasonable to monitor pregnancy and infant outcomes, noting that topical PDE-4 inhibitors have been marketed for nearly a decade without identification of specific pregnancy safety concerns.

Pediatrics and Assessment of Effects on Growth

This application includes assessments of pediatric subjects 2 years of age and older with mild to moderate atopic dermatitis. The pediatric development program was conducted in accordance with an agreed Initial Pediatric Study Plan (iPSP) dated July 16, 2019, which included a waiver for assessments in pediatric patients 0 to 3 months of age and a deferral for assessments in pediatric subjects ≥3 months to <2 years of age.

The clinical development program included adequate pediatric representation across multiple trials, with safety and efficacy data supporting the proposed indication in pediatric patients 2 years of age and older. Refer to Section 8.1 for efficacy findings in pediatric subpopulations and Section 8.2 for comprehensive safety analysis across age groups.

Given that oral PDE-4 inhibitors are associated with weight loss and effects on growth, a detailed assessment of the impact of difamilast ointment, 1% on weight and growth in pediatric populations was conducted as an Adverse Event of Special Interest. This analysis, including specialized pediatric growth assessment using z-score methodology, is thoroughly discussed in Section 8.2.5.1. The comprehensive weight monitoring data demonstrated that the use of topical difamilast 1% result in the weight loss profile characteristic of systemic PDE-4 inhibitors, with age-appropriate weight gain observed in pediatric populations and growth rates comparable to CDC standards.

The approval letter will include a postmarketing requirement to conduct an adequate and well-controlled trial in subjects ages 3 months to <2 years with mild-to-moderate atopic dermatitis, with a final report submission by 6/2029. Refer to Section 12 for complete postmarketing requirements and commitments.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No subjects reported overdose, withdrawal or rebound during the clinical development program. The Applicant stated that were was no data to support “dependence” or abuse potential in the clinical trials.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Difamilast ointment (tradename Moizerto®) was approved in Japan by the Pharmaceuticals and Medical Devices Agency (PMDA) on September 27, 2021, for the treatment of atopic dermatitis in adult and pediatric patients 2 years of age and older.

Postmarket Exposure Data

Per the Applicant from June 2022 (when sales began) through July 2025, there have been:

- 4,908,648 total prescriptions dispensed (3,969,803 for the 1% strength)
- 671,706 patient-years of exposure for all strengths (556,322 patient-years for 1% strength)

Safety Signal Analysis

As of the last Periodic Safety Update Report (Edition 5 reported on November 29, 2024), the limited postmarket experience (approximately 3 years) has not appeared to identify any new safety signals beyond those observed in clinical trials. There were 11 cases of eczema herpeticum (with a reporting rate of 0.00022%), with insufficient evidence to establish a causal relationship between difamilast ointment and eczema herpeticum.

Per the Applicant (response to IR dated 11/14/25), the most commonly reported postmarket adverse events were application site reactions:

- “Application site erythema: 0.001793% reporting rate
- Application site irritation: 0.000632% reporting rate
- Application site swelling: 0.000367% reporting rate.”

Proposed Labeling

The applicant proposes the following for section 6.2 Postmarketing Experience:

> "The following adverse events have been (b) (4) Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: General disorders and administration site condition: (b) (4) application site swelling."

Expectations on Safety in the Postmarket Setting

The Applicant has substantial postmarket exposure data from Japan (over 4.9 million prescriptions and 671,706 patient-years) which support the established safety profile of l difamilast ointment observed in clinical trials, with no new safety signals identified to date in the postmarket setting.

8.2.11. Integrated Assessment of Safety

In the vehicle-controlled trials of difamilast ointment, 1% up to 4 weeks (Trials -002, -007, -008, and MEDI-MM36-301) there were no differences in TEAEs incidence rates of greater than 1% between difamilast and vehicle groups. The most common TEAE was nasopharyngitis, occurring in 19/386 (4.9%) subjects in the difamilast ointment, 1% group versus 16/348 (4.6%) in the vehicle group. Viral infections occurred in 11/386 (2.8%) subjects receiving difamilast ointment,

1% compared to 9/348 (2.6%) receiving vehicle. No other TEAEs occurred at ≥1% frequency in the difamilast 1% group while being higher than vehicle. Nasopharyngitis was consistently the most common adverse event across all age-stratified populations, though it occurred more frequently in children (7.5%) than in adults (4.4%) receiving difamilast ointment.

TEAEs occurring at <1% frequency in the difamilast ointment,1% group but absent in the vehicle group included: molluscum contagiosum (3/386, 0.8%), and single cases (0.3% each) of eczema herpeticum, herpangina, herpes simplex, oral herpes, abscess limb, cystitis, folliculitis, pharyngitis streptococcal, streptococcal infection, body tinea, tinea pedis, eye contusion, contusion, back pain, bronchospasm/asthma, depression, fatigue, lethargy, malaise, thyroid cancer, peripheral edema, renal and urinary infection/cystitis, somnolence/lethargy, and systemic hypertension.

Based on the available data, the local tolerability profile of difamilast ointment demonstrates acceptable safety across both short-term controlled and long-term open-label treatment periods:

- **Short-term tolerability:** In vehicle-controlled trials, difamilast ointment demonstrated similar or improved local tolerability compared to vehicle. Local tolerability symptoms and application site reactions when present were predominantly mild in severity, with improvement observed over the treatment period.
- **Long-term tolerability:** Extended treatment up to 52 weeks generally maintained stable symptom severity with predominantly mild events when present. However, local reactions led to trial discontinuation in 1/386 (0.26%) subjects in vehicle-controlled trials and 13/857 (1.52%) subjects in long-term trials. The most common reactions leading to discontinuation in the long-term trials were application site pain (5 subjects), application site pruritus (4 subjects), and contact dermatitis (4 subjects), with additional cases of application site erythema, application site vesicles, blistering, and burning.
- **Age-related tolerability patterns:** Age-stratified analyses showed variation in local tolerability symptoms (burning, stinging, and itching) across age groups. However, symptoms when present were predominantly mild in severity across all age groups, with improvement observed over time in both pediatric and adult populations.
- **Contact dermatitis and application site reactions**: Contact dermatitis occurred in 1/386 (0.26%) subjects in vehicle-controlled trials and 4/857 (0.47%) subjects in long-term trials, leading to study discontinuation. These reactions appeared to be primarily irritant contact dermatitis rather than allergic hypersensitivity, based on limited patch testing data and clinical presentation patterns. The available data do not support hypersensitivity as a significant safety signal.

The overall local tolerability profile supports the safety of difamilast ointment, 1% for both short-term and long-term use across all age groups, with recognition that certain patients may develop clinically significant application site reactions requiring treatment discontinuation."

Serious adverse events were infrequent across the integrated safety analysis and were generally not related to difamilast treatment. No serious TEAEs occurred in the pivotal trials

pool (271-102-00007 and 271-102-00008). In the vehicle-controlled trials pool, 1 serious TEAE occurred in 1 subject - thyroid cancer in a subject receiving difamilast ointment, 1%, which was considered not related to treatment by the investigator or the clinical reviewer and did not result in study discontinuation.

The long-term uncontrolled trials included 857 subjects (320 Japanese subjects in trial -006, 537 USA subjects in trial -302). Results of long-term safety trials, including age-stratified analyses, were generally comparable with those observed in the vehicle-controlled trials, with no new systemic safety signals identified by the review team.

No clinically meaningful changes or trends were observed in laboratory findings or vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) for subjects treated with difamilast 1% ointment compared to vehicle in any of the clinical trials. The findings were consistent across all age groups.

Although oral PDE-4 inhibitors are associated with weight loss and growth effects, topical difamilast 1% does not exhibit the weight loss profile characteristic of systemic PDE-4 inhibitors. Pediatric growth analysis using z-score methodology showed age-appropriate weight gain comparable to CDC standards, with no overall clinical signal for drug-related weight loss. Most subjects experiencing severe weight loss in long-term trials were overweight or obese at baseline, suggesting intentional weight management rather than drug-related effects. No labeling recommendations for weight monitoring are warranted. Refer to Section 8.2.5.1 for comprehensive weight and growth assessment.

Although oral PDE-4 inhibitors carry warnings for depression and suicidal ideation/behavior, clinical trial data for topical difamilast did not demonstrate a causal link to psychiatric adverse events. Only one psychiatric adverse event (depression) occurred in the difamilast group, with low rates in long-term trials. The absence of concerning safety signals, combined with topical formulation and minimal systemic exposure, supports that routine pharmacovigilance is adequate. No warnings or precautions for psychiatric disorders are recommended for labeling. Refer to Section 8.2.5.2 for psychiatric safety assessment.

Regarding the safety profiles of difamilast between populations, no population-specific safety signals were identified when analysis was performed by age, sex, or race. The safety profile was generally consistent across all subgroups evaluated. Refer to Section 8.2.7 for details. Overall, no significant imbalances in adverse events were observed between Japanese and US subjects across the clinical development program. Refer to Section 8.2.5.3 for details. The safety profiles were comparable between populations, with no population-specific safety signals identified.

Overall Safety Profile Assessment:

The overall safety profile of difamilast ointment, 1%, supports approval for the proposed indication. The most clinically significant safety considerations relate to local tolerability reactions, which are manageable through appropriate patient counseling and labeling. The absence of systemic safety signals characteristic of oral PDE-4 inhibitors (weight loss, psychiatric effects) supports the favorable benefit-risk profile for topical administration.

8.3.Statistical Issues

There were no major statistical issues that would preclude approval. Although the Applicant terminated a phase 3 trial (MEDI-MM36-301) in the United States due to "business reasons", the Applicant submitted data from one multinational phase 2 trial (271-12-205), two phase 2 trials (271-15-001 and 271-102-00002) in Japan, and two phase 3 trials (271-102-00007 and 271-102-00008) in Japan that demonstrated substantial evidence of effectiveness. As noted in Section 8.1.3, there was some heterogeneity in treatment effects and response rates across the trials.

8.4.Conclusions and Recommendations

To establish the effectiveness of difamilast ointment, 1%, for the treatment of mild to moderate AD, the Applicant submitted data from two adequate and well-controlled clinical trials conducted in Japan. Trials 271-102-00007 and 271-102-00008 enrolled subjects ≥15 years and 2-14 years of age, respectively, with mild to moderate AD (IGA score of 2 or 3) affecting ≥5% to ≤40% BSA. Both trials evaluated difamilast ointment, 1%, applied BID compared to vehicle for 4 weeks and assessed the primary endpoint of IGA success at Week 4, defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

In both trials, difamilast ointment, 1%, was statistically superior to vehicle on the primary efficacy endpoint. The results demonstrated clinically meaningful treatment effects with absolute differences from vehicle of 25.9% in Trial 271-102-00007 and 28.7% in Trial 271-102-00008. These findings were supported by consistent efficacy results across multiple phase 2 trials, including multinational trial 271-12-205 which enrolled subjects from the United States, Australia, and Poland, demonstrating an 18.2% treatment difference from vehicle (p=0.017).

The safety profile of difamilast ointment, 1%, was adequately characterized during the development program. The primary safety database consisted of pooled data from 386 subjects exposed to difamilast 1% and 348 subjects exposed to vehicle in controlled trials with treatment duration up to 4 weeks. Long-term safety data included 857 subjects exposed to difamilast 1% for up to 52 weeks, with 257 subjects receiving treatment for up to 52 weeks.

In the vehicle-controlled trials, difamilast 1% demonstrated an acceptable safety profile across all age groups with no clinically significant systemic safety signals identified. No TEAEs occurred with an incidence rate difference of ≥1% between the difamilast and vehicle groups. The most frequently reported TEAEs were nasopharyngitis (4.9% versus 4.6%) and viral infections (2.8% versus 2.6%), both occurring at similar rates between difamilast and vehicle treatment groups.

The most clinically relevant safety considerations relate to local tolerability reactions. While difamilast showed similar or improved local tolerability compared to vehicle in controlled trials, several subjects experienced clinically significant local reactions that led to trial discontinuation. In the vehicle-controlled trials, 1/386 (0.26%) subject receiving difamilast 1% discontinued due to local reactions (contact dermatitis). In the long-term trials, 13/857 (1.52%) subjects discontinued due to local reactions, including application site pain (5 subjects), application site

pruritus (4 subjects), contact dermatitis (4 subjects), with additional cases of application site erythema, application site vesicles, blistering, and burning. Age-stratified analyses showed some variation in local tolerability patterns, though symptoms when present were predominantly mild across all age groups.

Importantly, the safety data suggest that topical difamilast ointment, 1% does not demonstrate the characteristic systemic adverse reaction profile associated with systemic PDE-4 inhibitors. Weight monitoring across trials in the clinical program, including detailed review of pediatric growth analysis using z-score methodology, showed no overall clinical signal for drug-related weight loss, with age-appropriate weight gain observed in pediatric populations comparable to CDC standards. Similarly, clinical trial data did not support a causal link between difamilast and psychiatric adverse events, including depression or suicidal ideation/behavior, with only one psychiatric adverse event (depression) occurring in the difamilast group versus none in vehicle groups across controlled trials.

Although the majority of subjects in the safety database were from Japan, the review team concluded that the demographics of the study population are sufficiently representative of the target population in the United States. The epidemiological characteristics of AD are comparable between Japan and the United States, with similar prevalences (~10%) and severity distributions. Comparative safety analyses between Japanese and US populations demonstrated consistent safety profiles with no population-specific safety signals identified. Current clinical guidelines from the American Academy of Dermatology do not propose differential diagnosis or treatment approaches for AD by racial subgroup, and therapeutic guidelines recommend identical treatment approaches irrespective of race and ethnicity (refer to “Applicability of Foreign Data to the US Population below for further details.”

The clinical pharmacology assessment demonstrated that difamilast ointment, 1% achieves measurable but low systemic exposure following topical administration. Support for systemic safety is provided by pharmacokinetic and safety findings from a maximal use trial (MEDI-MM36-206) conducted in pediatric subjects 2 to <18 years of age with AD at the upper range of disease severity, which resulted in substantially greater systemic exposure compared to phase 3 trials and demonstrated a favorable safety profile with no serious systemic adverse events.

Based on the totality of evidence, including substantial evidence of effectiveness from two pivotal phase 3 trials, an acceptable safety profile characterized primarily by manageable local tolerability reactions, absence of concerning systemic effects characteristic of oral PDE-4 inhibitors, and applicability of foreign clinical data to the US population, the review team concludes that the benefit-risk of difamilast ointment, 1%, is favorable in the population of adults and pediatric patients 2 years of age and older with mild to moderate atopic dermatitis.

The review team recommends **approval** of this application with appropriate labeling (currently under negotiation with the Applicant) to address local tolerability reactions, and a postmarketing requirements to evaluate safety and pharmacokinetics in the deferred pediatric population (3 months to <2 years of age) in pediatric subjects in the US population.

Applicability of Foreign Data to the US Population:

The safety and efficacy assessment for difamilast ointment, 1%, relies substantially on clinical trial data generated in Japanese populations. The pivotal phase 3 trials (271-102-00007 and 271-102-00008) supporting this NDA were conducted exclusively in Japan and enrolled a total of 615 subjects. The US phase 3 trial (MEDI-MM36-301) was terminated by the Applicant early for business reasons after enrolling only 153 of 336 planned subjects. Given this reliance on foreign data, the review team evaluated whether safety and efficacy data from Japanese subjects can be extrapolated to support approval in the intended US patient population.

Epidemiological Comparability

The epidemiological characteristics of atopic dermatitis are comparable between Japan and the United States. Prevalence rates are approximately 10% in both populations, with similar distributions of disease severity that are primarily mild-to-moderate in nature. The age of onset and natural history patterns are comparable across populations, as is the impact on quality of life and disease burden. These similarities provide a foundation for considering the applicability of Japanese clinical data to the US population.

Population Differences and Clinical Relevance

While some genetic variability and clinical presentation differences exist between Japanese patients with atopic dermatitis and other races/ethnicities, the clinical relevance of these differences remains unclear (Kaufman et al. 2018). From a genetic and immunological perspective, Asian populations demonstrate increased TH22/TH17 activity compared to other ethnic groups. Filaggrin (FLG) mutations, which contribute to impaired skin barrier function, occur in up to 27% of Asian patients versus up to 50% in European Americans. These immunological differences could theoretically influence inflammatory responses and drug metabolism, though the clinical significance of these variations has not been definitively established.

Clinical presentation differences have also been documented. Asian patients typically present with better demarcated lesions and more scaling/lichenification compared to other populations. Additionally, erythema may be more difficult to assess in patients with darker skin tones, potentially affecting the detection of local skin reactions or irritation in diverse populations.

Despite these documented differences, current clinical guidelines do not propose differential diagnosis or treatment approaches for atopic dermatitis by racial subgroup (Sidbury et al. 2023; AAAAI ACAAI JTF Atopic Dermatitis Guideline Panel et al. 2024). Therapeutic guidelines recommend identical treatment approaches for AD irrespective of race and ethnicity, suggesting that such differences do not meaningfully impact response to treatment. This consensus among dermatology experts provides important context for evaluating the applicability of Japanese clinical data to the broader US population.

Comparative Safety Analysis: Japanese Versus US Populations

The review team conducted comprehensive comparative analyses of treatment-emergent adverse events between the Japanese phase 3 trials (271-102-00007 and 271-102-00008) and the US phase 3 trial (MEDI-MM36-301). In the vehicle-controlled phase 3 trials, the most common treatment-emergent adverse events in both Japanese and US populations were nasopharyngitis. In the Japanese trials, nasopharyngitis occurred in 6.0% of difamilast-treated subjects compared to 4.5% receiving vehicle, while in the US trial, rates were 2.1% for difamilast versus 3.4% for vehicle.

In the long-term uncontrolled safety trials, some numerical differences were observed between populations, though interpretation is limited by the absence of vehicle control groups. Consistent with the controlled trial experience, nasopharyngitis was the most common TEAE in both the Japanese trial 271-102-00006 (14.4%) and the US trial MEDI-MM36-302 (13.0%). Bacterial infections showed higher rates in the Japanese population (15.6%) compared to US subjects (7.1%). Specific bacterial infections more prevalent in Japanese subjects included paronychia (2.8% versus 0%), application site folliculitis (3.1% versus 0.6%), and hordeolum (1.6% versus 0%). Conversely, certain bacterial infections were more common in US subjects, particularly pharyngitis streptococcal (0% versus 2.4%). Viral infection rates were similar between populations (9.4% Japan versus 8.8% US). Regarding dermatological adverse events, Japanese subjects showed higher rates of application site urticaria (2.8% versus 0.2%) and application site acne (1.6% versus 0%), while application site pain was slightly more common in US subjects (1.3% versus 0.9%). Systemic adverse events also showed some population differences in the long-term uncontrolled trials. Depression was more commonly observed in US subjects (0% versus 1.7%), as was headache (0.3% versus 1.7%). Gastrointestinal events such as vomiting (0.3% versus 1.9%) and nausea were also more prevalent in the US population.

The observed regional differences in treatment-emergent adverse event patterns should be interpreted with caution given the substantial differences in sample sizes between the Japanese (N=320) and US (N=537) long-term trials, as well as the uncontrolled nature of these trials. Many of the apparent imbalances may reflect underlying population characteristics, environmental factors, genetic predisposition, or differences in trial conduct rather than true drug-related safety signals. The controlled phase 3 trial data, which provides the most reliable safety comparison, showed generally similar and low rates of adverse events between difamilast and vehicle in both populations. The higher rates of certain infections and dermatological reactions in Japanese subjects, and systemic events in US subjects, likely represent regional baseline differences rather than clinically significant safety concerns, particularly given the overall favorable benefit-risk profile demonstrated in the controlled trials.

Pharmacokinetic Considerations

Cross-study pharmacokinetic comparisons were conducted at Week 4 in adults with atopic dermatitis following twice-daily topical administration of difamilast ointment, 1%, stratified by race. These analyses included PK data derived from four clinical pharmacology trials: US trials MEDI-MM36-302 (QTc sub-study within the phase 3 open-label extension trial), 271-12-205

(multinational phase 2 trial), and 271-12-204 (Phase 1b proof-of-concept trial), and Japanese trial 271-15-001 (phase 2 dose-ranging study). The comparison evaluated steady-state PK parameters including maximum plasma concentration (Cmax), area under the plasma concentration-time curve from 0 to 12 hours (AUC0-12h), and trough plasma concentration (Ctrough) between White, Asian, and Black adult subjects with mild-to-moderate atopic dermatitis.

The highest mean nominal systemic exposure was observed in Asian subjects; however, these subjects also had the greatest mean body surface area involvement and received the highest topical doses. When normalized for dose, exposure was generally comparable between White and Black subjects, with only slightly higher dose-normalized exposure observed in Asian subjects. The mean predicted topical dose administered in Asian subjects was approximately 2- to 3-fold higher than in White or Black subjects due to greater baseline body surface area involvement. Following dose-normalization, Cmax, AUC0-12h, and Ctrough were slightly higher in Asians compared to White and Black subjects, but generally comparable to the overall population. These findings indicate that population differences in drug metabolism or absorption are minimal and do not result in clinically meaningful exposure differences that would impact safety. The slightly higher dose-normalized exposure in Asian subjects did not translate into increased adverse event rates, supporting the conclusion that these pharmacokinetic differences are not clinically significant from a safety perspective.

Efficacy Considerations

Treatment effects demonstrated heterogeneity across trials conducted in different geographic regions. The Japanese phase 3 trials showed larger treatment effects, with absolute differences from vehicle of 25.9% in Trial 271-102-00007 (subjects ≥15 years) and 28.7% in Trial 271-102-00008 (pediatric subjects 2-14 years). In contrast, the multinational phase 2 trial (271-12-205), which enrolled subjects from the United States, Australia, and Poland, showed a smaller treatment effect with an 18.2% absolute difference from vehicle. The terminated US phase 3 trial (MEDI-MM36-301) showed no treatment effect difference between difamilast 1% and vehicle (11.7% versus 11.9%), though the early termination of this trial for business reasons substantially limits meaningful interpretation of the efficacy results in the US population.

The reasons for these differences in treatment effects across geographic regions are unclear but may relate to several factors. Differences in diagnostic criteria were employed, with Japanese trials using the Japanese Dermatological Association criteria while the US trial used American Academy of Dermatology AD diagnostic criteria. The IGA scale definitions also differed between trials, particularly in the characterization of the "almost clear" category, which was not as distinct from the "mild" category in the Japanese trials. Baseline disease characteristics varied across trials, with different proportions of subjects having mild versus moderate disease at baseline. Study conduct factors, including differences in investigator training, assessment practices, and subject expectations, may also have contributed to the observed heterogeneity in treatment effects.

Conclusion

The review team concludes that the demographics of the study population are sufficiently representative of the target population in the United States, and safety and efficacy findings from the Japanese trials may be extrapolated to the US population based on the following considerations:

- Comparable disease epidemiology between Japanese and US populations, with similar prevalence rates (approximately 10%), disease severity distributions, and natural history patterns
- No population-specific safety signals identified in comparative analyses between Japanese and US subjects across controlled and long-term trials
- Consistent safety profiles across Japanese and US populations in controlled trials, with the most common adverse events (nasopharyngitis, viral infections) occurring at similar rates between treatment groups regardless of geographic region
- Similar pharmacokinetic profiles when adjusted for dose and body surface area involvement, with only minimal differences in dose-normalized exposure that did not translate into clinically meaningful differences in safety outcomes
- Established treatment guidelines that do not differentiate therapeutic approaches by race or ethnicity, supporting the biological plausibility of similar treatment responses across populations
- Supportive efficacy data from multinational phase 2 trial 271-12-205 that included US subjects and demonstrated statistically significant treatment effects, albeit with smaller magnitude than observed in Japanese phase 3 trials

The totality of evidence supports the applicability of foreign clinical data to the US population for regulatory decision-making. The absence of population-specific safety signals, combined with comparable adverse event rates and types between populations, supports approval for the proposed indication in the US population. While the terminated US phase 3 trial creates uncertainty regarding direct confirmation of efficacy in the US population, the consistency of efficacy findings across multiple phase 2 and phase 3 trials, clear dose-response relationships, and established PDE-4 inhibitor mechanism of action provide substantial evidence of effectiveness that is reasonably expected to apply to US patients with mild to moderate atopic dermatitis.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not hold an Advisory Committee Meeting for this application, because there were no efficacy, safety, or novel/complex regulatory issues that required input from an Advisory Committee. The Division presented the regulatory challenges related to this application to Medical Policy and Program Review Council Meeting (MPPRC). While the drug demonstrates therapeutic activity, the preponderance of data is from Japanese subjects with variable response rates between U.S. and ex-U.S. data. The Division sought guidance regarding how to accurately capture the magnitude of the treatment effect and expected response rates for U.S. patients and how to convey that effect in labeling.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant submitted proposed Prescribing Information (PI), Patient Information, and carton and container labels for difamilast ointment, 1%. The following table provides a summary of the major labeling changes.

Table 59: Prescribing Information

Key Prescribing Information Sections[1]	**Rationale for Major Changes to the Finalized Prescribing Information Compared to the Applicant's Original Draft PI**
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	No major changes
2 DOSAGE AND ADMINISTRATION	No major changes
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	No major changes
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 this review for local tolerability analysis.
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Incorporated DPMH-recommended pregnancy and lactation labeling with clinical considerations for breastfeeding women. Omitted section 8.3 per DPMH recommendation. Refer to Section 8.2.10 of this review for DPMH consultation summary.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	N/A
12 CLINICAL PHARMACOLOGY	Added statement regarding QTc interval based on interdisciplinary assessment. Refer to Section 8.2.4 for QTc evaluation.
13 NONCLINICAL TOXICOLOGY	No major changes.

14 CLINICAL STUDIES	Included results from the multinational phase 2 trial (271-12-205).
17 PATIENT COUNSELING INFORMATION	No major changes
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	No major changes

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) reviewed the proposed ADQUEY (difamilast) ointment, 1% Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors (Review by Kristine Needleman, RPh dated August 8, 2025). The Office of Prescription Drug Promotion (OPDP) also reviewed the same proposed labeling (PI, PPI) and labels (carton and container) (Review by Eunice Chung-Davies, Regulatory Review Officer dated February 4, 2026). Both review teams provided comments to be conveyed to the Applicant. Labeling is ongoing at the time of this review. Final labeling will be attached to the approval letter.

In labeling, the following trials were identified numerically as follows:

- **Trial 1:** 271-12-205 (ages 10-70 years), 0.3% and 1%): Phase 2 US double-blind, randomized, vehicle controlled (8 weeks treatment) n=119
- **Trial 2:** 271-102-00007 (≥15 years-70 years, 1%): Phase 3 Japan pivotal, double-blind, randomized, vehicle controlled (4 weeks treatment) n=364
- **Trial 3:** 271-102-00008 (ages ≥2 to <15 years, 0.3 and 1%): Phase 3 Japan pivotal double-blind, randomized, vehicle controlled (4 weeks treatment) n=251
- **Trial 4:** 271-102-00002 (ages 2-14 years, 0.3 and 1%): Phase 2 Japan double-blind, randomized, vehicle controlled (4 weeks treatment) n=73
- **Trial 5:** 271-15-001 (ages 15 to 70 years, 0.3 and 1%) Phase 2 Japan double-blind, randomized, vehicle controlled (8 weeks treatment) n=200

Other Prescription Drug Labeling

The Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) teams performed a collaborative review of the patient labeling for ADQUEY (difamilast) ointment, 1% and provided recommendations to enhance clarity, remove redundant or promotional language and ensure consistency with the PPI and comparator labeling. The final labeling will reflect these recommendations. (Review by Helen Young, MSN, MPH, CRRN, PHN, RN and Eunice Chung-Davies, PharmD dated February 4, 2026).

11 Risk Evaluation and Mitigation Strategies

Based on the favorable safety profile of difamilast ointment, the proposed labeling (prescribing information and patient labeling) and routine pharmacovigilance are considered adequate to manage risks of this product in the treatment of mild to moderate AD. A risk evaluation and mitigation strategy would not reduce the known risks associated with treatment with difamilast ointment, 1% and is not warranted at this time. The benefits of treatment with difamilast ointment, 1% were demonstrated in adequate and well controlled trials. Potential risks in the target population and subgroups will continue to be evaluated using standard surveillance tools and postmarketing assessments.

12 Postmarketing Requirements and Commitment

During the review cycle, the Agency and Applicant agreed on the clinical postmarketing requirements (PMRs) and milestone dates that would be issued with the product approval.

The Applicant will be required to conduct a pediatric assessment under Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). This study will address the deferred assessment included in the agreed Initial Pediatric Study Plan for the age group 3 months to <2 years and specifies pharmacokinetic assessments under maximal use conditions to ensure adequate characterization of potential systemic exposure. The clinical development program was predominantly conducted in Japanese subjects, and notably, a lower magnitude of treatment effect was observed in the US population compared to Japanese trials. Given these population-specific differences in treatment response, an adequate and well-controlled trial conducted specifically in US subjects ages 3 months to <2 years is necessary to establish both treatment effect and safety in this youngest age group.

The maternal health team did not recommend postmarketing studies to evaluate the effects of difamilast ointment, 1% in pregnancy or lactation. DPMH concluded that routine drug pharmacovigilance and published literature reviews were adequate to monitor pregnancy and infant outcomes, noting that topical PDE-4 inhibitors have been marketed for nearly a decade without identification of specific pregnancy safety concerns.

In addition, the review team concluded that the long-term safety of difamilast ointment, 1% was adequately characterized with data from two open-label trials MEDI-MM36-302 (N=542 subjects) and 271-102-00006 (N=366 [320 subjects received difamilast ointment, 1%]). There were no unexpected adverse reactions or adverse events with long latency periods that warranted further long-term evaluation.

Required Pediatric Study Under PREA

Conduct an adequate and well-controlled trial in the United States in subjects ages 3 months to <2 years with mild to moderate atopic dermatitis. Evaluate the safety and pharmacokinetics of

difamilast under maximal use conditions in an adequate number of subjects with disease at the upper range of severity.

Final Protocol Submission:	6/2026
Study Completion:	1/2029
Final Report Submission:	6/2029

Postmarketing Commitments (PMCs)

The review team recommended no postmarketing commitments.

13 Division Director (OCP) Comments

None.

14 Division Director (OB) Comments

None.

15 Division Director (Clinical) Comments

I concur with the review team's recommendation to approve NDA 219474 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 (AD). Recommended dosage is to be applied twice daily to affected area. The Applicant developed the product under the 505(b)(1) regulatory pathway.

Atopic dermatitis is a chronic, relapsing, inflammatory cutaneous disorder which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals. Patients with AD often experience sleep disturbance, largely attributable to the associated pruritus. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning (Camfferman et al. 2010). Affected children may experience depression and anxiety (Yaghmaie et al. 2013), social isolation, and impaired psychosocial functioning (Drucker et al. 2017).

Difamilast is a new-molecular-entity and is a phosphodiesterase Type 4 (PDE4) inhibitor. Difamilast ointment,1% was approved in Japan on September 27, 2021, for the treatment of AD.

The efficacy of ADQUEY for the treatment of mild to moderate AD was assessed in three multicenter, randomized, double-blind, vehicle-controlled trials (Trial1-phase 2, dose-ranging; Trial 2, and Trial 3 – phase 3) in 612 subjects. Trial 1 enrolled adult and pediatric subjects 10 years of age and older in the United States, Australia, and Poland. Trial 2 enrolled adult and pediatric subjects 15 years of age and older in Japan, and Trial 3 enrolled pediatric subjects 2 to 14 years of age in Japan. In these trials, subjects were randomized 1:1 to receive ADQUEY or vehicle ointment, applied topically to the entire treatment area twice daily for at least 4 weeks.

At baseline, 29%, 15%, and 15% of the subjects had an IGA of mild, and 71%, 85%, and 85% had an IGA of moderate in Trials 1, 2, and 3, respectively.

The primary efficacy endpoint for all trials was the proportion of subjects who achieved IGA success, defined as an IGA grade of clear (0) or almost clear (1) and with a 2-grade or greater improvement from baseline, at Week 4. Substantial evidence of effectiveness has been demonstrated from two phase 3 trials (Trial 2 and Trial 3) in Japanese subjects, that showed statistically significant and clinically meaningful improvements in atopic dermatitis severity. In Trial 2, ADQUEY, achieved IGA success in 70/182 (38.5%) subjects compared to 23/182 (12.6%) receiving vehicle, representing a 25.9% absolute treatment difference (95% CI: [17.5%, 34.4%], p<0.001). Similarly, in Trial 3, 40/85 (47.1%) subjects achieved IGA success versus 15/83 (18.1%) receiving vehicle, with a 28.7% absolute difference (95% CI: [15.0%, 42.5%], p<0.001). The multinational phase 2 trial, Trial 1, showed IGA success rates of 9/43 (20.9%) for difamilast ointment,1% versus 1/37 (2.7%) for vehicle, representing an 18.2% treatment difference (95% CI: [5.0%, 31.5%], p=0.017), which was notably smaller than the 25.9% and 28.7% differences observed in Trial 2 and Trial 3 in Japanese subjects. While the overall treatment effect was smaller in this trial, the data were supportive of a treatment effect of difamilast ointment, 1% in the adult US. The efficacy data from this trial will be included into product labeling to inform prescribers and patients of the treatment effect that may be expected in the US population.

An additional phase 3 trial (MEDI-MM36-301) was conducted in US. However, this trial was terminated early. This trial showed no treatment effect difference between difamilast ointment, 1% and vehicle (11.7% versus 11.9%, p=0.702). However, the early termination of this trial for “business reasons” limits meaningful interpretation of the efficacy results in the US population.

The safety profile of ADQUEY, was adequately characterized during the development program. The safety of ADQUEY was assessed in two double-blind, vehicle-controlled clinical trials (Trial 2 and Trial 3) that enrolled 267 (ADQUEY) and 265 (vehicle) adult and pediatric subjects 2 years of age and older in Japan with mild to moderate AD. Subjects applied ADQUEY or vehicle ointment topically twice daily for 4 weeks. Adverse reaction, nasopharyngitis is observed in 6% of ADQUEY-treated subjects and more frequently than in subjects receiving vehicle. Less common (<1%) adverse reactions in subjects treated with ADQUEY included application site folliculitis, contact dermatitis, application site rash, and molluscum contagiosum. In Trial 1, a vehicle-controlled dose ranging trial, 43 subjects 10 years of age and older in the United States, Australia, and Poland received ADQUEY topically twice daily for 8 weeks and the safety profile was consistent with Trials 2 and 3. In two additional vehicle -controlled dose ranging trials (Trial 4 and Trial 5) 92 subjects 2 years of age and older in Japan received ADQUEY topically twice daily for 4 weeks (Trial 4) and twice daily for 8 weeks (Trial 5) and the safety profile was consistent with Trials 2 and 3. Overall, no significant imbalances in adverse events were observed between Japanese and US subjects across the clinical development program (refer to Section 8.2.5.3 of Unireview). Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling are not required at this time.

Because phase 3 clinical trials (Trial 2 and 3) were conducted in Japanese subjects, the question was raised if data obtained from those trials are applicable to US population. Review team concluded that the totality of evidence supports the applicability of foreign clinical data to the US population based on comparable disease epidemiology, safety profile observed during clinical trials between Japanese and US populations, pharmacokinetic profiles between Japanese and US populations as well as supportive efficacy data from phase 2 trial that included US population (Trial 1). In addition, established treatment guidelines for AD do not differentiate therapeutic approaches by race or ethnicity, supporting the biological plausibility of similar treatment responses across populations. These complex regulatory issues were discussed at MPPRC (refer to Section 8.4 of Unireview, Applicability of foreign data to the US population).

In conclusion, the available safety and efficacy data support approval of 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 (AD).

Approval of ADQUEY will include postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c):

- Conduct an adequate and well-controlled trial in the United States in subjects ages 3 months to <2 years with mild to moderate atopic dermatitis. Evaluate the safety and pharmacokinetics of difamilast under maximal use conditions in an adequate number of subjects with disease at the upper range of severity.

16 Office Director (or designated signatory authority) Comments

I have carefully and thoroughly reviewed the data and information submitted under NDA 219474. I concur with the review team's and the Division signatory's assessment and recommendations, detailed in this review, that the available safety and efficacy data support approval of 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 (AD).

The regulatory action is Approval of the NDA with the above-mentioned postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

17 Appendices

17.1. References

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17.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for difamilast. The investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv). However, there were 16 sites where investigators provided no financial disclosure information. The reasons for non-disclosure included investigator death, retirement or movement to another facility, hospital closure, relocation or absence of contact information.

The covered clinical studies as defined in 21 CFR 54.2(e) were phase 3 Trial 271-102-00007 and 271-102-00008.

Table 60: Covered Clinical Studies

Phase	Protocol Number	Protocol Title	Subjects Enrolled
3	271-102-00007	A Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Comparison Trial to Demonstrate the Superiority of 1% OPA-15406 Ointment to the Vehicle in Adult Patients with Atopic Dermatitis	364
	271-102-00008	A Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Comparison Trial to Demonstrate the Superiority of 0.3% and 1% OPA-15406 Ointment to the Vehicle in Pediatric Patients with Atopic Dermatitis	251

Source: NDA 219474 Section 1.3 Administration Information, Table 1

Table 61: Covered Clinical Study: 271-102-00007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 27		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none identified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none identified		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none identified Significant payments of other sorts: none identified Proprietary interest in the product tested held by investigator: none identified Significant equity interest held by investigator in Sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Table 62: Covered Clinical Study: 271-102-00008

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

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17.3. Nonclinical Pharmacology/Toxicology

17.3.1. Review of the 2-Year Dermal Carcinogenicity Study Reports

17.3.1.1. Study 1: A 104-Week Carcinogenicity Study of OPC-271 Ointments by Percutaneous Administration in Rats

Study no.:	B-8051
Study report location:	SDN 1
Study initiation date:	July 5, 2016
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	0.3% OPC-271 Ointment: Lot number: 86227 and 100614 Content: 100.2% (Lot No. 86227) and 101.5% (Lot No. 100614) 1% OPC-271 Ointment Lot number: 86228 and 100202 Content: 101.2% (Lot No. 86228) and 100.7% (Lot No. 100202) 3% OPC-271 Ointment Lot number: 85433 and 100294 Content: 100.8% (Lot No. 85433) and 101.6% (Lot No. 100294)
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	MTD

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative

ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings:

A complete list of tissues was examined histopathologically for all main study animals. For either male or female rats, the tumor data analysis did not show any statistically significant positive dose response relationships across the sham control and the treated groups or the vehicle control and the treated groups. The pairwise comparisons did not show any statistically significant increases of any tumor types in any treated groups compared to the sham control or the vehicle control for either males or females.

The corresponding mean C_{max} and $AUC_{0\text{-}24h}$ values for OPC-271 for the high dose on Week 26 (Day 180) were 42 ng/mL and 873 ng*h/mL for males and 116 ng/mL and 2419 ng*h/mL for females, respectively. The mean $AUC_{0\text{-}24h}$ value for OPA-15406 at steady state in a maximal use clinical study (MEDI-MM36-206) was 237 ng·h/mL.

In conclusion, no test article-related neoplastic findings were observed in male or female rats that received difamilast at dermal doses up to 3% ointment, i.e., 8.2 mg/kg/day for males and 10.2 mg/kg/day for females, respectively (3.7 times the MRHD for males and 10 times the MRHD for females, respectively, based on AUC comparison).

Methods

Doses:	0 (sham control), 0 (vehicle control), 0.3%, 1%, and 3% (equivalent to 0, 0, 0.8, 2.7, and 8.2 mg/kg/day for males and 0, 0, 1.0, 3.3, and 10.2 mg/kg/day for females)
Frequency of dosing:	Once daily
Number/Sex/Group:	55
Dose volume:	0.008 mL/cm^2 applied to 3% body surface area
Formulation/Vehicle:	Ointment/ White petrolatum (b) (4)%, paraffin (b) (4)%, mineral oil (b) (4)%, white wax (b) (4)% and propylene carbonate (b) (4)%
Route of administration:	TOPICAL
Species:	RAT
Strain:	SPRAGUE-DAWLEY
Age:	6 weeks
Comment on Study Design and Conduct:	None
Dosing Comments (Dose Adjustments or Early Termination):	Due to decreased survival across all groups, all surviving males in Groups 1-5 were prematurely sacrificed after administration for 99 weeks. All surviving females in Groups 1-5 were prematurely sacrificed after administration for 100 weeks.
Dosing Solution Analysis:	Verification of concentration of test article was not conducted in this study. A tube of each test article (0.3%, 1% and 3% OPC-271 Ointments) and vehicle (0% OPC-271 Ointment) were used for administration without preparation.

Observations and Results

Mortality

Due to decreased survival across all groups, all surviving males in Groups 1-5 were prematurely sacrificed after administration for 99 weeks. All surviving females in Groups 1-5 were

prematurely sacrificed after administration for 100 weeks. The mortality and survival rates were summarized in the following table.

Table 64: Summary of Mortality and Survival Rate

Sex	Male					Female				
Concentration (%)	**0 [a, c]**	**0 [b, c]**	**0.3 [c]**	**1 [c]**	**3 [c]**	**0 [a, d]**	**0 [b, d]**	**0.3 [d]**	**1 [d]**	**3 [d]**
No. of animals used	55	55	55	55	55	55	55	55	55	55
Week of administration										
1-26	0	0	1	0	1	0	1	1	0	1
1-52	4	0	4	4	1	0	2	2	0	3
1-78	12	18	11	12	7	8	10	12	7	14
1-100	30	36	38	33	28	35	33	35	31	35
1-101	NA	NA	NA	NA	NA	35	34	36	32	36
No. of survivors	25	19	17	22	27	20	21	19	23	19
Survival rate (%)	45.5	34.5	30.9	40.0	49.1	36.4	38.2	34.5	41.8	34.5

Source: Study report submitted by the Applicant
Values in the table indicate the cumulative number of animals that died including the animals that were sacrificed as moribund.
[a] Sham control group
[b] Vehicle control group
[c] All surviving males were prematurely sacrificed after administration for 99 weeks.
[d] All surviving females were prematurely sacrificed after administration for 100 weeks.

The numbers (percents) of survival were 25 (46%), 19 (35%), 17 (31%), 22 (40%) and 27 (49%) in males, and 20 (36%), 21 (38%), 19 (35%), 23 (42%) and 19 (35%) in females in the sham, vehicle, low, mid, and high dose groups, respectively.

Per the statistical review, there were no treatment-related effects on survival in males or females.

Clinical Signs

There were no test article or vehicle-related clinical signs in either sex in any group. There were no test article or vehicle-related palpable masses in either sex in any group.

Body Weights

There were no vehicle-related changes in body weights in either sex in the vehicle control group when compared to the sham control group.

Significant test article-related decreases in the mean terminal body weights were observed in males at 0.3% and in both males and females at 1% (−12% in males and −15% in females) and 3% (−25% in males and −15% in females) groups when compared to the sham group.

Minimal decreases in the mean body weights observed at several points in females at 0.3% group when compared to the sham group were not considered test article-related.

Feed Consumption

There were no test article- or vehicle-related changes in feed consumption in either sex.

Hematology

There were no test article- or vehicle-related changes in hematology in either sex.

Organ Weights

There were no test article- or vehicle-related changes in organ weights in either sex.

Gross Pathology

There were no test article- or vehicle-related findings in either sex.

Histopathology

Peer Review Conducted: Yes

Historical Control Provided for Tumor Incidence: N/A

Neoplastic

A complete list of tissues was examined histopathologically for all main study animals. The tumor incidence data were analyzed by the statistical reviewer Dr. Zhuang Miao. Two dose-response relation tests (trend tests) were conducted across the vehicle control group, low, mid, and high dose groups and across the untreated control group, low, mid, and high dose groups, respectively. Pairwise comparison tests were conducted for untreated control group and three dose groups against the vehicle control group.

According to the FDA guidance for statistical design and data analysis of carcinogenicity studies, Dr. Miao used significance levels of α =0.005 for common tumors and α =0.025 for rare tumors (with a background incidence rate of 1% or less) for dose response relation tests and significance levels of α =0.01 for common tumors and α =0.05 for rare tumors for multiple pairwise comparisons.

Refer to Dr Miao's review for the complete results of tumor incidence data analysis. For either male or female rats, the tumor data analysis did not show any statistically significant positive dose response relationships across the sham control and the treated groups. The pairwise comparisons did not show any statistically significant increases of any tumor types in any treated groups compared to the sham control for either males or females.

For either male or female rats, the tumor data analysis did not show any statistically significant positive dose response relationships across the vehicle control and the treated groups. The pairwise comparisons did not show any statistically significant increases of any tumor types between the vehicle control and any of the treated groups for either male or female rats.

Non-Neoplastic

There were no significant test article- or vehicle-related findings in either sex.

Minimal or mild epidermal hyperplasia was observed at the application site in both sexes in the 0.3%, 1% and 3% groups. This finding was also observed in both sexes in the vehicle control group, and the incidence and severity were comparable.

Toxicokinetics

Blood samples were collected from the satellite animals on 3 Days: Day 1, Week 13 (Day 89) and Week 26 (Day 180) of administration at the following time points: 4 time points at 2, 4, 8 and 24 hours after dosing for test article groups and once at 4 hours after dosing for vehicle control group.

The systemic exposure to OPC-271 was demonstrated. The T_{max} values were 1 to 4 hours for OPC-271, 2 to 8 hours for MAP-15484, and1 to 8 hours for MAP-15485 and MAP-15497, respectively. The C_{max} and AUC_{24h} values for OPC-271 and its three metabolites (MAP-15484, MAP-15485 and MAP-15497) increased with increasing dose levels.

The molar ratios of AUC_{24h} of three metabolites to OPC-271 were 21.9% to 59.7% for

MAP-15484, 5.6% to 9.5% for MAP-15485, and 3.4% to 11.3% for MAP-15497, respectively. The AUC_{24h} of these metabolites were lower than that of OPC-271 in both sexes.

The C_{max} values for OPC-271 in Weeks 13 and 26 were similar to those on Day 1 in both sexes (0.5 to 0.9 times), except for the females dosed with 1% OPC-271 ointment in which the C_{max} values in Week 26 was slightly lower than that on Day 1 (0.4 times). The C_{max} values for three metabolites in Weeks 13 and 26 were similar to those on Day 1 in both sexes (0.5 to 1.9 times), except for MAP-15484 in the females dosed with 3% OPC-271 ointment in which the C_{max} value in Week 13 was slightly lower than that of Day 1 (0.4 times).

For OPC-271, the C_{max} and AUC_{24h} for the females were similar to those for the males on all occasions (0.6 to 1.8 times). The C_{max} and AUC_{24h} for three metabolites for the females were similar to or higher than those for the males on all occasions (0.6 to 4.0 times).

The TK parameters for OPC-271 and its metabolites (MAP-15484, MAP-15485 and MAP-15497) are summarized in the following table.

Table 65: Summary of TK Parameters

Sex	Male (n=3)			Female (n=3)		
Concentration (%)	**0.3**	**1**	**3**	**0.3**	**1**	**3**
OPC-271						
t_{max} (h)						
Day 1	4	8	8	4	8	8
Week 13 (Day 89)	2	2	2	4	4	2
Week 26 (Day 180)	2	4	24	4	4	8
C_{max} (ng/mL)						
Day 1	5.632	13.18	20.05	17.21	32.48	59.55
Week 13 (Day 89)	9.500	19.88	49.04	29.66	47.12	116.2
Week 26 (Day 180)	9.330	17.31	42.13	17.94	58.16	115.6
AUC_{24h} (ng·h/mL)						
Day 1	59.83	220.3	407.8	228.6	696.8	1167
Week 13 (Day 89)	141.2	379.6	915.2	369.8	941.3	2339
Week 26 (Day 180)	165.7	386.8	873.0	324.4	920.0	2419
MAP-15484						
t_{max} (h)						
Day 1	4	8	8	8	24	8
Week 13 (Day 89)	4	2	2	8	4	2
Week 26 (Day 180)	2	8	2	8	4	8
C_{max} (ng/mL)						
Day 1	2.022	6.085	8.983	2.659	5.854	11.94
Week 13 (Day 89)	1.942	6.489	28.64	2.972	11.82	37.52
Week 26 (Day 180)	2.145	8.242	22.82	3.019	8.841	33.20
AUC_{24h} (ng·h/mL)						
Day 1	28.28	96.76	172.9	46.73	115.2	225.9
Week 13 (Day 89)	36.78	121.8	425.0	61.34	209.9	640.7
Week 26 (Day 180)	39.40	163.6	356.5	51.06	171.5	618.4
MAP-15485						
t_{max} (h)						
Day 1	4	8	8	4	8	8
Week 13 (Day 89)	4	2	4	4	2	2
Week 26 (Day 180)	4	8	2	8	4	8
C_{max} (ng/mL)						
Day 1	5.438	15.69	21.91	11.36	21.69	52.69
Week 13 (Day 89)	8.893	22.58	65.47	20.44	41.31	127.9
Week 26 (Day 180)	9.225	21.03	54.79	16.10	44.29	119.8
AUC_{24h} (ng·h/mL)						
Day 1	65.05	250.1	448.2	168.1	461.7	872.1
Week 13 (Day 89)	172.8	441.6	1319	323.6	837.7	2324
Week 26 (Day 180)	183.0	463.0	1124	291.0	777.0	2197

Sex	Male (n=3)			Female (n=3)		
Concentration (%)	**0.3**	**1**	**3**	**0.3**	**1**	**3**
MAP-15497						
t_{max} (h)						
Day 1	NT	8	8	4	8	8
Week 13 (Day 89)	2	2	2	4	2	2
Week 26 (Day 180)	2	2	24	8	4	8
C_{max} (ng/mL)						
Day 1	<0.05	0.1245	0.1609	0.06973	0.1506	0.4649
Week 13 (Day 89)	0.08311	0.1794	0.7695	0.2907	0.6968	3.129
Week 26 (Day 180)	0.1021	0.2235	0.6066	0.2389	0.7568	2.804
AUC_{24h} (ng·h/mL)						
Day 1	NC	1.589	3.435	1.178	2.878	9.288
Week 13 (Day 89)	1.140	3.459	12.87	4.534	12.76	61.47
Week 26 (Day 180)	1.643	4.341	12.43	4.409	12.82	65.03

Values in the table indicate group mean. NT: Not determined, NC: Not calculated
Determination was also conducted on the vehicle control group (4 hours after dosing on Day 1, in Week 13 and in Week 26 of administration), and the OPC-271 concentrations in plasma were less than the lower limit of quantification.
Abbreviations: AUC_{24}, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum plasma concentration; t_{max}, time to C_{max}; TK, toxicokinetic

17.3.1.2. Study 2: A 104-Week Carcinogenicity Study of OPC-271 Ointments by Percutaneous Administration in Mice

Study no.:	B-8052
Study report location:	SDN 1
Study initiation date:	July 8, 2016
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	0.3% OPC-271 Ointment: Lot number: 86227 and 100614 Content: 100.2% (Lot No. 86227) and 101.5% (Lot No. 100614) 1% OPC-271 Ointment: Lot number: 86228 and 100202 Content: 101.2% (Lot No. 86228) and 100.7% (Lot No. 100202) 3% OPC-271 Ointment: Lot number: 85433 and 100294 Content: 100.8% (Lot No. 85433) and 101.6% (Lot No. 100294)
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	MFD

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative

ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings:

A complete list of tissues was examined histopathologically for all main study animals.

For either male or female mice, the tumor data analysis did not show any statistically significant positive dose response relationships across the sham control and the treated groups or the vehicle control and the treated groups. The pairwise comparisons did not show any statistically significant increases of any tumor types in any treated groups compared to the sham control or the vehicle control for either males or females.

The corresponding mean C_{max} and $AUC_{0\text{-}24h}$ values for OPC-271 for the high dose on Week 26 (Day 181) were 95 ng/mL and 1106 ng*h/mL for males and 81 ng/mL and 868 ng*h/mL for females, respectively, after 27 weeks of treatment. The mean $AUC_{0\text{-}24h}$ value for OPA-15406 at steady state in a maximal use clinical study (MEDI-MM36-206) was 237 ng·h/mL.

In conclusion, no test article-related neoplastic findings were observed in male or female mice that received difamilast at dermal doses up to 3% ointment, i.e., 51.8 mg/kg/day for males and 56.8 mg/kg/day for females, respectively (4.7 times the MRHD for males and 3.7 times the MRHD for females, respectively, based on AUC comparison).

Methods

Doses:	0 (sham control), 0 (vehicle control), 0.3%, 1%, and 3% (equivalent to 0, 0, 5.2, 17.2, and 51.8 mg/kg/day for males and 0, 0, 5.7, 19.2, and 56.8 mg/kg/day for females)
Frequency of dosing:	Once daily
Number/Sex/Group:	55
Dose volume:	0.008 mL/cm^2 applied to 10% body surface area
Formulation/Vehicle:	Ointment/ White petrolatum (b) (4)%, paraffin (b) (4)%, mineral oil (b) (4)%, white wax (b) (4)% and propylene carbonate (b) (4)%
Route of administration:	TOPICAL
Species:	MOUSE
Strain:	CD1(ICR)
Age:	4 weeks
Comment on Study Design and Conduct:	None
Dosing Comments (Dose Adjustments or Early Termination):	Due to decreased survival across all groups, all surviving females in the 1% group were prematurely sacrificed after administration for 93 weeks. All surviving females in the 3% group were prematurely

sacrificed after administration for 98 weeks. All surviving males were prematurely sacrificed after administration for 101 weeks. All surviving females in the sham control group, vehicle control group and 0.3% group were prematurely sacrificed after administration for 101 weeks.

Dosing Solution Analysis: Verification of concentration of test article was not conducted in this study. A tube of each test article (0.3%, 1% and 3% OPC-271 Ointments) and vehicle (0% OPC-271 Ointment) were used for administration without preparation.

Observations and Results

Mortality

Due to decreased survival across all groups, all surviving females in the 1% group were prematurely sacrificed after administration for 93 weeks. All surviving females in the 3% group were prematurely sacrificed after administration for 98 weeks. All surviving males were prematurely sacrificed after administration for 101 weeks. All surviving females in the sham control group, vehicle control group and 0.3% group were prematurely sacrificed after administration for 101 weeks. The mortality and survival rates were summarized in the following table.

Table 66: Summary of Mortality and Survival Rate

Sex	Male					Female				
Concentration (%)	**0 [a, e]**	**0 [b, e]**	**0.3 [e]**	**1 [e]**	**3 [e]**	**0 [a, f]**	**0 [b, f]**	**0.3 [f]**	**1 [c]**	**3 [d]**
No. of animals used	55	55	55	55	55	55	55	55	55	55
Week of administration										
1-26	0	0	1	2	1	1	2	1	0	0
1-52	3	7	8	8	6	5	6	7	8	1
1-78	17	21	24	29	17	23	20	27	34	28
1-93	29	28	30	35	28	28	27	35	40	37
1-98	33	31	32	36	34	30	29	37	NA	40
1-102	33	34	34	37	40	36	34	39	NA	NA
No. of survivors	22	21	21	18	15	19	21	16	15	15
Survival rate (%)	40.0	38.2	38.2	32.7	27.3	34.5	38.2	29.1	27.3	27.3

Values in the table indicate the cumulative number of animals that died including the animals that were sacrificed as moribund.
[a] Sham control group,
[b] Vehicle control group, NA: Not applicable
[c] All surviving females in the 1% group were prematurely sacrificed after administration for 93 weeks.
[d] All surviving females in the 3% group were prematurely sacrificed after administration for 98 weeks.
[e] All surviving males were prematurely sacrificed after administration for 101 weeks.
[f] All surviving females in the sham control group, vehicle control group and 0.3% group were prematurely sacrificed after administration for 101 weeks.

The numbers (percents) of survival were 22 (40%), 21 (38%), 21 (38%), 18 (33%), and 15 (27%) in male mice, and 19 (35%), 21 (38%), 16 (29%), 15 (27%), and 15 (27%) in female mice in sham control, vehicle control, low, medium, and high dose groups, respectively.

Per the statistical review, there were no treatment-related effects on survival in males or females.

Clinical Signs

There were no test article- or vehicle-related clinical signs in either sex in any groups. There were no test article- or vehicle-related palpable masses in either sex in any groups.

Body Weights

There were no test article- or vehicle-related changes in body weights in either sex when compared to the vehicle or sham control group.

Feed Consumption

There were no test article- or vehicle-related changes in feed consumption in either sex.

Hematology

There were no test article- or vehicle-related changes in hematology in either sex.

Organ Weights

There were no test article or vehicle-related changes in organ weights in either sex.

Gross Pathology

There were no test article- or vehicle-related findings in either sex.

Histopathology

Peer Review Conducted: Yes

Historical Control Provided for Tumor Incidence: N/A

Neoplastic

A complete list of tissues was examined histopathologically for all main study animals. The tumor incidence data were analyzed by the statistical reviewer Dr. Miao. Two dose-response relation tests (trend tests) were conducted across the vehicle control group, low, mid, and high dose groups and across the untreated control group, low, mid, and high dose groups, respectively. Pairwise comparison tests were conducted for untreated control group and three dose groups against the vehicle control group.

According to the FDA guidance for statistical design and data analysis of carcinogenicity studies, Dr. Miao used significance levels of α =0.005 for common tumors and α =0.025 for rare tumors (with a background incidence rate of 1% or less) for dose response relation tests and

significance levels of α =0.01 for common tumors and α =0.05 for rare tumors for multiple pairwise comparisons.

Refer to Dr Miao's review for the complete results of tumor incidence data analysis.

For either male or female mice, the tumor data analysis did not show any statistically significant positive dose response relationships across the sham control and the treated groups. The pairwise comparisons did not show any statistically significant increases of any tumor types between the sham control and any of the treated groups for either male or female mice.

For either male or female mice, the tumor data analysis did not show any statistically significant positive dose response relationships across the vehicle control and the treated groups. The pairwise comparisons did not show any statistically significant increases of any tumor types between the vehicle control and any of the treated groups for either male or female mice.

Non Neoplastic

There were no significant test article- or vehicle-related findings in either sex.

Minimal or mild epidermal hyperplasia was observed at the application site in both sexes in the 0.3%, 1% and 3% groups. This finding was also observed in both sexes in the vehicle control group and in males in the sham control group, and the incidence and severity were comparable. This change was considered not to be a test article- or vehicle-related effect. It appeared to be related to the study method of preparing the application site, i.e., hair clipping and "wipe off."

Toxicokinetics

The C_{max} and AUC_{24h} values for OPC-271 and its three metabolites (MAP-15484, MAP-15485 and MAP-15497) increased with increasing dose levels. The t_{max} values were 1 to 4 hours for OPC-271, 2 to 8 hours for MAP-15484, and 1 to 8 hours for both MAP-15485 and MAP-15497 after dosing, respectively.

The C_{max} values for OPC-271 in Weeks 13 and 26 were slightly lower than those on Day 1. The C_{max} values for three metabolites in Weeks 13 and 26 were similar to those on Day 1 in both sexes, except for MAP-15484 in the females dosed with 3% OPC-271 ointment in which the C_{max} values in Weeks 13 and 26 were slightly lower than that on Day 1. For OPC-271, the C_{max} and AUC_{24h} values in females were similar to those for the males on all occasions. Both parameters of three metabolites in females were similar to or higher than those in males on all occasions.

The TK parameters for OPC-271 and its metabolites (MAP-15484, MAP-15485 and MAP-15497) are summarized in the following table.

Table 67: Summary of TK Parameters

Sex	Male (n=3)			Female (n=3)		
Concentration (%)	**0.3**	**1**	**3**	**0.3**	**1**	**3**
OPC-271						
t_{max} (h)						
Day 1	1	1	2	1	2	4
Week 13 (Day 90)	1	1	2	1	1	2
Week 26 (Day 181)	4	4	4	1	1	4
C_{max} (ng/mL)						
Day 1	32.06	92.69	158.3	34.85	116.1	170.6
Week 13 (Day 90)	25.54	71.76	98.01	22.90	59.04	115.6
Week 26 (Day 181)	17.80	55.89	95.03	31.72	50.62	80.83
AUC_{24h} (ng·h/mL)						
Week 26 (Day 181)	136.4	545.7	1106	132.3	322.0	867.6
MAP-15484						
t_{max} (h)						
Day 1	2	4	4	2	2	4
Week 13 (Day 90)	2	4	4	4	4	2
Week 26 (Day 181)	4	2	8	2	2	8
C_{max} (ng/mL)						
Day 1	3.882	7.809	15.92	5.950	16.31	28.77
Week 13 (Day 90)	3.325	6.995	17.99	7.878	12.80	12.00
Week 26 (Day 181)	1.853	8.932	16.17	7.363	12.30	30.56
AUC_{24h} (ng·h/mL)						
Week 26 (Day 181)	20.95	84.32	223.3	46.81	124.8	363.2
MAP-15485						
t_{max} (h)						
Day 1	1	2	4	1	2	4
Week 13 (Day 90)	1	1	4	1	2	2
Week 26 (Day 181)	2	2	4	2	1	8
C_{max} (ng/mL)						
Day 1	1.088	2.653	5.386	1.459	5.384	8.200
Week 13 (Day 90)	1.025	2.359	5.720	1.311	3.616	4.818
Week 26 (Day 181)	1.019	2.323	6.818	1.917	3.382	4.732
AUC_{24h} (ng·h/mL)						
Week 26 (Day 181)	7.140	28.64	93.02	10.27	23.48	77.31
MAP-15497						
t_{max} (h)						
Day 1	1	2	4	1	2	4
Week 13 (Day 90)	2	2	4	1	2	2
Week 26 (Day 181)	2	2	4	2	1	8
C_{max} (ng/mL)						
Day 1	0.8644	3.173	5.316	1.612	7.420	9.547
Week 13 (Day 90)	0.8185	1.971	5.400	1.305	3.658	6.143
Week 26 (Day 181)	0.6464	2.300	9.886	2.081	3.772	6.416
AUC_{24h} (ng·h/mL)						
Week 26 (Day 181)	4.817	30.57	110.3	14.20	33.01	101.5

Values in the table indicate group mean.
Determination was also conducted on the vehicle control group (2 hours after dosing on Day 1, in Week 13 and in Week 26 of administration), and the OPC-271 concentrations in plasma were less than the lower limit of quantification.
Abbreviations: AUC_{24}, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum plasma concentration; t_{max}, time to C_{max}; TK, toxicokinetic

Overall Conclusions

The carcinogenic potential of difamilast was assessed in 2-year rat and 2-year mouse dermal studies.

No test article-related neoplastic findings were observed in male or female rats that received difamilast at dermal doses up to 3% difamilast ointment, i.e., 8.2 mg/kg/day for males and 10.2 mg/kg/day for females, respectively (3.7 times the MRHD for males and 10 times the MRHD for females, respectively, based on AUC comparison).

No test article-related neoplastic findings were observed in male or female mice that received difamilast at dermal doses up to 3% difamilast ointment, i.e., 51.8 mg/kg/day for males and 56.8 mg/kg/day for females, respectively (4.7 times the MRHD for males and 3.7 times the MRHD for females, respectively, based on AUC comparison).

Overall, difamilast was not carcinogenic in the 2-year dermal carcinogenicity studies in rats or mice.

17.3.2. Labeling

Multiple of Human Exposure Calculations

The multiples of human exposure values contained in the proposed label provided by the applicant are based on AUC comparisons.

The multiples of human exposure based on AUC comparisons between the NOAELs identified in pivotal toxicology studies and the MRHD are provided in the following table. One set of human exposure multiples, i.e., exposure multiples for adolescents, will be used in the label because the data are fairly indistinguishable in both adolescent and adult populations.

Table 68: Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies

Study	Route	NOAEL (mg/kg/day)	$AUC_{0\text{-}24h}$ (ng*hr/mL)	Multiples of Human Exposure[a] (Based on AUC Comparison)
39-Week dog study	SC	3	5422[b]	23
26-Week rat study	Dermal	0.9/1.1 (0.3%)	92.8[b]	0.4
39-Week minipig study	Dermal	8.1/8.3 (3%)	71[b]	0.3
Embryofetal development study in rats	SC	Maternal: 1 Embryofetal: 10	911[c] 7179[c]	3.8 30
Embryofetal development study in rabbits	SC	Maternal: 3 Embryofetal: 1	3256 700[d]	14 3
Prenatal and postnatal development study in rats	SC	Maternal: 0.3 Developmental: 3	321[e] 3002[e]	1.4 13

Study	Route	NOAEL (mg/kg/day)	AUC_{0-24h} (ng*hr/mL)	Multiples of Human Exposure[a] (Based on AUC Comparison)
Fertility and early embryonic development study in rats	SC	Paternal: 1 Maternal: 10 Male fertility: 10 Female fertility: 10 Early embryonic: 10	573[f] 7179[f] 4699[f] 7179[f] 7179[f]	2.4 30 20 30 30
Juvenile animal toxicity study in rats	Dermal	3%/ 1%	731.8[b]	3
Juvenile animal toxicity study in rats	SC	10	7347[b]	31
104-Week carcinogenicity study in mice	Dermal	51.8/56.8 (3%)[g]	867.6[b]	4
104-Week carcinogenicity study in rats	Dermal	8.2/10.2 (3%)[g]	873[b]	4

[a] Compared with a AUC_{0-24h} of 237 ng*hr/mL for human subjects at the MRHD (from Clinical trial# MEDI-MM36-206).
[b] The lower mean AUC_{0-24h} value between males and females was used.
[c] The AUC_{0-24h} value from a 4-week repeat-dose study was used.
[d] The AUC_{0-24h} value from a 13-day TK study was used.
[e] The AUC_{0-24h} value from a 4-week TK study was used.
[f] The AUC_{0-24h} values from a 4-week repeat-dose study was used.
[g] Dose levels of no neoplastic findings in the carcinogenicity study
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; NOAEL, no observed adverse effect level; SC, subcutaneous

An estimate AUC_{24h} value of 237 ng*hr/mL for human subjects at the MRHD (Difamilast ointment, 1%, the to-be-marketed concentration, was applied twice daily for 2 weeks to a median BSA of 40%) was obtained from a phase 2 clinical maximal-use trial in atopic dermatitis patients ages 2 to 18 years (Clinical trial# MEDI-MM36-206).

Exposure multiples for both the EFD (Study /Report # 027637) and FEFD (Study /Report # 027770) studies in rats are based on exposure data from the 4-week repeat-dose rat study (Study B100031/Report # 025360). Exposure multiples for the pre- and postnatal development study (Study /Report # 027637) are based on exposure data from the 4-week rat TK study (Study 037254/Report # 037254). Exposure multiples for the EFD study in rabbits (Study /Report # 027637) are based on exposure data from the 13-day rabbit TK study (Study 032776/Report # 028047). The lower mean AUC value between males and females was used.

Recommended Revision to the Nonclinical Portions of Labeling

(b) (4)

215 5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

17.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

17.4.1. Individual Study Reports

17.4.1.1. Study MEDI-MM36-206 (Maximal Use PK Trial)

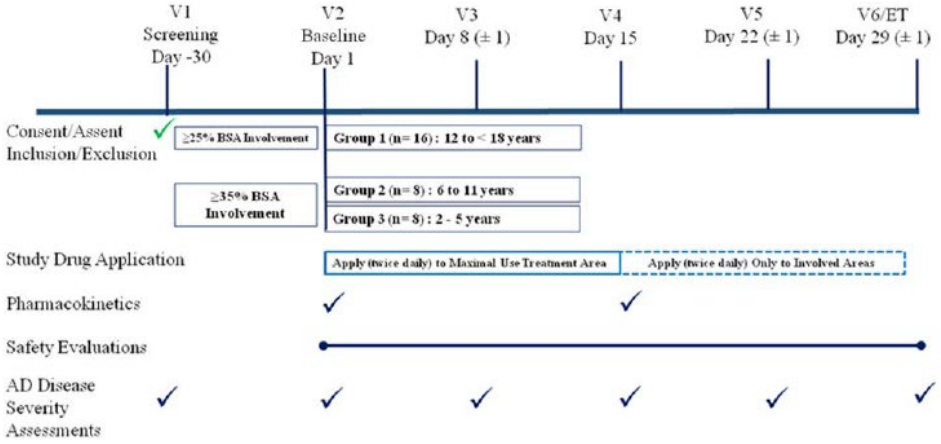
Title:

A phase 2 multi-center, open-label study to assess pharmacokinetic parameters and safety of topical MM36 [difamilast] 1% in pediatric subjects 2 to <18 years of age with atopic dermatitis under maximal use conditions

Study Design:

Study MEDI-MM36-206 was a multicenter, open-label study to evaluate the PK, safety, tolerability, and effectiveness of difamilast ointment, 1%, following administration under maximal use conditions in pediatric subjects 2 to <18 years of age with AD at the upper range of disease severity (Figure 16). Following a 30-day screening period, all subjects received difamilast ointment, 1% BID for 28 days. For the first 14 days, treatment was administered under maximal use conditions, which was defined as topical application to ≥35% BSA for subjects 2 to <12 years of age and ≥25% BSA for those 12 to <18 years of age. Subjects were instructed to continually apply difamilast ointment, 1%, to the entire originally affected BSA at baseline, even if the area cleared, until after the PK samples had been collected on Day 15. For the latter 14 days (i.e., Days 15 to 28), treatment was administered to only the affected areas.

Figure 16: Overall Study Design for Study MEDI-MM36-206



Source. CSR for Study MEDI-MM36-206 (Figure 1, pg. 26)
Abbreviations: AD, atopic dermatitis; BSA, body surface area; CSR, clinical study report; N, number of subjects; V, visit;

This study enrolled male and female pediatric subjects 2 to <18 years of age (inclusive) with a diagnosis of AD affecting at least 25% BSA (for subjects 12 to <18 years of age) or 35% BSA (for

subjects 2 to <12 years of age), excluding scalp and venous access areas. Excluded medications included systemic or topical therapy with PDE-4 inhibitors within 60 days of baseline, systemic immunomodulators, corticosteroids, or antimetabolites within 28 days of baseline, and topical corticosteroids and antihistamines within 14 and 7 days of baseline, respectively.

Demographics and Disposition:

All PK analyses were conducted based on the safety analysis dataset, for which a summary of baseline demographics and disease characteristics is provided below in Table 69 and Table 70, respectively.

Table 69: Summary of Demographic and Baseline Characteristics for PK-Evaluable Subjects (MEDI-MM36-206; Safety Population)

Demographic Statistic	Children 2 to 5 years (N=9)	Children 6 to 11 years (N=15)	Adolescents 12 to 17 years (N=7)	All Subjects (N=31)
Sex				
n	9	15	7	31
Male	3 (33.3%)	7 (46.7%)	5 (71.4%)	15 (48.4%)
Female	6 (66.7%)	8 (53.3%)	2 (28.6%)	16 (51.6%)
Race				
n	9	15	7	31
White	5 (55.6%)	8 (53.3%)	4 (57.1%)	17 (54.8%)
Black	1 (11.1%)	2 (13.3%)	1 (14.3%)	4 (12.9%)
Asian	0	0	1 (14.3%)	1 (3.2%)
American Indian or Alaska Native	0	1 (6.7%)	1 (14.3%)	2 (6.5%)
Multiple/Other	3 (33.3%)	4 (26.7%)	0	7 (22.6%)
Ethnicity				
n	9	15	7	31
Hispanic or Latino	8 (88.9%)	11 (73.3%)	1 (14.3%)	20 (64.5%)
Not Hispanic or Latino	1 (11.1%)	4 (26.7%)	6 (85.7%)	11 (35.5%)
Weight (kg)				
n	9	15	7	31
Mean (SD)	14.9 (2.8)	34.0 (12.2)	68.5 (27.8)	36.3 (24.7)
Median (Min, Max)	14.0 (12.2, 21)	32.5 (18.0, 58.8)	64.1 (44.1, 122)	29.0 (12.2, 122)
Height (cm)				
n	9	15	7	31
Mean (SD)	95.2 (6.1)	134 (13.5)	164 (9.3)	130 (27.5)
Median (Min, Max)	93.0 (88.0, 106)	139 (109, 159)	169 (150, 173)	137 (88.0, 173)
BSA (m^2)[a]				
n	9	15	7	31
Mean (SD)	0.6 (0.1)	1.1 (0.3)	1.7 (0.4)	1.1 (0.5)
Median (Min, Max)	0.6 (0.6, 0.8)	1.1 (0.7, 1.6)	1.8 (1.4, 2.4)	1.1 (0.6, 2.4)
BMI (kg/m^2)				
n	9	15	7	31
Mean (SD)	16.3 (1.3)	18.3 (3.4)	25.3 (9.4)	19.3 (5.9)
Median (Min, Max)	16.2 (14.4, 18.7)	17.4 (13.4, 24.7)	21.7 (16.7, 42.7)	17.3 (13.4, 42.7)

Source. Reviewer's analysis based on adsl.xpt for Study MEDI-MM36-206
[a] The Mosteller Formula [BSA (m^2) = √((Ht(cm) × Wt (kg)) / 3600] was utilized to calculate BSA for each subject
Abbreviations: BMI, body mass index; BSA, body surface area; Ht, height; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; Wt, weight

Table 70: Summary of Baseline EASI Score, IGA-AD Score, and BSA Involvement for PK-Evaluable Subjects (MEDI-MM36-206; Safety Population)

Demographic Statistic	Children 2 to 5 years (N=9)	Children 6 to 11 years (N=15)	Adolescents 12 to 17 years (N=7)	All Subjects (N=31)
EASI total				
N	9	15	7	31
Mean (SD)	15.6 (6.3)	19.8 (6.4)	17.4 (8.4)	18.0 (6.9)
Median (min, max)	13.9 (8.8, 24.5)	18.4 (11.1, 32.0)	15.6 (7.6, 29.0)	15.7 (7.6, 32.0)
IGA-AD				
N	9	15	7	31
0: clear	0	0	0	0
1: almost clear	0	0	0	0
2: mild	1 (11.1%)	2 (13.3%)	0	3 (9.7%)
3: moderate	7 (77.8%)	11 (77.4%)	5 (71.4%)	23 (74.2%)
4: severe	1 (11.1%)	2 (13.3%)	2 (28.6%)	5 (16.1%)
BSA involvement (%)[a]				
n	9	15	7	31
Mean (SD)	44.0 (9.0)	47.2 (14.3)	36.9 (15.1)	43.9 (13.4)
Median (min, max)	42.0 (35.0, 64.0)	41.0 (36.0, 80.0)	32.0 (25.0, 65.0)	41.0 (25.0, 80.0)

Source. Reviewer's analysis based on adsl.xpt and adpk.xpt for Study MEDI-MM36-206
[a] If percent BSA affected decreased during treatment period, the same amount of study medication defined at baseline would continue to be applied; If overall BSA affected worsened, additional study medication would be applied to cover the increased affected BSA
Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; IGA-AD, Investigator's Global Assessment for Atopic Dermatitis; N, number of subjects; P, pharmacokinetic; SD, standard deviation

A total of 32 pediatric subjects 2 to <18 years of age with AD were enrolled. The safety analysis set comprised 97% (N=31) of those enrolled, as a single subject (b) (6), age 4) was excluded from further analysis due to the lack of post-baseline safety assessments. Additionally, two subjects discontinued treatment prior to Day 15 due to parent/guardian withdrawal ((b) (6), age 3) and development of a moderate TEAE of application site rash ((b) (6), age 10). Overall, baseline disease severity, based on EASI and IGA-AD scores, was comparable across age groups, although mean percent BSA involvement was slightly lower in the adolescent sub-group compared to the 2 to 5 and 6 to 11 sub-groups.

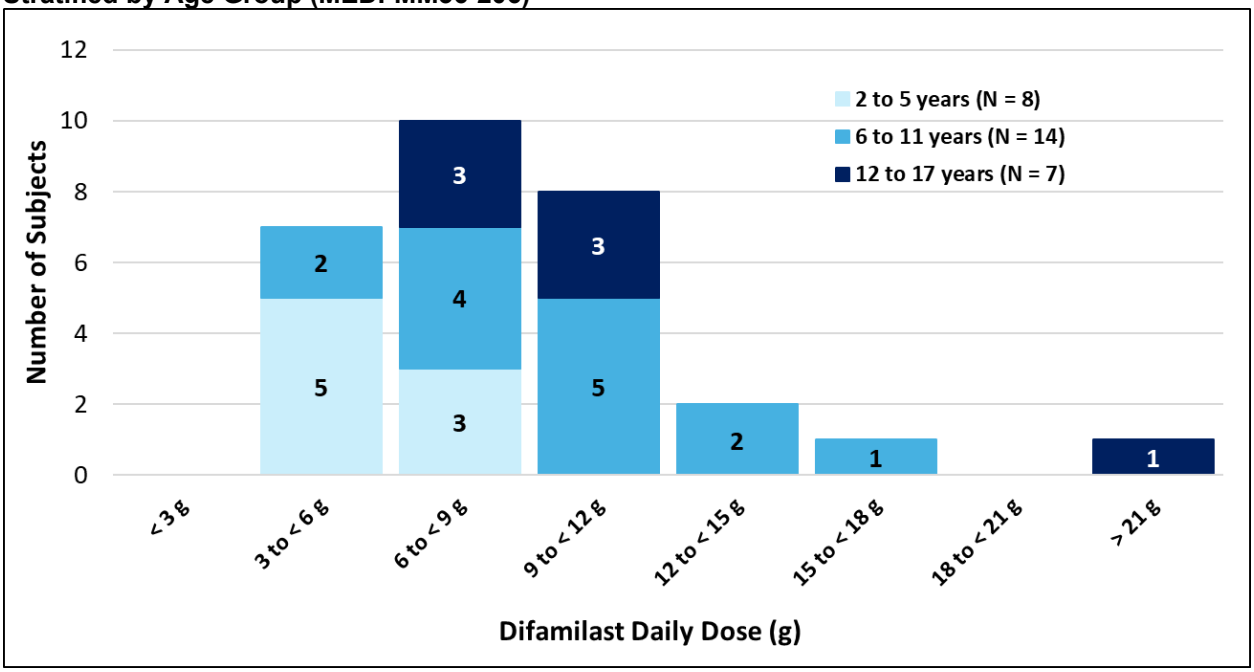
Dosing Trend in Maximal Use Trial:

The average daily application dose of difamilast ointment, 1%, used in Study MEDI-MM36-206, stratified by age group, is provided below in Figure 17. Daily dose was calculated based on the weight difference of the medication tube between clinical site visits. Two subjects ((b) (6) and (b) (6)) who discontinued treatment prior to the PK sampling period and did not return the study drug tubes were excluded from this calculation.

Of the 29 subjects for whom the average daily dose could be derived, approximately 83% (N=24) applied at least 5 g of ointment per day. The mean (SD) average daily ointment administration in the overall trial population was 8.5 (4.2) g, ranging from 3.3 to 23.3 g per day. This corresponded to a mean (SD) predicted difamilast dose of approximately 42.7 (21.1) mg difamilast per dose application (range: 16.7 to 117 mg). Additionally, the mean (SD) average daily amount of ointment administered increased with age across the three sub-groups: 5.0

(1.5) g for 2 to 5 years of age, 9.5 (3.2) g for 6 to 11 years of age, and 10.8 (5.7) g for 12 to 17 years of age.

Figure 17: Distribution of Average Daily Dose of Difamilast Ointment, 1% (g) in Maximal Use Trial, Stratified by Age Group (MEDI-MM36-206)[a]



Source. Reviewer's analysis based on adpk.xpt for Study MEDI-MM36-206
[a] Average daily dose calculated based on the weight difference of the medication tube between visits; Two subjects ((b) (6) (b) (6) were excluded from this calculation due to early treatment discontinuation and failure to return study drug tubes.
Abbreviations: N, number of subjects

PK Analysis/Results:

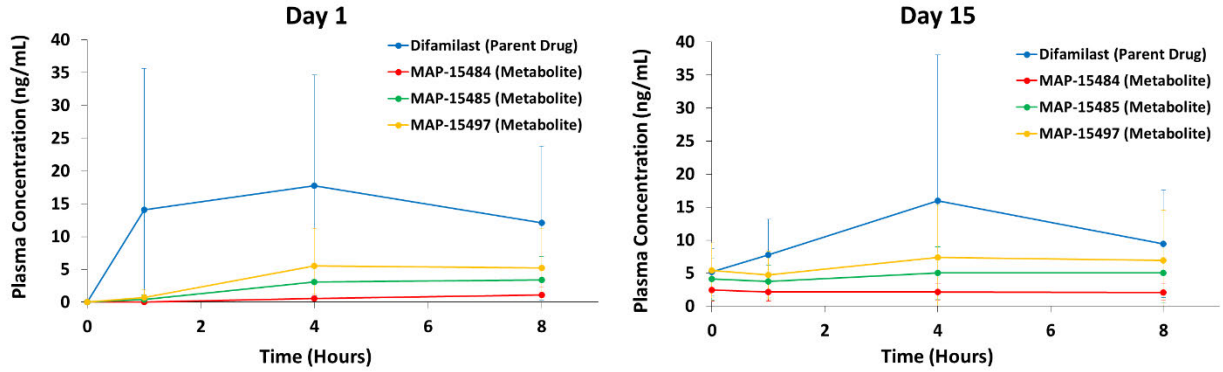
Pre-dose blood samples were collected on Days 1 and 15, with post-dose samples drawn at 1, 4, and 8 h relative to the first of the BID doses. PK parameters for difamilast and its metabolites were derived using NCA and summarized by study day with descriptive statistics (Table 71). The arithmetic mean (SD) plasma concentration-time profiles of difamilast and its metabolites (MAP-15484, MAP-15485, and MAP-15497) at Days 1 and 15 were plotted on a linear scale (Figure 18). For summaries of plasma concentration-time profiles and PK parameters, all quantifiable concentrations at pre-dose on Day 1 as well as post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to zero. All PK analyses were conducted based on the safety population, which included 97% (N=31/32) of enrolled subjects. Analysis of PK data by age sub-group is described in Section 6.3.2.3.1.1.

Table 71: Summary of PK Parameters for Difamilast and Metabolites Following Administration of Difamilast Ointment, 1%, Under Maximal Use Conditions (MEDI-MM36-206; PK Population)[a]

Study Day / PK Parameter[b]	Analyte			
	Difamilast	MAP-15484	MAP-15485	MAP-15497
Day 1 (no. of subj =31)				
C_{max} (ng/mL)	23.1 (23.4)	1.25 (1.10)	3.68 (3.51)	6.03 (6.07)
C_{max}N (ng/mL/mg)[c]	0.64 (0.79)	0.04 (0.04)	0.11 (0.14)	0.16 (0.16)
AUC_{0-8h} (ng*h/mL)	107 (94.1)	4.78 (4.71)	17.2 (18.5)	29.0 (35.4)
AUC_{0-8h}N (ng*h/mL/mg)[c]	3.02 (3.39)	0.14 (0.18)	0.52 (0.73)	0.79 (0.94)
T_{max} (h)	4.00 (0.97, 8.87)	7.43 (3.92, 8.87)	7.10 (3.67, 8.87)	7.08 (3.67, 8.87)
Day 15 (no. of subj =29)				
C_{max} (ng/mL)	16.9 (21.9)	2.79 (1.60)	5.88 (4.32)	8.40 (7.92)
C_{max}N (ng/mL/mg)[c]	0.48 (0.59)	0.08 (0.07)	0.17 (0.17)	0.23 (0.22)
AUC_{0-8h} (ng*h/mL)	86.2 (79.6)	16.2 (9.35)	35.1 (26.8)	49.1 (49.5)
AUC_{0-8h}N (ng*h/mL/mg)[c]	2.45 (2.54)	0.45 (0.35)	1.00 (0.98)	1.32 (1.29)
T_{max} (h)	4.00 (0.00, 8.50)	0.92 (0.00, 8.07)	4.00 (0.00, 8.50)	3.92 (0.00, 8.07)
C_{trough} (ng/mL)	5.16 (3.53)	2.47 (1.66)	4.11 (3.16)	5.39 (4.17)
C_{trough}N (ng/mL/mg)[c,d]	0.14 (0.12)	0.07 (0.06)	0.11 (0.10)	0.14 (0.11)

Source. Reviewer's analysis based on adpc.xpt and adpk.xpt for Study MEDI-MM36-206
[a] Maximal use conditions defined as topical application of difamilast ointment, 1% BID to ≥35% BSA for children 2 to <12 years of age and ≥25% BSA for adolescents 12 to <18 years of age
[b] PK parameters reported as arithmetic mean (SD), except for T_{max}, which is reported as median (min, max); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[c] Normalized according to the predicted topical dose of difamilast (mg) per application
[d] Pre-dose plasma concentration on Day 15
Abbreviations: AUC_{0-8h}, area under the plasma concentration-time curve from 0 to 8 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; PK, pharmacokinetics; SD, standard deviation

Figure 18: Arithmetic Mean (SD) Plasma Concentration-Time Profiles for Difamilast and Metabolites Following Administration of Difamilast Ointment, 1%, Under Maximal Use Conditions (MEDI-MM36-206; PK Population)[a,b]

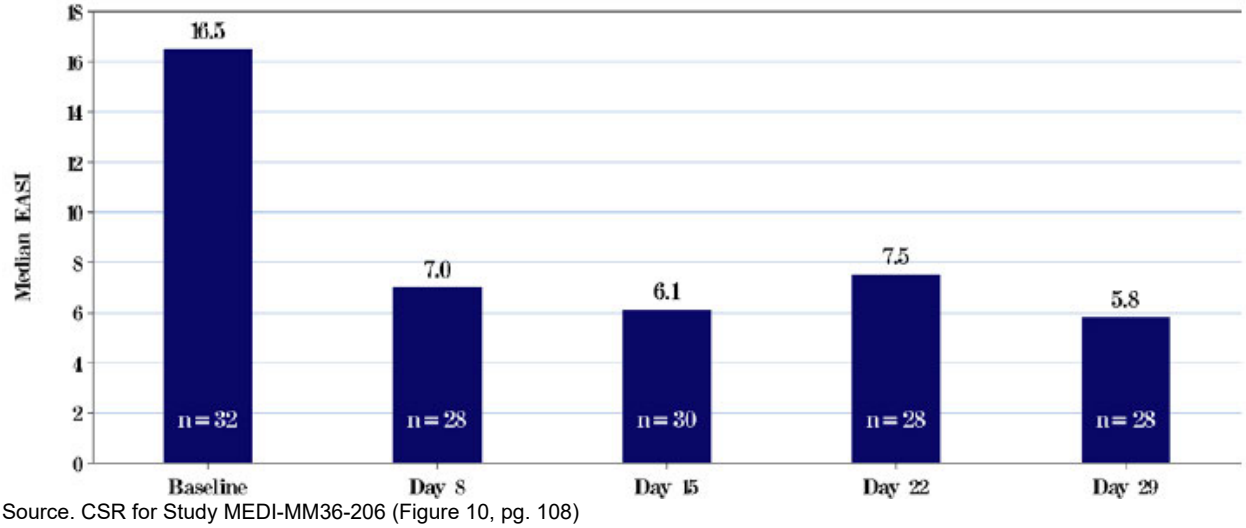


Source. Reviewer's analysis based on adpc.xpt for Study MEDI-MM36-206
[a] Maximal use conditions defined as topical application of difamilast ointment, 1% BID to ≥35% BSA for children 2 to <12 years of age and ≥25% BSA for adolescents 12 to <18 years of age
[b] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for generation of PK profiles
Abbreviations: BID, twice daily; BSA, body surface area; LLOQ, lower limit of quantitation; PK, pharmacokinetic; SD, standard deviation

Systemic exposure of difamilast was generally low, with a high degree of inter-individual variability. Of note, plasma concentrations observed at Day 15 were lower compared to those at Day 1, which may have been related to the resolution of AD lesions over time, thereby leading to improved integrity of the skin barrier and lower dermal absorption. This is supported

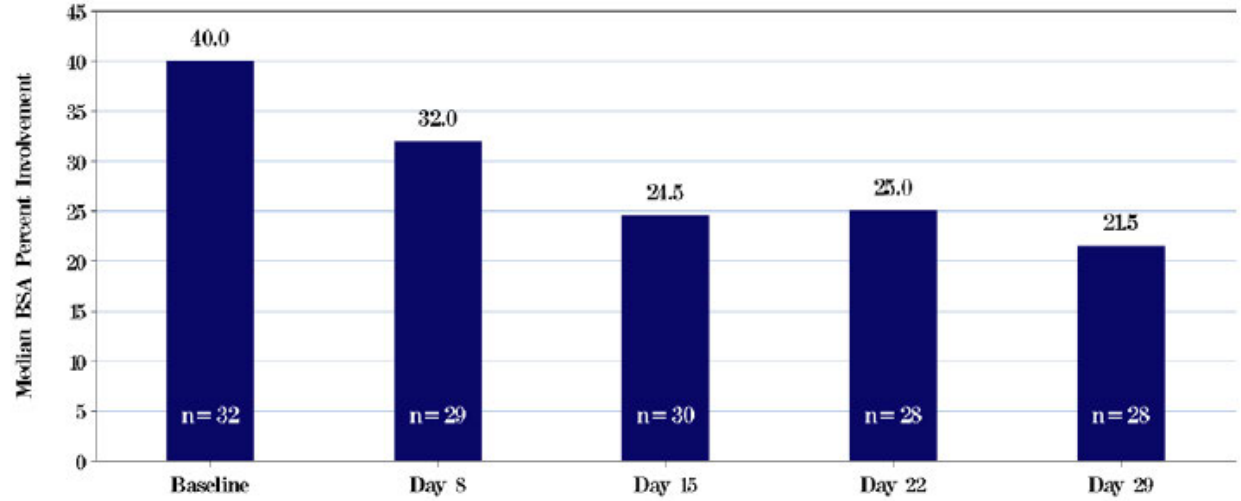
by the drug effectiveness findings reported below in Figure 19 and Figure 20, which demonstrate reductions from baseline at Day 15 in median EASI score and BSA involvement, respectively.

Figure 19: Median EASI Score Over Time (MEDI-MM36-206; ITT Population)



Source. CSR for Study MEDI-MM36-206 (Figure 10, pg. 108)
Abbreviations: CSR, clinical study report; EASI, Eczema Area and Severity Index; ITT, intent-to-treat; N, number of subjects

Figure 20: Median BSA Involvement Over Time (MEDI-MM36-206; ITT Population)



Source. CSR for Study MEDI-MM36-206 (Figure 11, pg. 109)
Abbreviations: BSA, body surface area; CSR, clinical study report; ITT, intent-to-treat; N, number of subjects

Regarding the metabolites (MAP-15484, MAP-15485, and MAP-15497), approximately 2- to 4-fold accumulation was observed at Day 15. The highest exposure was observed for MAP-15497, followed by MAP-15485 and MAP-15484. Relative to difamilast, the mean molar C_{max} ratios at Day 15 for MAP-15497, MAP-15485, and MAP-15484 were approximately 47.9%, 37.1%, and 23.5%, respectively. Similarly, mean molar AUC_{last} ratios to the parent drug at Day 15 for MAP-15497, MAP-15485, and MAP-15484 were approximately 55.0%, 43.4%, and 26.8%, respectively. It was also noted that on Day 15, the mean pre-dose concentration of MAP-15497 exceeded that of the parent drug.

However, there were significant deficiencies identified with the validation of the bioanalytical assay used to measure plasma concentrations of MAP-15484, MAP-15485, and MAP-15497 in this study. Additionally, incurred sample reanalysis (ISR) data for all three metabolites failed to meet the acceptance criteria. Therefore, the reported metabolites PK data in this trial may be unreliable and should be interpreted with caution. However, despite these issues, the metabolite PK data are considered to be acceptable because (1) metabolites are produced down-stream of the site of action and hence are unlikely to contribute to efficacy, and (2) the safety of MAP-15484, MAP-15485, and MAP-15497 based on animal toxicity data suggested that further assessment of these metabolites would not be necessary for this topically applied product. Refer to Section 5.5 and Section 17.4.4 for additional details regarding assessment of Pharmacology/Toxicology data and of bioanalytical method validation and performance, respectively.

Safety Results:

A summary of TEAEs according to organ system is provided below in Table 72. A total of 7 (22.6%) subjects reported 9 TEAEs, of which 3 (33.3%) were considered related to the study drug. Of the TEAEs reported, 8 were considered mild, with 1 categorized as moderate (application site rash) which led to withdrawal of this subject from the study. There were no SAEs or deaths reported. By organ class, the most common TEAEs were general disorders and administration site conditions and infections and infestations, which were reported in 4 (12.9%) and 3 (9.7%) subjects, respectively.

No abnormal vital signs or physical findings were noted at the final examination on Day 29. One subject had mildly elevated eosinophils prior to first application of study drug (pre-dose) which was reported as an AE, although this event was not considered related to study drug. No clinically significant changes from baseline were observed for clinical chemistry, hematology, and urinalysis parameters on Day 29. Overall, based on these data, difamilast appeared to be generally well-tolerated. See Section 8.2 for detailed review of safety.

Table 72: Summary of TEAEs by MedDRA System Organ Class and Preferred Term (MEDI-MM36-206; Safety Population)[a]

System Organ Class Preferred Term	Difamilast Ointment, 1% BID Subject Frequency[a] (N=31)	 Event Frequency[b] (N=9)
Gastrointestinal Disorders	1 (3.2%)	1 (11.1%)
Vomiting	1 (3.2%)	1 (11.1%)
General Disorders and Administration Site Conditions	4 (12.9%)	4 (44.4%)
Application Site Pain	1 (3.2%)	1 (11.1%)
Application Site Rash	1 (3.2%)	1 (11.1%)
Influenza-like Illness	1 (3.2%)	1 (11.1%)
Pyrexia	1 (3.2%)	1 (11.1%)
Infections and Infestations	3 (9.7%)	3 (33.3%)
Nasopharyngitis	1 (3.2%)	1 (11.1%)
Tonsillitis	1 (3.2%)	1 (11.1%)
Upper Respiratory Tract Infection	1 (3.2%)	1 (11.1%)
Investigations	1 (3.2%)	1 (11.1%)
Eosinophil Count Increased	1 (3.2%)	1 (11.1%)

Source. Adapted from CSR for Study MEDI-MM36-206 (Table 31, pg. 121)
[a] TEAEs were those for which onset occurred after use of study drug.
[b] Reflects number of subjects reporting ≥1 AEs mapped to MedDRA. Subjects were counted only once at each level of summarization (System Organ Class or Preferred Term). Percentages based on total number of subjects in the Safety population.
[c] Reflects number of AEs reported that map to MedDRA. Percentages based on total number of AEs reported.
Abbreviations: AE, adverse event; BID, twice daily; CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; TEAE, treatment-emergent adverse event

17.4.1.2. Study MEDI-MM36-302 (QTc Sub-Study)

Title:

A multicenter, open-label study to assess the long-term safety of difamilast ointment, 1%, in the treatment of children, adolescents and adults with mild-to-moderate atopic dermatitis

Study Design:

This was a phase 3, multicenter, 52-week OLE study designed to assess the long-term safety, tolerability, and efficacy of topical administration of difamilast ointment, 1% BID in adult and pediatric subjects 2 years and older with mild-to-moderate AD. This study included (1) rollover subjects from parent study MEDI-MM36-301 who received either active treatment or placebo, as well as (2) new subjects not enrolled in prior clinical trials (i.e., "*de novo*" subjects).

Additionally, to characterize the potential effects of difamilast on the QT interval, the Applicant conducted a 4-week QTc repolarization sub-study, which included only adult subjects not previously enrolled in Study MEDI-MM36-301. These subjects were instructed to continue to apply the study drug to the affected areas defined at baseline through Day 29, even if the lesions improved or resolved, in addition to any new lesions that developed post-baseline. The PK of difamilast and its metabolites (MAP-15484, MAP-15485, and MAP-15497) was also evaluated, as described below. Refer to the QT Study Review conducted by the IRT-CS dated July 22, 2025 for evaluation of the ECG data derived from this QTc sub-study (DARRTS Reference ID: 5628165).

Demographics and Disposition:

A summary of baseline demographics and disease characteristics for both the QTc sub-study as well as the overall safety population is provided below in Table 73 and Table 74, respectively.

Table 73: Summary of Demographic and Baseline Characteristics for QTc Sub-Study and Overall Safety Population (MEDI-MM36-302)

Demographic Statistic	QTc Sub-Study PK Population (N=31)	Overall Safety Population (N=537)
Sex		
n	31	537
Male	13 (41.9%)	224 (41.7%)
Female	18 (58.1%)	313 (58.3%)
Race		
n	31	537
White	20 (64.5%)	334 (62.2%)
Black	7 (22.6%)	135 (25.1%)
Asian	3 (9.7%)	40 (7.5%)
American Indian or Alaska Native	0	5 (0.9%)
Multiple/Other	1 (3.2%)	23 (4.3%)
Ethnicity		
n	31	537
Hispanic or Latino	8 (25.8%)	90 (16.8%)
Not Hispanic or Latino	23 (74.2%)	447 (83.2%)
Age (years)		
n	31	537
Mean (SD)	40.1 (13.6)	32.2 (22.4)
Median (Min, Max)	41.0 (18.0, 70.0)	29.0 (2.0, 83.0)
Weight (kg)		
n	31	537
Mean (SD)	87.2 (16.0)	70.4 (32.8)
Median (Min, Max)	86.2 (58.5, 119)	71.6 (10.9, 230)
Height (cm)		
n	31	537
Mean (SD)	169 (11.1)	156 (25.1)
Median (Min, Max)	170 (148, 191)	163 (78.7, 198)
BSA (m^2)[a]		
n	31	537
Mean (SD)	2.01 (0.21)	1.72 (0.54)
Median (Min, Max)	2.00 (1.60, 2.50)	1.80 (0.50, 3.40)
BMI (kg/m^2)		
n	31	537
Mean (SD)	30.6 (6.0)	26.8 (8.4)
Median (Min, Max)	30.1 (19.2, 42.4)	25.8 (13.6, 70.0)

Source. Reviewer's analysis based on adsl.xpt for Study MEDI-MM36-302
[a] The Mosteller Formula [BSA (m^2) = √((Ht(cm) × Wt (kg)) / 3600] was utilized to assess overall BSA of each subject in this study
Abbreviations: BMI, body mass index; BSA, body surface area; Ht, height; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; Wt, weight

Table 74: Summary of Baseline EASI Score, IGA-AD Score, and BSA Involvement in QTc Sub-Study and Overall Safety Population (MEDI-MM36-302)

Demographic	QTc Sub-Study PK Population (N=31)	Overall Safety Population (N=537)
EASI total		
n	31	535
Mean (SD)	4.8 (3.0)	6.5 (5.3)
Median (min, max)	3.6 (1.6, 15.6)	5.2 (0.0, 50.7)
IGA-AD		
n	31	537
0: clear	0	4 (0.7%)
1: almost clear	0	14 (2.6%)
2: mild	7 (22.6%)	182 (33.9%)
3: moderate	24 (77.4%)	336 (62.6%)
4: severe	0	1 (0.2%)
BSA involvement (%)		
N	31	537
Mean (SD)	5.5 (3.0)	9.6 (10.7)
Median (min, max)	4.0 (3.0, 19.0)	6.0 (0.0, 86.0)

Source. Reviewer's analysis based on adsl.xpt and adqs.xpt for Study MEDI-MM36-302
Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; IGA-AD, Investigator's Global Assessment for Atopic Dermatitis; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

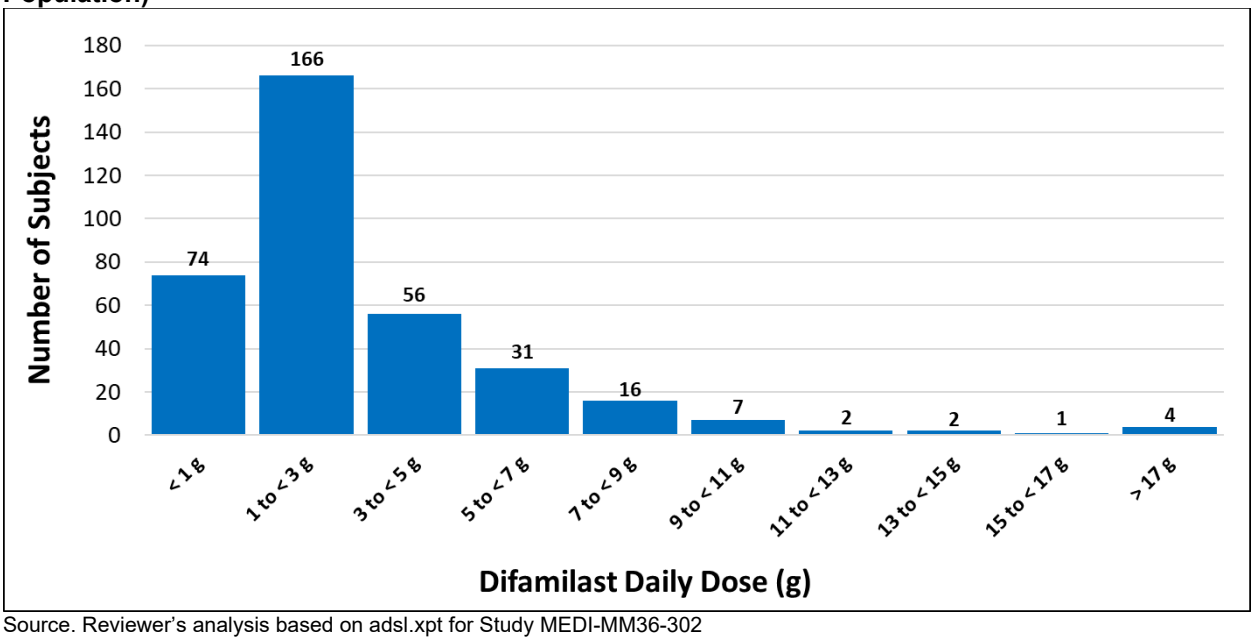
A total of 31 adult subjects with AD were enrolled in the QTc sub-study to receive difamilast ointment, 1% BID, all of whom were included in the PK analysis population. Of these, 97% (N=30) completed their assigned treatment and PK assessments through Day 29, with the exception one subject who voluntarily withdrew from the study after a single dose on Day 1 ([(b) (6)]).

Overall, baseline demographics in the QTc sub-study were comparable to those of the overall population. However, the QTc/PK population had a lower baseline mean EASI score, and mean percent BSA involvement at baseline was approximately one-half of that of the safety analysis population. Of note, although the QTc prolongation assessment was not conducted at a supra-therapeutic systemic exposure range, the review team determined that additional TQT assessment was not necessary based on the totality of nonclinical data (i.e., hERG assay and animal cardiovascular safety pharmacology studies), clinical safety data, and experience from other PDE-4 inhibitor drugs. Refer to Section 8.2.4 for additional information. The potential for difamilast to prolong the QTc interval is also briefly discussed in Section 6.3.2.2.

Dosing Trend in Overall Safety Population versus QTc Sub-Study:

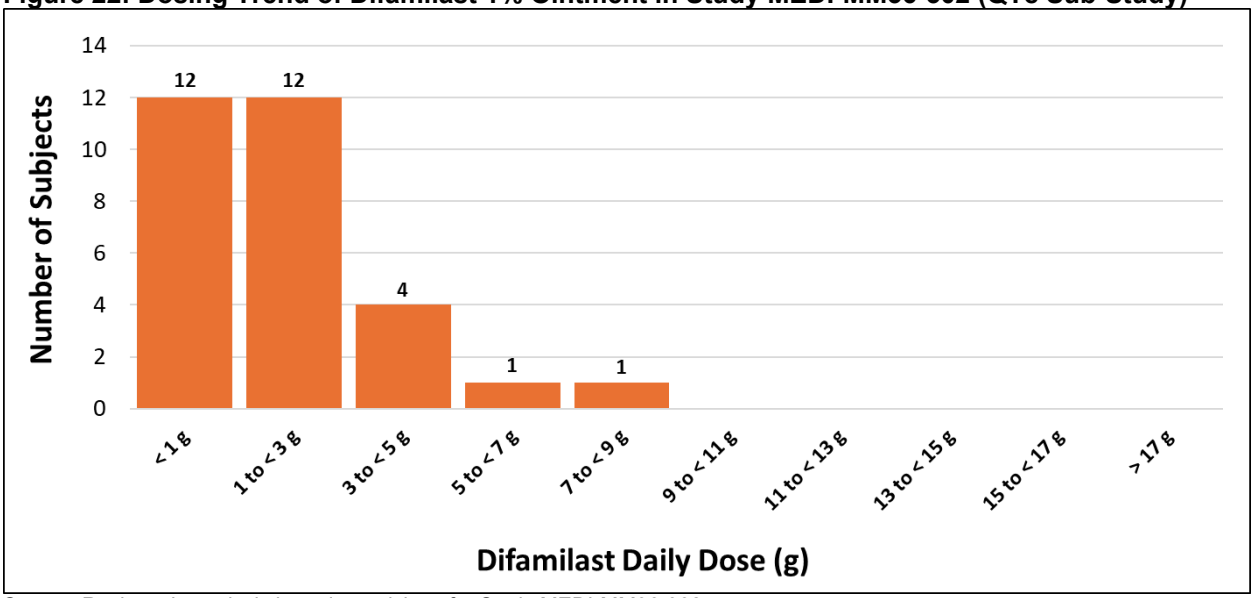
The average daily application dose of difamilast ointment, 1%, used in trial MEDI-MM36-302 is provided below for the overall safety population and the QTc sub-study in Figure 21 and Figure 22, respectively. Daily dose was calculated based on the weight difference of the medication tube between clinical site visits. Therefore, subjects who failed to return all of the dispensed study drug tubes were excluded from this calculation (N=148 and 1 in overall safety and PK populations, respectively).

Figure 21: Dosing Trend of Difamilast 1% Ointment in Study MEDI-MM36-302 (Overall Safety Population)[a]



Source. Reviewer's analysis based on adsl.xpt for Study MEDI-MM36-302
[a] Average daily dose calculated based on the weight difference of the medication tube between visits (N=389 in overall safety population); A total of 148 subjects who failed to return the all of the dispensed study drug tubes were excluded from this calculation
Abbreviations: N, number of subjects

Figure 22: Dosing Trend of Difamilast 1% Ointment in Study MEDI-MM36-302 (QTc Sub-Study)[a]



Source. Reviewer's analysis based on adsl.xpt for Study MEDI-MM36-302
[a] Average daily dose calculated based on the weight difference of the medication tube between visits (N=30 in PK population); One subject (b) (6)) was excluded from this calculation due to early treatment discontinuation and failure to return study drug tubes.
Abbreviations: PK, pharmacokinetic; N, number of subjects

Among those included in the overall safety population for which dosing trend could be determined (N=389), the mean (SD) average daily ointment administration was 3.0 (3.2) g, ranging from 0.1 to 31.2 g per day. This corresponded to a mean (SD) of approximately 14.8 (16.2) mg difamilast per dose application (range: 0.7 to 156 mg). For subjects enrolled in the

QTc sub-study with available dosing information (N=30), the mean (SD) average daily ointment administration was 1.8 (1.8) g, ranging from 0.2 to 7.5 g per day. This corresponded to a mean (SD) of approximately 9.0 (8.8) mg difamilast per dose application (range: 1.2 to 37.5 mg). Note that the overall safety population includes subjects enrolled in the QTc sub-study.

PK Analysis/Results:

Blood samples collected at the following timepoints:

- **Day 1:** Pre-dose, then post-dose at 2, 4, 6, and 12 h
- **Day 29:** Pre-dose, then post-dose at 2, 4, 6, 12, 24, and 36 h

PK parameters for difamilast and its metabolites were derived using NCA and summarized by study day with descriptive statistics (Table 75). The arithmetic mean (SD) plasma concentration-time profiles of difamilast and its metabolites (MAP-15484, MAP-15485, and MAP-15497) at Days 1 and 29 were plotted on a linear scale (Figure 23). For summaries of concentration-time profiles and PK parameters, all quantifiable concentrations at pre-dose on Day 1, as well as post-baseline samples below the assay LLOQ (0.050 ng/mL for difamilast, MAP-15485, and MAP-15497; 0.125 ng/mL for MAP-15484), were imputed to zero. Of the 31 subjects included in this PK sub-study, 97% (N=30/31) completed all study assessments through Day 29, with one subject who withdrew following application of the first dose ((b) (6)).

Overall, systemic exposure of difamilast and its metabolites in Study 302 was substantially lower compared to that observed in the maximal use trial (Study 206). Mean difamilast C_{max} and AUC values were lower at Day 29 relative to Day 1, which aligns with the observed PK data from Study 206. As discussed previously, this finding may be related to response to the treatment and disease resolution, which could have influenced the degree of dermal absorption of the parent drug over time. This is supported by the mean (SD) change from baseline in EASI score and BSA involvement (%) of −2.6 (2.3) and −2.3 (1.8), respectively, at the 1-month visit for the PK population, indicating improvement in AD lesions.

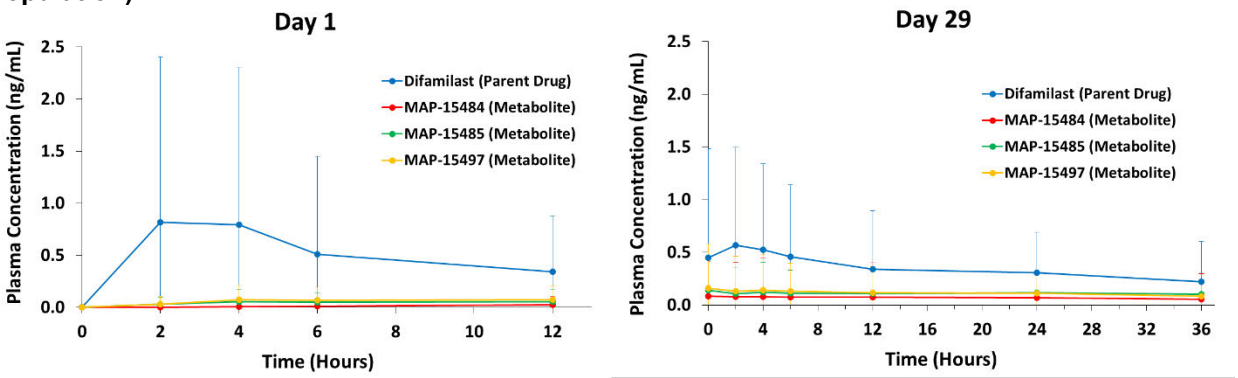
Mean terminal half-life of difamilast ranged from approximately 5.3 to 8.6 h, although there is considerable uncertainty in this finding due to the large number of BLQ samples in the terminal elimination phase, which precluded calculation of half-life in the majority of subjects. Regarding the metabolites, there were insufficient PK data for the calculation of half-life in any subjects. Additionally, although some accumulation of metabolites was observed, MAP-15484, MAP-15485, and MAP-15497 were detectable in only 17% (N=5), 63% (N=19), and 63% (N=19) of subjects, respectively, at Day 29.

Table 75: Summary of PK Parameters for Difamilast and Metabolites Following BID Topical Administration of Difamilast Ointment, 1% (MEDI-MM36-302; PK Population)

Study Day	Analyte							
	Difamilast		MAP-15484		MAP-15485		MAP-15497	
PK Parameter[a]	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Day 1 (No. of subj =31)								
C_{max} (ng/mL)	24	1.28 (1.94)	3	0.25 (0.13)	10	0.19 (0.16)	12	0.22 (0.17)
$C_{max}N$ (ng/mL/mg)[b]	24	0.14 (0.17)	3	0.01 (0.08)	10	0.02 (0.01)	12	0.02 (0.02)
AUC_{0-12h} (ng*h/mL)	19	9.48 (13.0)	2	1.68 (1.82)	9	1.54 (1.46)	11	1.69 (1.51)
$AUC_{0-12h}N$ (ng*h/mL/mg)[b]	19	1.07 (0.92)	2	0.07 (0.08)	9	0.14 (0.06)	11	0.19 (0.16)
$t_{1/2}$ (h)	3	5.27 (2.03)	0	NC	0	NC	0	NC
T_{max} (h)[c]	24	4.0 (2.0-12.0)	3	12.0 (11.9-12.0)	10	4.1 (4.0-12.0)	12	5.0 (4.0-12.1)
Day 29 (No. of subj =30)								
C_{max} (ng/mL)	28	0.76 (1.16)	5	0.58 (0.80)	19	0.24 (0.39)	19	0.28 (0.51)
$C_{max}N$ (ng/mL/mg)[b]	28	0.12 (0.16)	5	0.03 (0.03)	19	0.03 (0.02)	19	0.03 (0.02)
AUC_{0-12h} (ng*h/mL)	27	6.10 (8.85)	4	7.15 (9.78)	18	2.29 (3.49)	19	2.52 (4.21)
$AUC_{0-12h}N$ (ng*h/mL/mg)[b]	27	0.99 (1.23)	4	0.35 (0.33)	18	0.27 (0.21)	19	0.29 (0.23)
$t_{1/2}$ (h)	5	8.61 (3.27)	0	NC	0	NC	0	NC
T_{max} (h)[b]	28	4.0 (0.0-12.0)	5	4.0 (0.0-11.9)	19	2.0 (0.0-12.0)	19	4.2 (0.0-12.0)
C_{trough} (ng/mL)[d]	30	0.45 (1.03)	30	0.09 (0.33)	30	0.14 (0.33)	30	0.16 (0.42)
$C_{trough}N$ (ng/mL/mg)[b,d]	30	0.054 (0.067)	30	0.01 (0.02)	30	0.02 (0.02)	30	0.02 (0.02)

Source. Reviewer's analysis based on pc.xpt and adpk.xpt for Study MEDI-MM36-302
[a] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL for difamilast, MAP-15485, and MAP-15497; 0.125 ng/mL for MAP-15484) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Normalized according to the predicted topical dose of difamilast (mg) per application
[c] T_{max} reported as median (min, max)
[d] Pre-dose plasma concentration on Day 29
Abbreviations: AUC_{0-12h}, area under the plasma concentration-time curve from 0 to 12 hours; BID, twice daily; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; NC, not calculated; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal half-life; T_{max}, time of C_{max}

Figure 23: Arithmetic Mean (SD) Plasma Concentration-Time Profiles for Difamilast and Metabolites Following BID Topical Administration of Difamilast Ointment, 1% (MEDI-MM36-302; PK Population)[a]



Source. Reviewer's analysis based on pc.xpt for Study MEDI-MM36-302
[a] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL for difamilast, MAP-15485, and MAP-15497; 0.125 ng/mL for MAP-15484) were imputed to 0 for generation of PK profiles
Abbreviations: BID, twice daily; LLOQ, lower limit of quantitation; PK, pharmacokinetic; SD, standard deviation

17.4.1.3. Study 271-12-204

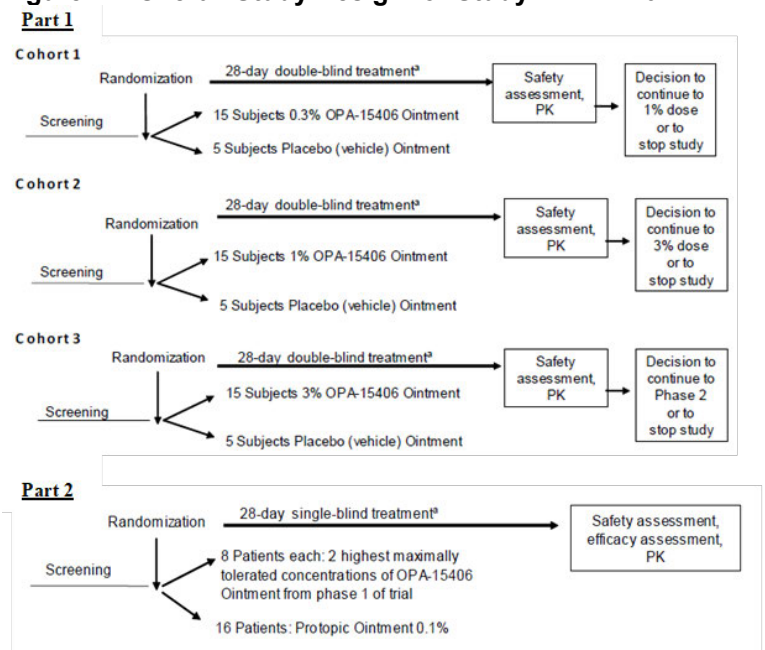
Title:

A multiple-dose (0.3%, 1%, and 3% [w/w]), randomized, blinded, vehicle- and active comparator-controlled, sequential dose cohorts, multi-center trial to assess the safety, pharmacokinetics, and proof-of-concept efficacy of topical OPA-15406 [difamilast] ointment, applied twice daily for 28 days, in adult subjects with atopic dermatitis

Study Design:

Study 271-12-204 was a two-part phase 1b, randomized, vehicle- and active comparator-controlled, sequential proof-of-concept study to assess the safety, tolerability, PK, and efficacy of ascending topical doses of difamilast ointment in adults with mild-to-moderate AD (Figure 24).

Figure 24: Overall Study Design for Study 271-12-204



Source. Adapted from CSR for Study 271-12-204 (Figure 9.1-1 [pg. 33], Figure 9.1-2 [pg. 34])
Abbreviations: CSR, clinical study report; OPA-15406, difamilast; PK, pharmacokinetics

In Part 1, 60 subjects were randomized to one of three ascending dose cohorts in a 3:1 ratio to receive difamilast ointment or placebo (N=20 per cohort). The three ascending difamilast doses which were evaluated included 0.3%, 1%, and 3% ointment strengths, with escalation to the next highest dose based upon acceptable safety, tolerability, and PK data derived from the previous dose level. In each cohort, subjects received their assigned treatment via BID topical administration to 5% BSA, regardless of the combined size of the lesion(s), for a total of 28 days. Following completion of Part 1, the two highest tolerated difamilast ointment strengths (1% and 3%) were carried forward to be studied in Part 2, in which 30 subjects were randomized in a 1:1:2 ratio to receive difamilast ointment, 1% (N=7), difamilast ointment, 3%

(N=8), or tacrolimus ointment, 0.1% (N=15) via topical BID administration to *at least* 10% BSA for a total of 28 days. Subjects were instructed to continue to apply their assigned treatment to the BSA defined at baseline for the duration of the treatment period, even if the AD lesion(s) improved over time.

This study enrolled male and female subjects 18 to 65 years of age (inclusive) with a diagnosis of mild-to-moderate AD affecting at least 5% BSA (Part 1) or 10% BSA (Part 2), excluding the face, neck, and head at screening and baseline. Subjects taking systemic or topical therapy for AD within 30 days of the screening visit, including but not limited to cyclosporine, corticosteroids, and methotrexate, were excluded. Additionally, strong or moderate inducers and inhibitors of CYP1A2 and/or CYP3A4, as well as oral or topical antihistamines, were prohibited within 7 days of the baseline visit through the end of the treatment period. Oral contraceptives, as well as prescription or nonprescription emollients, were permitted.

Dosing and Baseline BSA Involvement:

A summary of baseline BSA involvement and difamilast dosing in Study 271-12-204 according to study part and treatment arm is provided in Table 76.

Table 76: Baseline BSA Involvement and Predicted Difamilast Dose per Application (mg), Stratified by Treatment Arm and Study Part (Study 271-12-204; PK Population)

Parameter Summary Statistics	Difamilast Ointment, 0.3% BID	Difamilast Ointment, 1% BID	Difamilast Ointment, 3% BID
Part 1 (N=45)			
BSA involvement (%)[a]			
n	15	15	15
Mean (SD)	5 (0)	5 (0)	5 (0)
Predicted difamilast dose (mg)[b]			
n	15	15	15
Mean (SD)	3 (0)	10 (0)	30 (0)
Part 2 (N=15)			
BSA Involvement (%)[a]			
n	NA	7	8
Mean (SD)	NA	25.1 (21.8)	27.0 (15.2)
Median (Min, Max)	NA	15.0 (10.0, 66.0)	25.0 (10.0, 56.0)
Predicted difamilast Ddse (mg)[b]			
n	NA	7	8
Mean (SD)	NA	48.6 (43.7)	52.5 (31.1)
Median (Min, Max)	NA	29.9 (20.0, 130)	50.0 (19.9, 110)

Source. Reviewer's analysis based on CSR for Study 271-12-204 (PKT-21 through PKT-26 [pg. 576-583])
[a] In Part 1, assigned treatments were administered topically BID to approximately 5% BSA; In Part 2, assigned treatments were administered topically BID to at least 10% BSA, even if the AD lesion(s) improved
[b] Denotes predicted difamilast dose (mg) per application; In Part 1, predicted dose was calculated based on assumption of approximately 1 g ointment per 5% BSA; In Part 2, predicted dose was calculated based on the weight difference of the medication tube between visits
Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA: Body Surface Area; CSR, clinical study report; N, number of subjects; NA, not applicable; SD, standard deviation

In Study Part 1, predicted difamilast dose per BID application was estimated to be approximately 3, 10, and 30 mg for the 0.3%, 1%, and 3% treatment groups respectively, assuming approximately 1 g ointment applied per 5% BSA. In Part 2, the predicted difamilast dose was calculated based on the weight difference of the medication tube between visits and

the difamilast ointment strength. The percent BSA involvement and estimated dose per application at baseline were comparable between the 1% and 3% treatment arms in Part 2.

PK Sampling/Analysis:

Blood samples were collected for PK assessment at the following timepoints in both study parts:

- **Days 1 and 28**: Pre-dose, then post-dose at 2, 3 (Part 1 only), 4, 8, 12 (Part 1 only), and 24 h relative to the first of the BID doses
- **Day 14:** Pre-dose (trough sample)

Arithmetic mean (SD) plasma concentration-time profiles of difamilast at Days 1 and 28 were plotted on a linear scale for each difamilast treatment arm in both Study Parts 1 and 2. Difamilast PK parameters were derived using NCA and summarized with descriptive statistics according to treatment arm and study day for each part of the study. For summaries of plasma concentrations and PK parameters, all pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to zero. Dose-normalized PK parameters were also calculated based on the predicted dose of difamilast administered per application (mg).

Of note, the Applicant also collected PK data for the major metabolites of difamilast, including MAP-15484, MAP-15485, and MAP-15497. However, due to deficiencies with the bioanalytical assay used to measure these metabolites in the plasma, these data are considered unreliable and have therefore not been reported. Refer to Section 17.4.3 for additional details regarding bioanalytical method validation and performance throughout the clinical pharmacology program.

PK Results:

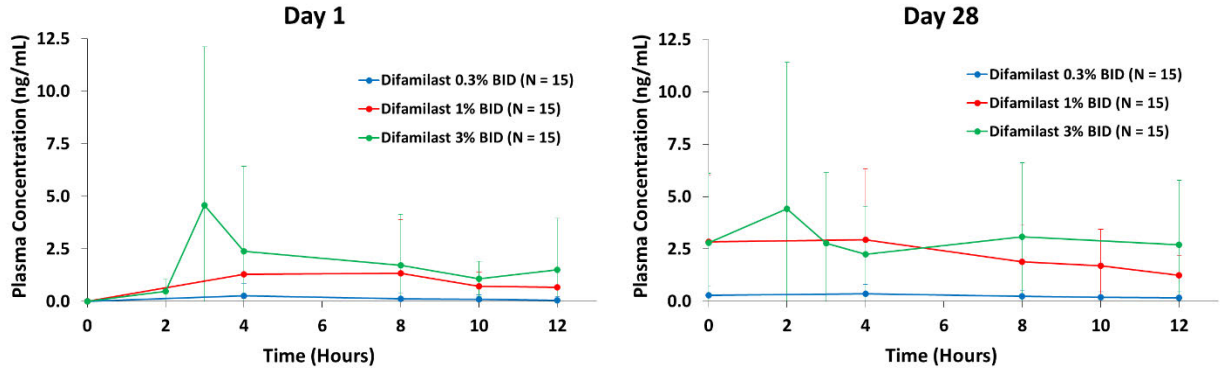
***Study Part 1*:** Difamilast PK parameters at Days 1 and 28 are summarized below for each treatment arm in Table 77. The mean (SD) difamilast plasma concentration-time profiles for each cohort are similarly summarized in Figure 25. Difamilast C_{max} and AUC generally increased with higher ointment strength, although no dose-proportionality was observed. Nominal trough concentrations at Day 28 were comparable between the 1% and 3% treatment groups, although dose-normalized C_{trough} was approximately 3-fold higher for the 1% arm. Mild accumulation was also observed for the 1% and 3% treatment arms, but not with the 0.3% arm. However, PK data from the 0.3% cohort should be interpreted cautiously due to the high number of samples below LLOQ, which limited the calculation of PK parameters for these subjects.

Table 77: Summary of Difamilast PK Parameters on Day 1/Day 28 by Treatment Arm in Adult Subjects With AD (Study 271-12-204, Part 1; PK Population)

Study Day	Difamilast Ointment, 0.3% BID (N=15)		Difamilast Ointment, 1% BID (N=15)		Difamilast Ointment, 3% BID (N=15)	
PK Parameter[a]	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Day 1						
C_{max} (ng/mL)	6	0.67 (0.80)	14	2.15 (2.64)	13	3.83 (4.78)
C_{max}N (ng/mL/mg)[b]	6	0.23 (0.27)	14	0.22 (0.27)	13	0.13 (0.16)
$AUC_{0\text{-}12h}$ (ng*h/mL)	2	9.42 (7.62)	11	14.0 (10.3)	11	22.5 (21.2)
$AUC_{0\text{-}12h}$N (ng*h/mL/mg)[b]	2	3.14 (2.54)	11	1.40 (1.03)	11	0.75 (0.71)
Day 28						
C_{max} (ng/mL)	10	0.62 (0.45)	14	3.69 (3.51)	14	5.75 (7.47)
C_{max}N (ng/mL/mg)[b]	10	0.21 (0.15)	14	0.37 (0.35)	14	0.19 (0.25)
$AUC_{0\text{-}12h}$ (ng*h/mL)	5	6.76 (4.90)	13	23.1 (15.8)	12	42.4 (36.2)
$AUC_{0\text{-}12h}$N (ng*h/mL/mg)[b]	5	2.25 (1.63)	13	2.31 (1.58)	12	1.41 (1.21)
C_{trough} (ng/mL)[c]	15	0.30 (0.44)	15	2.85 (3.20)	15	2.80 (3.31)
C_{trough}N (ng/mL/mg)[b,c]	15	0.099 (0.147)	15	0.29 (0.32)	15	0.093 (0.110)

Source. Reviewer's analysis based on CSR for Study 271-12-204 (PKT-1 through PKT-3 [pg. 556-558]; PKT-21 and PKT-22 [pg. 576-579])
[a] Assigned treatments in Part 1 were administered topically BID to 5% BSA (approximately 1 g ointment per 5% BSA); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Normalized according to the predicted topical dose of difamilast (mg) per application
[c] Pre-dose trough concentration on Day 28
Abbreviations: AD, atopic dermatitis; $AUC_{0\text{-}12h}$, area under the plasma concentration-time curve from 0 to 12 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal half-life; T_{max}, time of C_{max}

Figure 25: Arithmetic Mean (SD) Difamilast Plasma Concentration-Time Profile on Day 1/Day 28 by Treatment Arm in Adult Subjects With AD (Study 271-12-204, Part 1; PK Population)[a,b]



Source. Reviewer's analysis based on CSR for Study 271-12-204 (PKT-1 through PKT-3 [pg. 556-558])
[a] Assigned treatments in Part 1 were administered topically BID to 5% BSA (approximately 1 g ointment per 5% BSA)
[b] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for generation of PK profiles
Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA, body surface area; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

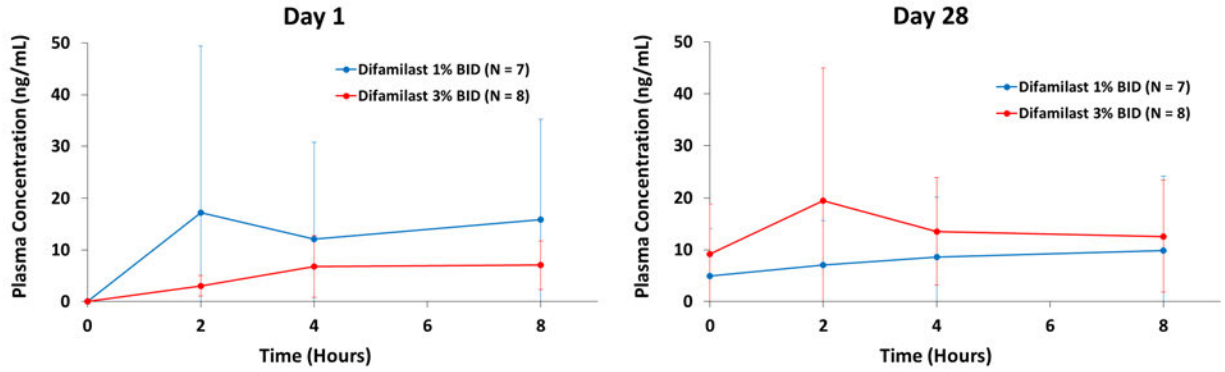
Study Part 2: Difamilast PK parameters at Days 1 and 28 are summarized below for each treatment arm in Table 78. The mean (SD) difamilast plasma concentration-time profiles for each cohort are similarly summarized in Figure 26.

Table 78: Summary of Difamilast PK Parameters on Day 1/Day 28 by Treatment Arm in Adult Subjects With AD (Study 271-12-204, Part 2; PK Population)

Study Day	Difamilast Ointment, 1% BID (N=7)		Difamilast Ointment, 3% BID (N=8)	
PK Parameter[a]	N	Mean (SD)	N	Mean (SD)
Day 1				
C_{max} (ng/mL)	6	30.9 (33.7)	8	8.14 (5.96)
C_{max}N (ng/mL/mg)[b]	6	0.53 (0.62)	8	0.16 (0.09)
AUC_{0-8h} (ng*h/mL)	6	121 (142)	7	36.1 (28.0)
AUC_{0-8h}N (ng*h/mL/mg)[b]	6	1.79 (1.46)	7	0.77 (0.41)
Day 28				
C_{max} (ng/mL)	6	11.0 (14.3)	6	22.3 (25.2)
C_{max}N (ng/mL/mg)[b]	6	0.19 (0.18)	6	0.47 (0.64)
AUC_{0-8h} (ng*h/mL)	6	64.7 (87.4)	6	115 (104)
AUC_{0-8h}N (ng*h/mL/mg)[b]	6	1.00 (0.93)	6	2.31 (2.53)
C_{trough} (ng/mL)[c]	6	4.90 (9.16)	7	9.20 (9.57)
C_{trough}N (ng/mL/mg)[b,c]	6	0.058 (0.099)	7	0.19 (0.21)

Source. Reviewer's analysis based on CSR for Study 271-12-204 (PKT-4 and PKT-5 [pg. 559-560]; PKT-23 through PKT-26 [pg. 580-583])
[a] Assigned treatments were administered topically BID to at least 10% BSA for the duration of the treatment period, even if the AD lesion(s) improved; All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Normalized according to the predicted topical dose of difamilast (mg) per application
[c] Pre-dose trough concentration on Day 28
Abbreviations: AD, atopic dermatitis; AUC_{0-8h}, area under the plasma concentration-time curve from 0 to 8 hours; BID, twice daily; BSA, body surface area; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Figure 26: Arithmetic Mean (SD) Difamilast Plasma Concentration-Time Profile on Day 1/Day 28 by Treatment Arm in Adult Subjects With AD (Study 271-12-204, Part 2; PK Population)[a,b]



Source. Reviewer's analysis based on CSR for Study 271-12-204 (PKT-4 and PKT-5 [pg. 559-560])
[a] Assigned treatments were administered topically BID to at least 10% BSA for the duration of the treatment period, even if the AD lesion(s) improved
[b] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for generation of PK profiles
Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA, body surface area; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Of note, two individual concentrations of difamilast taken on Day 1 (198 ng/mL at 24 hours post-dose [Subject (b) (6)] and 246 ng/mL at 4 hours post-dose [Subject (b) (6)]) were excluded from descriptive statistics and NCA, as these values were substantially higher than those observed for all other subjects. The Applicant states that these unexpected values were likely caused by a dilution error in the assay.

Difamilast $AUC_{0\text{-}8h}$ and C_{max} on Day 1 were nearly 4- and 3-fold higher, respectively, in the 1% treatment arm compared to the 3% group, despite application of similar difamilast doses. Furthermore, based on cross study comparison, the mean difamilast C_{max} (30.9 ng/mL) and $AUC_{0\text{-}8h}$ (121 ng*h/mL) values reported on Day 1 for the 1% group exceeded those observed at Day 1 in the overall population in the maximal use study MEDI-MM36-206, in which mean C_{max} and $AUC_{0\text{-}8h}$ were 23.1 ng/mL and 107 ng*h/mL, respectively (refer to Section 17.4.1.1). On Day 28, systemic exposure in the 1% cohort was less than one-half of that observed at Day 1. Conversely, approximately 3-fold accumulation was observed on Day 28 for the 3% treatment arm, with a mean difamilast C_{max} and $AUC_{0\text{-}8h}$ of 22.3 ng/mL and 115 ng*h/mL, respectively. Of note, it is unclear why accumulation was observed for the 3% arm and not the 1% arm.

Additionally, the unexpectedly high nominal exposures in the 1% arm of the current study appear to be primarily driven by two subjects ((b) (6) and (b) (6)) with substantially higher percent BSA involvement (45% and 66%) and estimated topical difamilast doses (90 and 130 mg per application) relative to the remaining subjects. When considered along with the relatively low sample size in Study 271-12-204 as well as the high inter-individual variability observed in both dosing arms, these PK data should be interpreted with caution.

17.4.1.4. Study 271-12-205

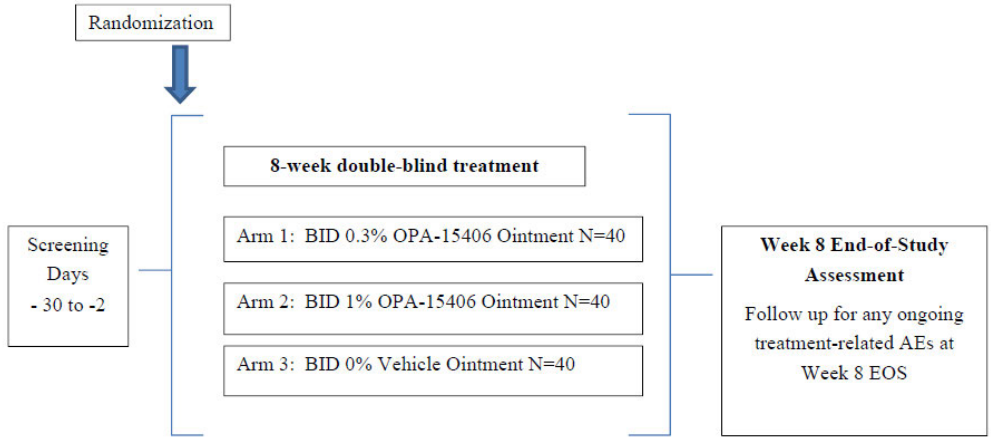
Title:

A Phase 2 multi-center, randomized, double-blind, vehicle-controlled, three-arm, parallel group study to assess the safety, tolerability, and efficacy of topical OPA-15406 [difamilast] ointment, in subjects with mild/moderate atopic dermatitis

Study Design:

Study 271-12-205 was a phase 2, randomized, double-blind, vehicle-controlled, three-arm, parallel-group, dose-ranging study to evaluate the efficacy and safety of difamilast ointment following topical administration of different ointment strengths in adult and pediatric subjects with mild-to-moderate AD (Figure 27). A total of 121 subjects were randomized in a 1:1:1 ratio to receive difamilast ointment, 0.3% (N=41), difamilast ointment, 1% (N=43), or placebo (N=37) BID for 8 weeks, applied topically to AD lesions. Subjects were instructed to continue to apply the study drug to the affected areas defined at baseline throughout the treatment period, even if the lesions improved or went away, in addition to new lesions that developed post-baseline (up to a maximum of 40% BSA). The PK of difamilast was evaluated as a sub-study in a small number of subjects (N=9), as described below. The study enrolled males and females 10 to 70 years of age (inclusive) with a diagnosis of AD affecting 5% to 40% BSA (inclusive) at baseline, excluding face, neck, and head areas. Subjects were excluded if they received systemic immunomodulators, corticosteroids, or antimetabolites (within 28 days of baseline) or topical immunomodulators, corticosteroids, or antihistamines (within 7 days of baseline).

Figure 27: Overall Study Design for Study 271-12-205



Source. CSR for Study 271-12-205 (Figure 9.1-1, pg. 37)
Abbreviations: AE, adverse event; BID, twice Daily; CSR, clinical study report; EOS, end-of-study; N, number of subjects; OPA-15406, difamilast

Dosing and Baseline BSA Involvement:

A summary of percent BSA treated at baseline and predicted difamilast dose per application (mg) is provided below in Table 79.

Table 79: Baseline BSA Involvement and Predicted Difamilast Dose per Application (mg), Stratified by Treatment Arm (Study 271-12-205; PK Population)

Parameter Summary Statistics	Difamilast Ointment, 0.3% BID (N=5)	Difamilast Ointment, 1% BID (N=4)
BSA involvement (%)[a]		
n	5	4
Mean (SD)	13.2 (11.4)	7.0 (1.4)
Median (min, max)	10.0 (5.0, 33.0)	7.5 (5.0, 8.0)
Predicted difamilast dose (mg)[b]		
n	5	4
Mean (SD)	8.5 (3.7)	15.6 (3.0)
Median (min, max)	7.9 (4.3, 14.3)	15.6 (12.7, 18.4)

Source. Reviewer's analysis based on CSR for Study 271-12-205 (PKT-12 [pg. 585])
[a] If percent BSA affected decreased during treatment period, the same amount of study medication that was defined at baseline would be applied; if overall percent BSA affected worsened, additional study medication would be applied to cover the increased affected BSA, up to a maximum of 40% BSA
[b] Denotes predicted difamilast dose (mg) per application, calculated based on the weight difference of the medication tube between visits
Abbreviations: BID, twice daily; BSA, body surface area; CSR, clinical study report; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

The predicted difamilast dose was calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength. The estimated mean topical difamilast dose per application was approximately two-fold higher for the 1% treatment arm compared to the 0.3% group, although the mean baseline BSA involvement was higher in the 0.3% arm.

PK Sampling/Analysis:

Blood samples collected for PK assessment at the following timepoints:

- **Day 1/Week 4:** Pre-dose, then post-dose at 2, 4 and 8 h relative to the first of the BID doses
- **Weeks 1, 2, and 6:** Pre-dose (trough samples)
- **Week 8:** Post-dose at 24 and 26 h relative to the first of the BID doses

Arithmetic mean (SD) plasma concentration-time profiles of difamilast at Days 1 and 28 were plotted on a linear scale for each difamilast treatment arm. Difamilast PK parameters were derived using NCA and summarized with descriptive statistics according to treatment arm and study day. For summaries of plasma concentrations and PK parameters, all pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to zero. Dose-normalized PK parameters were also calculated based on the predicted dose of difamilast administered per application (mg).

PK Results:

Difamilast PK parameters at Days 1 and 28 are summarized below by treatment arm, along with difamilast trough concentrations over time (Table 80, Table 81). The mean (SD) difamilast plasma concentration-time profiles are similarly summarized by treatment in Figure 28.

Table 80: Summary of Difamilast PK Parameters on Day 1/Day 28 by Treatment Arm in Subjects With AD (Study 271-12-205; PK Population)

	Difamilast Ointment, 0.3% BID (N=5)		Difamilast Ointment, 1% BID (N=4)	
PK Parameter[a]	**Day 1**	**Day 28**	**Day 1**	**Day 28**
C_{max} (ng/mL)	3.18 (2.79)	2.94 (2.98)	4.74 (5.51)	1.38 (0.55)
$C_{max}N$ (ng/mL/mg)[b]	0.33 (0.17)	0.35 (0.18)	0.29 (0.29)	0.083 (0.031)
$AUC_{0\text{-}8h}$ (ng*h/mL)	16.0 (13.6)	20.1 (22.3)	20.7 (22.5)	8.59 (3.36)
$AUC_{0\text{-}8h}N$ (ng*h/mL/mg)[b]	1.67 (0.88)	2.25 (1.22)	1.25 (1.19)	0.52 (0.21)
T_{max} (h)	4.01 (2.00, 4.07)	4.15 (0, 8.00)	4.06 (4.00, 7.50)	4.98 (0, 8.00)

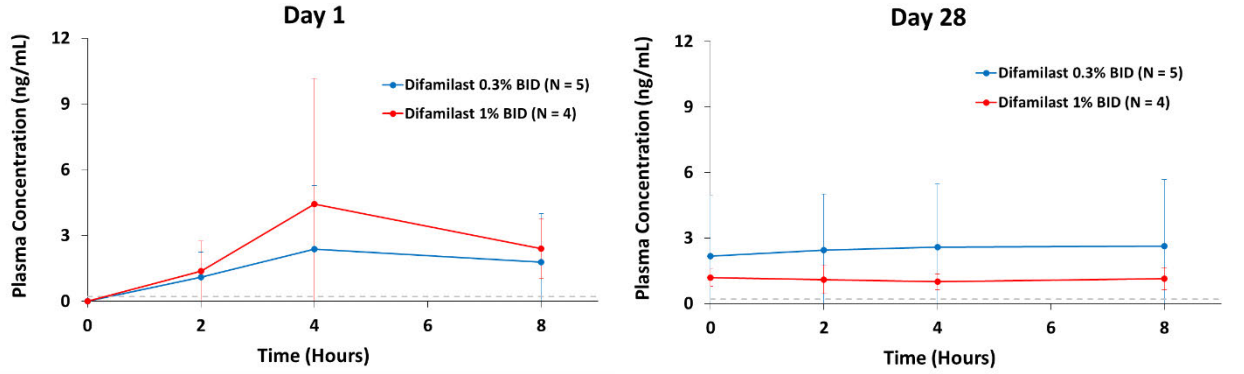
Source. Reviewer's analysis based on CSR for Study 271-12-205 (PKT-10 through PKT-12 [pg. 583-585])
[a] PK parameters reported as arithmetic mean (SD), except for T_{max}, which is reported as median (min, max); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Normalized according to the predicted dose of difamilast (mg) per application
Abbreviations: AD, atopic dermatitis; $AUC_{0\text{-}8h}$, area under the plasma concentration-time curve from 0 to 8 hours; BID, twice daily; C_{max}, maximum plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{max}, time of C_{max}

Table 81: Summary of Difamilast Trough Concentrations Over Time by Treatment Arm in Subjects With AD (Study 271-12-205; PK Population)

	Difamilast Ointment, 0.3% BID (N=5)			Difamilast Ointment, 1% BID (N=4)		
PK Parameter[a]	**Week 1**	**Week 4**	**Week 6**	**Week 1**	**Week 4**	**Week 6**
N subjects	5	5	4	4	4	4
BSA treated (%)	13.2 (11.4)	14.4 (11.6)	13.5 (13.2)	7 (1.4)	7 (1.4)	7 (1.4)
Predicted dose (mg)[b]	8.5 (3.7)	7.4 (5.6)	5.2 (3.0)	15.6 (3.0)	16.7 (2.0)	16.7 (2.0)
C_{trough} (ng/mL)	1.44 (0.77)	2.18 (2.77)	1.76 (2.88)	1.67 (0.88)	1.18 (0.39)	1.16 (0.73)
$C_{trough}N$ (ng/mL/mg)[c]	0.19 (0.11)	0.25 (0.15)	0.63 (1.14)	0.11 (0.04)	0.072 (0.025)	0.068 (0.036)

Source. Reviewer's analysis based on CSR for Study 271-12-205 (PKT-2 and PKT-3 [pg. 575-576]; PKT-12 [pg. 585])
[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.200 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Reported as predicted difamilast dose administered per application (mg); Calculated based on the weight difference of the medication tube between visits and the difamilast ointment strength
[c] Normalized according to the predicted difamilast dose (mg) per application
Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA, body surface area; C_{trough}, trough plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation;

Figure 28: Arithmetic Mean (SD) Difamilast Plasma Concentration-Time Profile on Day 1/Day 28 by Treatment Arm in Subjects With AD (Study 271-12-205; PK Population)[a]



Source. Reviewer's analysis based on CSR for Study 271-12-205 (PKT-2 and PKT-3 [pg. 575-576])
[a] Grey dashed line represents LLOQ of 0.200 ng/mL; All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ were imputed to 0 for generation of PK profiles
Abbreviations: AD, atopic dermatitis; BID, twice daily; CSR, clinical study report; LLOQ, lower limit of quantitation; PK, pharmacokinetic; SD, standard deviation

Of those enrolled in the PK sub-study, 5 subjects received difamilast 0.3% ointment (including a single 16-year-old pediatric subject) and 4 adult subjects received difamilast 1% ointment. Overall, difamilast exposure was low across both the 0.3% and 1% treatment groups following single dosing and at steady state. For the 1% arm, mean nominal difamilast C_{max} and AUC were higher at Day 1 compared to Day 28, which is consistent with findings PK reported in Studies 206 and 302 and may have been related, at least in part, to disease resolution over time. However, the low number of PK evaluable subjects limit the interpretability of these data.

17.4.1.5. Study 271-15-001

Title:

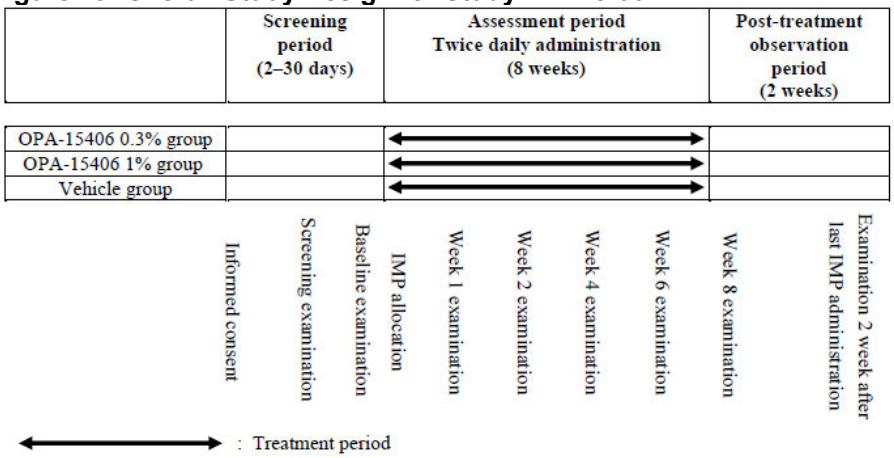
A multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison trial to assess the efficacy and safety of 0.3% and 1% OPA-15406 [difamilast] ointments in patients with atopic dermatitis

Study Design:

Study 271-15-001 was a phase 2, randomized, double-blind, vehicle-controlled, three-arm, parallel-group, dose-ranging study designed to evaluate the efficacy and safety of difamilast ointment compared to placebo following BID topical administration in Japanese adults and pediatric subjects 15 years of age and older with mild-to-moderate AD (Figure 29). A total of 200 subjects were randomized in a 1:1:1 ratio to receive difamilast ointment, 0.3% (N=67), difamilast ointment, 1% (N=67), or placebo (N=66) BID for 8 weeks, applied topically to AD lesions. All subjects randomized to receive difamilast treatment were adults, except for two 15-year-old pediatric subjects who received difamilast ointment, 0.3%.

Subjects were instructed to continue to apply the study drug to the affected areas defined at baseline throughout the duration of the treatment period, even if the lesions improved or went away, in addition to any new lesions that developed post-baseline up to a maximum of 40% BSA. The study enrolled male and female subjects 15 to 70 years of age (inclusive) with a diagnosis of AD affecting 5% to 40% BSA (inclusive) at baseline. Subjects were excluded if they received systemic immunomodulators, corticosteroids, or antimetabolites (within 28 days of baseline) or topical immunomodulators, corticosteroids, or antihistamines (within 7 days of baseline).

Figure 29: Overall Study Design for Study 271-15-001



Source. CSR for Study 271-15-001 (Figure 9.1-1, pg. 37)
Abbreviations: CSR, clinical study report; IMP, investigational medicinal product; OPA-15406, difamilast

Dosing and Baseline BSA Involvement:

The predicted difamilast dose was calculated according to the difamilast ointment strength, subject BSA, and percent BSA treated based on pre-specified ointment application instructions (see Table 9.4.1-1, pg. 43 of CSR for 271-15-001). Baseline BSA involvement was comparable between treatment groups, although the estimated mean topical difamilast dose per application was more than 3-fold higher in subjects enrolled in the 1% treatment arm. A summary of percent BSA treated at baseline and predicted difamilast dose per application (mg) is provided below in Table 82.

Table 82: Baseline BSA Involvement and Predicted Difamilast Dose per Application (mg), Stratified by Treatment Arm (Study 271-15-001; PK Population)

Parameter Summary Statistics	Difamilast Ointment, 0.3% BID (N=11)	Difamilast Ointment, 1% BID (N=9)
BSA involvement (%)[a]		
n	11	9
Mean (SD)	16.0 (8.2)	16.0 (6.1)
Median (min, max)	13.5 (6.0, 33.5)	16.5 (6.5, 27.0)
Predicted difamilast dose (mg)[b]		
n	11	9
Mean (SD)	11.4 (6.0)	38.1 (15.3)
Median (min, max)	10.1 (5.1, 25.1)	38.0 (19.5, 67.5)

Source. Reviewer's analysis based on CSR for Study 271-15-001 (PKT-2.1 and PKT-2.2 [pg. 487-492]; PKT-6.1 and PKT-6.2 [pg. 505-506])
[a] If percent BSA affected decreased during treatment period, the same amount of study medication that was defined at baseline would be applied; if overall percent BSA affected worsened, additional study medication would be applied to cover the increased affected BSA, up to a maximum of 40% BSA
[b] Reported as predicted dose of difamilast administered per application (mg), calculated based on pre-specified ointment application instructions according to the subject's BSA (0.1 g for BSA <1.0 m^2, 0.15 g for BSA 1 to <1.3 m^2, 0.2 g for BSA 1.3 to <1.6 m^2, 0.25 g for BSA 1.6 to <1.9 m^2, and 0.3 g for BSA ≥1.9 m^2)
Abbreviations: BID, twice daily; BSA, body surface area; CSR, clinical study report; N, number of subjectsl PK, pharmacokinetic; SD, standard deviation

PK Sampling/Analysis:

Pre-dose trough PK samples were collected in all subjects at Weeks 1, 4, and 8. Additionally, serial PK samples were collected in a sub-set of subjects (N=20) at pre-dose, then post-dose at 2, 4 and 8 h relative to the first of the BID doses on Days 1 and 28. For subjects enrolled in the PK sub-study, arithmetic mean (SD) plasma concentration-time profiles of difamilast at Days 1 and 28 were plotted on a linear scale by treatment arm. Additionally, difamilast PK parameters were derived using NCA and summarized with descriptive statistics according to treatment arm and study day. For summaries of plasma concentrations and PK parameters, all pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL) were imputed to zero. Dose-normalized PK parameters were also calculated based on the predicted dose of difamilast administered per application (mg).

PK Results:

Difamilast PK parameters and mean (SD) plasma concentration-time profiles at Days 1 and 28 are summarized below according to treatment group for subjects included in the PK sub-study (Table 83, Figure 30). Of those included in the PK sub-study, 11 subjects received difamilast

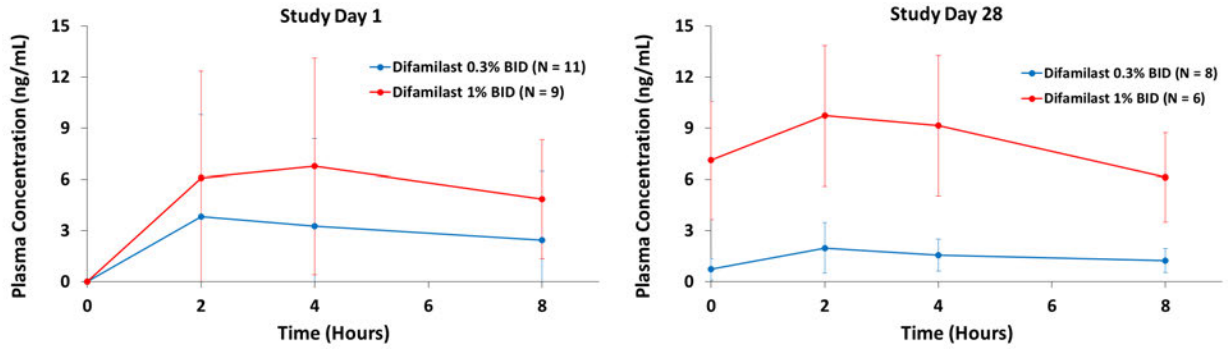
0.3% ointment (including a single 15-year-old pediatric subject) and 9 adult subjects received difamilast 1% ointment. Additionally, difamilast trough concentrations over time, which were collected in all subjects at Weeks 1, 4, and 8, are provided in Table 84.

Table 83: Summary of Difamilast PK Parameters on Day 1/Day 28 by Treatment Arm in Japanese Subjects With AD (Study 271-15-001; PK Population)

	Difamilast Ointment, 0.3% BID (N=11)		Difamilast Ointment, 1% BID (N=9)	
PK Parameter[a]	**Day 1 (N=11)**	**Day 28 (N=8)**	**Day 1 (N=9)**	**Day 28 (N=6)**
C_{max} (ng/mL)	4.01 (5.90)	2.07 (1.47)	7.27 (6.42)	10.4 (3.7)
$C_{max}N$ (ng/mL/mg)[b]	0.27 (0.30)	0.20 (0.13)	0.19 (0.15)	0.30 (0.11)
$AUC_{0\text{-}8h}$ (ng*h/mL)	22.0 (34.7)	11.6 (7.23)	41.6 (37.6)	65.2 (26.8)
$AUC_{0\text{-}8h}N$ (ng*h/mL/mg)[b]	1.49 (1.81)	1.16 (0.66)	1.09 (0.86)	1.86 (0.81)
T_{max} (h)	2.05 (1.83-7.90)	1.94 (1.83-8.03)	3.83 (1.95-7.87)	1.84 (0.00-3.83)

Source. Reviewer's analysis based on CSR for Study 271-15-001 (PKT-3 [pg. 493-496])
[a] PK parameters reported as arithmetic mean (SD), except for T_{max}, which is reported as median (min, max); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Normalized according to the predicted topical dose of difamilast (mg) per application
Abbreviations: AD, atopic dermatitis; $AUC_{0\text{-}8h}$, area under the plasma concentration-time curve from 0 to 8 hours; BID, twice daily; C_{max}, maximum plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{max}, time of C_{max}

Figure 30: Arithmetic Mean (SD) Difamilast Plasma Concentration-Time Profile on Day 1/Day 28 by Treatment Arm in Japanese Subjects With AD (Study 271-15-001; PK Population)



Source. Reviewer's analysis based on CSR for Study 271-15-001 (PKT-1.1 and PKT-1.2 [pg. 485-486])
[a] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL) were imputed to 0 for generation of PK profiles
Abbreviations: AD, atopic dermatitis; BID, twice daily; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Table 84: Summary of Difamilast Trough Concentrations Over Time by Treatment Arm in Japanese Subjects With AD (Study 271-15-001; PK Population)

	Difamilast Ointment, 0.3% BID (N=67)			Difamilast Ointment, 1% BID (N=67)		
PK Parameter[a]	**Week 1**	**Week 4**	**Week 8**	**Week 1**	**Week 4**	**Week 8**
N subjects	53	49	43	59	50	46
BSA treated (%)	19.6 (7.8)	20.9 (8.6)	21.5 (8.7)	18.2 (8.1)	19.0 (8.6)	19.5 (8.7)
Predicted dose (mg)[b]	13.7 (6.8)	13.7 (7.9)	13.6 (8.5)	43.8 (21.8)	46.0 (22.9)	47.2 (23.6)
C_{trough} (ng/mL)	1.74 (1.87)	1.71 (2.50)	1.51 (1.77)	4.96 (5.04)	5.22 (4.70)	5.52 (8.28)
$C_{trough}N$ (ng/mL/mg)[c]	0.11 (0.10)	0.10 (0.12)	0.091 (0.103)	0.11 (0.10)	0.13 (0.12)	0.14 (0.24)

Source. Reviewer's analysis based on CSR for Study 271-15-001 (PKT-2.1 and PKT 2.2 [pg. 487-492]; PKT 5.1 and PKT-5.2 [pg. 499-504])
[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Reported as predicted dose of difamilast administered per application (mg), calculated based on pre-specified ointment application instructions according to the subject's BSA (0.1 g for BSA <1.0 m^2, 0.15 g for BSA 1 to <1.3 m^2, 0.2 g for BSA 1.3 to <1.6 m^2, 0.25 g for BSA 1.6 to <1.9 m^2, and 0.3 g for BSA ≥1.9 m^2)
[c] Normalized according to the predicted difamilast dose (mg) per application
Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA, body surface area; C_{trough}, trough plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Overall, higher difamilast systemic exposure was observed in the 1% treatment arm, likely due to the greater estimated topical dose administered per application as compared to the 0.3% group. Mild accumulation (approximately 1.5-fold) was observed at Day 28 for the 1% treatment arm, despite similar dose administration and BSA involvement over time. However, it is difficult to draw clear conclusions from these data due to low sample size of subjects with intensive PK data, as well as the high degree of inter-individual variability in difamilast PK which was observed in both treatment arms.

17.4.1.6. Study 271-102-00002

Title:

A multicenter, randomized, double-blind, vehicle-controlled, parallel-group trial to assess the safety and efficacy of 0.3% and 1% OPA-15406 [difamilast] ointments when administered for 4 weeks in pediatric patients with atopic dermatitis

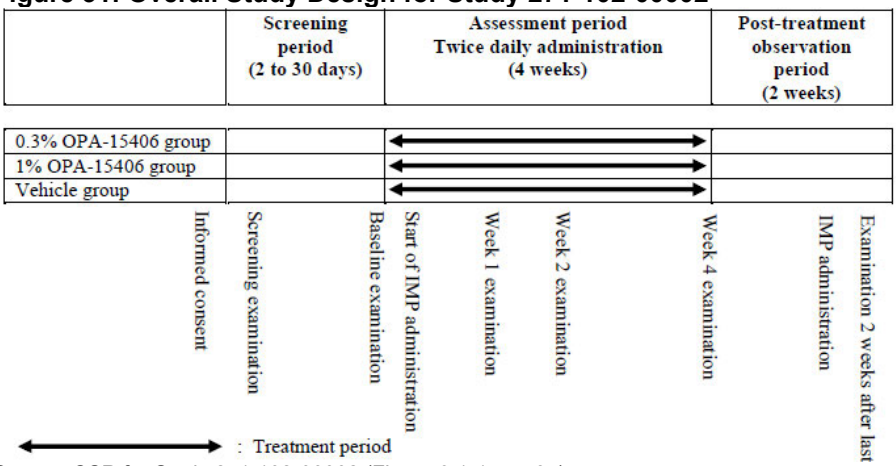
Study Design:

Study 271-102-00002 was a phase 2, randomized, double-blind, vehicle-controlled, three-arm, parallel-group, dose-ranging study designed to evaluate the safety, efficacy, and PK of difamilast ointment compared to placebo following BID administration in Japanese pediatric subjects 2 to <14 years of age with mild-to-moderate AD (Figure 31). A total of 73 subjects were randomized in a 1:1:1 ratio to receive difamilast ointment, 0.3% (N=24), difamilast ointment, 1% (N=25), or placebo (N=24) BID for 4 weeks, applied topically to AD lesions.

Subjects were instructed to continue to apply the study drug to the affected areas defined at baseline throughout the duration of the treatment period, even if the lesions improved or went away, in addition to any new lesions that developed post-baseline up to a maximum of 40% BSA. The study enrolled male and female pediatric subjects 2 to 14 years of age (inclusive) with

a diagnosis of AD affecting 5% to 40% BSA (inclusive) at baseline. Subjects were excluded if they received systemic immunomodulators, corticosteroids, or antimetabolites (within 28 days of baseline). Additional prohibited medications included topical immunomodulators, corticosteroids, or antihistamines (within 7 days of baseline).

Figure 31: Overall Study Design for Study 271-102-00002



Source. CSR for Study 271-102-00002 (Figure 9.1-1, pg. 35)
Abbreviations: CSR, clinical study report; OPA-15406, difamilast; IMP, Investigational Medicinal Product

PK Sampling/Analysis/Results:

Difamilast PK was assessed in 45 of the 49 subjects who were randomized to receive difamilast treatment, including 22 and 23 in the 0.3% and 1% treatment arms, respectively. PK analysis included the collection of trough PK samples at Weeks 1 and 4. The predicted difamilast dose was calculated according to the difamilast ointment strength, subject BSA, and percent BSA treated, assuming application of approximately 10 g ointment/m^2. Nominal and dose-normalized (based on the predicted dose of difamilast administered per application mg]) trough concentrations over time were summarized with descriptive statistics by study day and treatment arm (Table 85). All samples below the assay LLOQ (0.050 ng/mL) were imputed to zero.

Baseline BSA involvement was comparable between treatment groups. Estimated difamilast dose per application in subjects receiving difamilast ointment, 1%, was approximately 3-fold higher compared to those receiving the 0.3% strength. This higher topical dose resulted in correspondingly higher systemic drug levels, with trough concentrations that were also nearly 3 time higher. However, following dose-normalization, similar mean trough concentrations were observed between the two dose cohorts.

Table 85: Summary of Difamilast Trough Concentrations Over Time by Treatment Arm in Japanese Pediatric Subjects With AD (Study 271-102-00002; PK Population)[a]

	Difamilast Ointment, 0.3% BID (N=22)		Difamilast Ointment, 1% BID (N=23)	
PK Parameter[a]	**Week 1**	**Week 4**	**Week 1**	**Week 4**
N subjects	18	20	21	22
BSA treated (%)	17.8 (7.6)	20.5 (9.0)	16.1 (8.9)	18.6 (9.5)
Predicted dose (mg)[b]	5.4 (2.6)	6.4 (3.7)	16.5 (11.1)	18.6 (11.6)
C_{trough} (ng/mL)[c]	0.84 (0.58)	0.95 (1.16)	2.90 (2.74)	2.21 (1.81)
$C_{trough}N$ (ng/mL/mg)[c]	0.20 (0.20)	0.15 (0.11)	0.21 (0.17)	0.17 (0.15)

Source. Reviewer's analysis based on CSR for Study 271-102-00002 (PKT-1.1 and PKT-1.2 [pg. 419-420]; PKT-2.1 and PKT-2.2 [pg. 421-422])
[a] PK parameters, BSA treated (%), and predicted difamilast dose (mg) reported as arithmetic mean (SD); All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Reported as predicted dose of difamilast administered per application (mg), calculated based on difamilast ointment strength, subject BSA, and percent BSA treated, assuming application of approximately 10 g ointment/m^2
[c] Normalized according to the predicted difamilast dose (mg) per application
Abbreviations: AD, atopic dermatitis; BID, twice daily; BSA, body surface area; CSR, clinical study report; C_{trough}, trough plasma concentration; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

17.4.1.7. Study 271-14-001

Title:

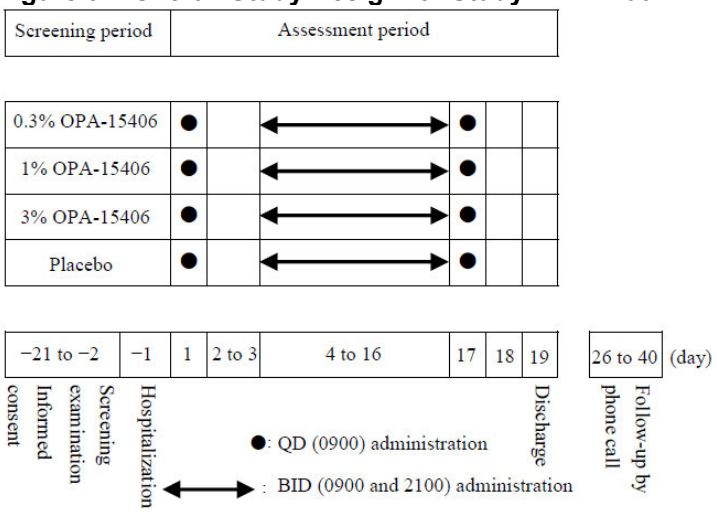
Single-center, placebo-controlled, randomized, double-blind, parallel-group comparison trial to assess the safety and pharmacokinetics of OPA-15406 [difamilast] ointment in healthy adult male subjects

Study Design:

Study 271-14-001 was a phase 1, randomized, double-blind, vehicle-controlled, parallel-group, two-period SAD/MAD study designed to evaluate the safety, tolerability, and PK of difamilast ointment compared to placebo following single- and multiple BID topical administrations in healthy Japanese male adult subjects (Figure 32). A total of 32 subjects were randomized in a 1:1:1:1 ratio to receive difamilast ointment, 0.3%, difamilast ointment, 1%, difamilast ointment, 3%, or placebo (N=8 per cohort). Subjects received their assigned treatment as a single dose in the SAD period (Study Day 1). Following a 3-day washout period, subjects topically applied their assigned treatment BID for 14 days during the MAD period (Study Days 4 to 16). All subjects were instructed to administer 5 g of study drug to a 1000 cm^2 area per application, correlating to an estimated dose of 15, 50, and 150 mg difamilast per application for the 0.3%, 1%, and 3% treatment arms, respectively.

The study enrolled healthy male subjects 20 to 40 years of age (inclusive) with a body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive) and body weight ≥50 kg at baseline. Subjects were excluded if they had any abnormal dermatologic findings during screening, such as sunburn, abrasions, or tattoos. Additionally over-the-counter or prescription drugs were prohibited within two weeks of baseline.

Figure 32: Overall Study Design for Study 271-14-001



Source. CSR for Study 271-14-001 (Figure 9.1-1, pg. 35)
Abbreviations: BID, twice daily; CSR, clinical study report; OPA-15406, difamilast; QD, once daily

PK Sampling/Analysis:

Both plasma and urine PK of difamilast and its metabolites, including MAP-15484, MAP-15485, MAP-15497, MAP-15583, and MAP-15585 were evaluated. A summary of the pre-specified timepoints for plasma PK sampling and urine collection is provided below:

- Blood samples collected for PK assessment at the following timepoints:
  - **Day 1/Day 17:** Pre-dose, then post-dose at 2, 3, 4, 8, 10, 12, 16, 24, and 48 h
  - **Day 10/Day 13:** Pre-dose (trough samples)
- Urine samples collected for PK assessment at the following timepoints:
  - **Day 1:** Pre-dose, then post-dose from 0 to 4 h, 4 to 8 h, 8 to 12 h, 12 to 16 h, 16 to 24 h, and 24 to 48 h
  - **Day 17:** Pre-dose, then post-dose from 0 to 4 h, 4 to 8 h, and 8 to 12 h

All enrolled subjects randomized to receive difamilast completed the study and were included in the PK population (N=24). Arithmetic mean (SD) plasma concentration-time profiles of difamilast at Days 1 and 17 were plotted on a linear scale by treatment arm. PK parameters for difamilast and its metabolites were derived using NCA and summarized with descriptive statistics according to treatment arm and study day. For summaries of plasma concentrations and PK parameters, all pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL for difamilast, MAP-15485, MAP-15497, MAP-15583, and MAP-15585; 0.100 ng/mL for MAP-15484) were imputed to zero. For each analyte, urinary excretion rate (f_e) through 12 hours post-dose was summarized with descriptive statistics at Day 17.

PK Results:

Plasma and urine PK parameters at Day 17 for difamilast and its metabolites are summarized by treatment arm in Table 86 and Table 87, respectively. The arithmetic mean (SD) plasma concentration-time profiles of difamilast are summarized below according to treatment arm

and study day (Figure 33). In general, higher plasma and urine concentrations were observed for all analytes with higher difamilast ointment strengths, although the increase was less than dose-proportional. The major metabolites identified in the plasma were MAP-15484, MAP-15485, and MAP-15497. Exposure of MAP-15583 was low, but quantifiable, whereas MAP-15585 was undetectable in all plasma PK samples. A mean half-life ranging from 19 to 21 hours was observed for difamilast. The major metabolites MAP-15484, MAP-15485, and MAP-15497 exhibited longer half-lives ranging from 32 to 41 hours, although metabolite PK data should be interpreted cautiously, particularly for the 0.3% treatment arm, due to the limited number of subjects with sufficient quantifiable concentrations in the terminal phase to calculate half-life.

Urine concentration of all analytes was very low following 14 days of BID dosing. Difamilast and MAP-15485 were undetectable in all urine samples. Among the remaining metabolites, MAP-15497 showed the highest urinary concentrations, although f_e remained well below 0.1%, indicating negligible renal elimination.

Table 86: Summary of Plasma PK Parameters of Difamilast and Metabolites Following BID Topical Administration for 14 Days, Stratified by Dose Cohort (Study 271-14-001; PK Population)

Treatment Arm	Analyte					
PK Parameter[a]	Difamilast	MAP-15484	MAP-15485	MAP-15497	MAP-15583	MAP-15585
Difamilast 0.3% (15 mg) BID (N=8)						
C_{max} (ng/mL)	0.51 (0.35)	0.15 (0.15)	0.28 (0.23)	0.26 (0.15)	0.04 (0.06)	NC
AUC_{0-12h} (ng*h/mL)	4.7 (3.1)	1.2 (1.3)	2.6 (2.1)	2.6 (1.5)	0.4 (0.6)	NC
$t_{1/2}$ (h)	19.3 (7.5)	NC	33.5 (14.3)	36.2 (22.7)	NC	NC
CL/F (L/h)	4370 (2440)	NC	NC	NC	NC	NC
T_{max} (h)	4.1	1.9	0.0	0.0	0.0	NC
	(0.0, 16.0)	(0.0, 23.8)	(0.0, 10.0)	(0.0, 16.0)	(0.0, 48.0)	
Difamilast 1% (50 mg) BID (N=8)						
C_{max} (ng/mL)	0.80 (0.21)	0.27 (0.11)	0.50 (0.13)	0.55 (0.15)	0.09 (0.01)	NC
AUC_{0-12h} (ng*h/mL)	7.8 (1.8)	2.4 (0.84)	4.7 (1.1)	5.4 (1.3)	1.0 (0.1)	NC
$t_{1/2}$ (h)	19.7 (5.8)	32.8 (7.5)	32.2 (9.9)	33.1 (14.7)	52.2[b]	NC
CL/F (L/h)	6740 (1880)	NC	NC	NC	NC	NC
T_{max} (h)	3.6	0.9	0.0	0.0	2.4	NC
	(0.0, 4.1)	(0.0, 23.8)	(0.0, 10.0)	(0.0, 4.1)	(0.0, 4.1)	
Difamilast 3% (150 mg) BID (N=8)						
C_{max} (ng/mL)	1.65 (0.46)	0.59 (0.17)	1.14 (0.38)	1.14 (0.52)	0.27 (0.12)	NC
AUC_{0-12h} (ng*h/mL)	16.6 (5.0)	5.4 (1.8)	10.4 (3.3)	10.7 (3.7)	2.9 (1.4)	NC
$t_{1/2}$ (h)	21.0 (6.5)	33.8[b]	37.9 (18.6)	41.4 (19.3)	NC	NC
CL/F (L/h)	9720 (2600)	NC	NC	NC	NC	NC
T_{max} (h)	6.1	0.9	0.0	0.0	2.4	NC
	(0.0, 10.0)	(0.0, 23.8)	(0.0, 10.0)	(0.0, 10.0)	(0.0, 4.1)	

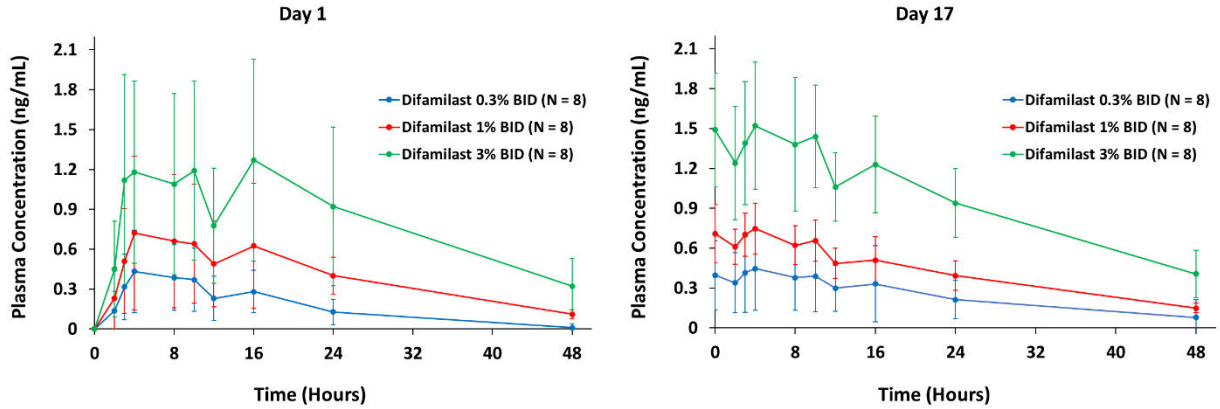
Source. Generated by reviewer based on CSR for Study 271-14-001 (Table 14.1.2.1-5 [pg. 386-403])
[a] PK Parameters reported as arithmetic mean (SD), except for T_{max}, which is reported as median (min, max); All post-baseline samples below the LLOQ (0.050 ng/mL for difamilast, MAP-15485, MAP-15497, MAP-15583, and MAP-15585; 0.100 ng/mL for MAP-15484) were imputed to 0 for calculation of PK parameters and descriptive statistics
[b] Insufficient data available for calculation of SD
Abbreviations: AUC_{0-12h}, area under the plasma concentration-time curve from 0 to 12 hours; BID, twice daily; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal half-life; T_{max}, time of C_{max}

Table 87: Summary of Fraction Excreted in Urine of Difamilast and Metabolites Following BID Topical Administration for 14 Days, Stratified by Dose Cohort (Study 271-14-001; PK Population)

Treatment Arm	Analyte					
PK Parameter[a]	Difamilast	MAP-15484	MAP-15485	MAP-15497	MAP-15583	MAP-15585
Difamilast 0.3% (15 mg) BID (N=8)						
$f_{e,4h}$ (%)	0 (0)	0.00454 (0.00455)	0 (0)	0 (0)	0 (0)	0.00221 (0.00161)
$f_{e,8h}$ (%)	0 (0)	0.00812 (0.00710)	0 (0)	0 (0)	0 (0)	0.00421 (0.00291)
$f_{e,12h}$ (%)	0 (0)	0.0104 (0.0103)	0 (0)	0.0000214 (0.0000606)	0 (0)	0.00644 (0.00422)
Difamilast 1% (50 mg) BID (N=8)						
$f_{e,4h}$ (%)	0 (0)	0.00345 (0.00179)	0 (0)	0.0000131 (0.0000294)	0.00000547 (0.0000102)	0.00139 (0.000425)
$f_{e,8h}$ (%)	0 (0)	0.00518 (0.00267)	0 (0)	0.0000224 (0.0000552)	0.00000939 (0.0000141)	0.00266 (0.000828)
$f_{e,12h}$ (%)	0 (0)	0.00588 (0.00317)	0 (0)	0.0000626 (0.000123)	0.0000129 (0.0000199)	0.00392 (0.00113)
Difamilast 3% (150 mg) BID (N=8)						
$f_{e,4h}$ (%)	0 (0)	0.00238 (0.000662)	0 (0)	0.0000288 (0.0000421)	0.0000104 (0.0000103)	0.00101 (0.000267)
$f_{e,8h}$ (%)	0 (0)	0.00333 (0.000729)	0 (0)	0.0000387 (0.0000522)	0.0000166 (0.0000180)	0.00190 (0.000477)
$f_{e,12h}$ (%)	0 (0)	0.00402 (0.00118)	0 (0)	0.0000766 (0.0000886)	0.0000221 (0.0000256)	0.00275 (0.000725)

Source. Generated by reviewer based on CSR for Study 271-14-001 (Table 14.1.2.1-14 [pg. 473-490])
[a] PK Parameters reported as arithmetic mean (SD)
Abbreviations: BID, twice daily; CSR, clinical study report; f_e, cumulative fraction excreted unchanged in the urine; N, number of subjects; PK, pharmacokinetics; SD, standard deviation

Figure 33: Arithmetic Mean (SD) Plasma Concentration-Time Profile of Difamilast on Day 1/Day 17 by Treatment Arm in Healthy Japanese Adult Subjects (Study 271-14-001; PK Population)



Source. Reviewer's analysis based on CSR for Study 271-14-001 (Table 14.1.2.1-1 [pg. 296-298] and Table 14.1.2.1-2 [pg. 314-316])
[a] All pre-dose quantifiable samples on Day 1 and post-baseline samples below the LLOQ (0.050 ng/mL for difamilast, MAP-15485, MAP-15497, MAP-15583, and MAP-15585; 0.100 ng/mL for MAP-15484) were imputed to 0 for generation of PK profiles
Abbreviations: BID, twice daily; CSR, clinical study report; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

17.4.2. In Vitro Studies

This NDA submission included a total of fourteen in vitro studies characterizing the metabolism, protein binding, and DDI potential of difamilast and its major metabolites MAP-15484, MAP-15485, and MAP-15497. A tabulated summary is provided below in Table 88.

Table 88: Summary of In Vitro Studies Supporting NDA 219474

Study Classification	Study Report ID	Primary Objective
Serum protein binding	023081	Assess serum protein binding of difamilast
	038197	Assess serum protein binding of difamilast metabolites[a]
Metabolite identification	032105	Identification and structural estimation of metabolites of difamilast in plasma and urine (sub-study within clinical study 271-14-001)
Metabolic profile	023473	Characterization of difamilast metabolic profile using human hepatic S9
Metabolic enzyme identification	025500	Identification of CYP enzymes involved in the metabolism of difamilast
CYP inhibition	029180	Assess CYP inhibition by difamilast
	032980	Assess CYP inhibition by difamilast metabolites[a]
CYP induction	032888	Assess CYP induction by difamilast and its metabolites[a]
	033432	Calculation of CYP induction parameters (i.e., EC_{50} and E_{max}) of difamilast
Transporter substrate	033090	Characterization of difamilast as a substrate of transporters (MDR1, BCRP, OATP1B1, and OATP1B3)
Transporter inhibition	032917	Assess transporter (MDR1) inhibition by difamilast and its metabolites[a]
	032921	Assess transporter (BCRP) inhibition by difamilast and its metabolites[a]
	032935	Assess transporter (OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE2-K) inhibition by difamilast and its metabolites[a]
	033611	Assess transporter (MATE1) inhibition by difamilast and its metabolites[a]

Source. Adapted from Summary of Clinical Pharmacology Studies (Table 1, pg. 11); Applicant's response to Agency request for information (response dated October 29, 2025)
[a] Difamilast major metabolites include MAP-15484, MAP-15485, and MAP-15497
Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; EC_{50}, half-maximal effective concentration; E_{max}, maximum induction effect; MDR1, multidrug resistance protein 1; MATE, multidrug and toxin extrusion; NDA, New Drug Application; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; S9, 9000 g supernatant fraction

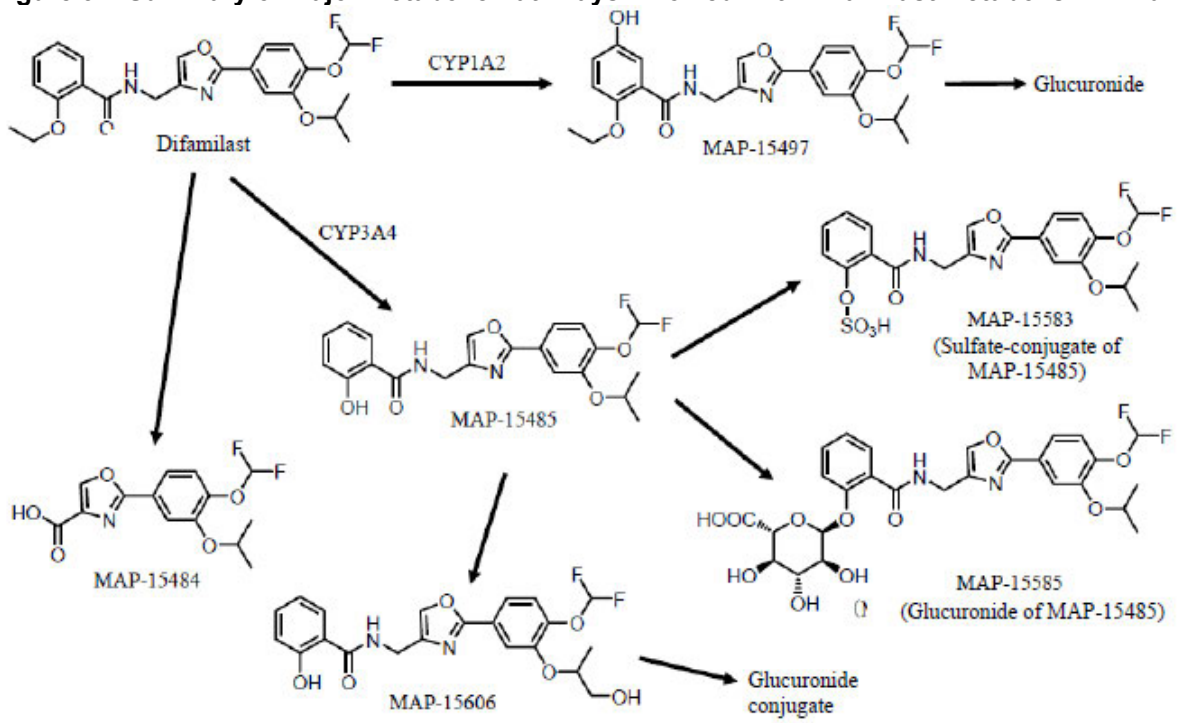
17.4.2.1. Characterization of Difamilast Metabolism

The metabolism of [^{14}C]-difamilast was investigated following incubation with human hepatic 9000 g Supernatant fraction (S9), human liver microsomes (HLMs), and recombinant human enzymes. Additionally, the Applicant conducted a sub-study (032105) within clinical study 271-14-001 to elucidate and structurally characterize the metabolites of difamilast in the plasma and urine following topical administration in healthy subjects. Three primary metabolic pathways for difamilast were identified:

(1) CYP1A2-mediated hydroxylation to form MAP-15497, followed by subsequent glucuronidation
(2) CYP3A4-mediated *O*-deethylation to form MAP-15485, followed by sulfation (MAP-15583), glucuronidation (MAP-15585), and/or further oxidation and subsequent conjugation (MAP-15606)
(3) Non-enzymatic hydrolysis to form MAP-15484

A summary of the major metabolites and enzymatic pathways involved in the metabolism of difamilast in humans is outlined below in Figure 34. Other unidentified metabolites primarily consisted of glucuronide or sulfate conjugates of the metabolites.

Figure 34: Summary of Major Metabolic Pathways Involved With Difamilast Metabolism in Humans



Source. Summary of Clinical Pharmacology Studies (Figure 1, pg. 13)

Incubation With Human S9 (Study 023473):

The metabolism of [^{14}C]-difamilast was assessed in vitro following incubation with human hepatic S9 in the presence and absence of coenzymes (NADPH and nicotinamide adenine dinucleotide [NADH]) for up to 120 minutes. The remaining ratios of [^{14}C]-difamilast were 99.8%, 86.3%, 69.4%, and 45.1% following incubation for 0, 10, 30, and 120 minutes, respectively. A total of seven human metabolites were identified via high performance liquid chromatography (HPLC) following centrifugation, including MAP-15485 (15.0%), MAP-15497 (8.8%), UK-20 (5.1%), UK-13 (3.1%), UK-14 (2.9%), UK-22 (2.7%), and UK-21 2.3%). The percentages of radioactivity associated with each peak were determined via liquid scintillation counting (LSC). Notably, [^{14}C]-difamilast was not metabolized or degraded in the absence of NADPH/NADH coenzymes.

Incubation With HLMs and Recombinant Human Enzymes (Study 025500):

[^{14}C]-difamilast (10 µM) was incubated with HLMs and recombinant human enzymes (Supersomes™; CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5) for 20 minutes. The rate of formation of metabolites was in the order of MAP-15485>MAP-15497>4 unknown metabolites. No substantial turnover of difamilast was observed with any of the enzymes tested except for with CYP3A4, 3A5, and 1A2, which had a turnover of 56.4%, 15%, and 79.8%, respectively. The formation of MAP-15485 and MAP-15497 correlated well with CYP3A4/5 (testosterone 6β-hydroxylation and midazolam 1'-hydroxylation) and CYP1A2 (7-ethoxyresorufin *O*-deethylation and phenacetin *O*-deethylation) activity, respectively.

Metabolism of [^{14}C]-difamilast was also evaluated following incubation with and without inhibitors of various CYP isoforms, including furafylline (CYP1A2), sulfaphenazole (CYP2C9), (S)-(+)-*N*-3-benzylnirvanol (CYP2C19), quinidine (CYP2D6), sodium *N*,*N*-diethyldithiocarbamate trihydrate (CYP2E1), and ketoconazole (CYP3A4). Formation of MAP-15485 was inhibited by ketoconazole (CYP3A4 inhibitor), while production of MAP-15497 was inhibited by furafylline (CYP1A2 inhibitor), supporting that the metabolism of difamilast to MAP-15485 and MAP-15497 is primarily mediated by CYP3A4 and CYP1A2, respectively.

Pharmacologic Activity of MAP-15484, MAP-15485, and MAP-15497:

The Applicant did not characterize the pharmacologic activity of the three major metabolites, including MAP-15484, MAP-15485, and MAP-15497. An information request was sent to the Applicant in the 74-day letter to justify this omission. Per the Applicant, based on a mass balance study of difamilast topical administration conducted in rats (Study 025077), the parent compound accounted for ≥90% of the radioactivity detected in the treated skin, indicating that metabolism of difamilast occurs primarily downstream of the site of activity. Based on these considerations, the Applicant determined that pharmacologic activity of the metabolites is unlikely to appreciably contribute to efficacy and contended that further characterization was not necessary. This justification is reasonable from a clinical pharmacology perspective.

17.4.2.2. Plasma Protein Binding of Difamilast, MAP-15484, MAP-15485, and MAP-15497

Plasma Protein Binding Ratio of Difamilast (Study 023081):

The protein binding ratio of [^{14}C]-difamilast in human sera was determined in vitro via LSC following ultracentrifugation of human plasma samples spiked with difamilast (30, 300, and 3,000 ng/mL; Study 023081). The mean protein binding ratio was 99.7% and was found to be concentration-independent over the concentration range evaluated. However, it was noted that the Applicant failed to validate the protein binding assay, which should include data with appropriate positive controls (i.e., range of compounds with high binding to relevant plasma proteins). Per the M12 Drug Interaction Studies – Guidance for Industry (August 2024), proper validation is necessary to authenticate the precision and accuracy of the method to confirm reliability of $f_{u,p}$ measurements <1%. Therefore, to align with current Agency best practices, the protein binding ratio of difamilast will be conservatively estimated to be 99% (i.e., $f_{u,p}$ of 1%).

Plasma Protein Binding Ratio of MAP-15484, MAP-15485, and MAP-15497 (Study 038197):

At the time of NDA submission, the Applicant had not determined the protein binding ratios for any of the major metabolites, including MAP-15484, MAP-15485, and MAP-15497. To facilitate the assessment of DDI potential for these metabolites, the Agency issued an information request to the Applicant to complete and submit additional in vitro assays to characterize plasma protein binding for each metabolite. In a response dated October 29, 2025, the Applicant submitted an additional study report in which the protein binding ratios of MAP-15484, MAP-15485, and MAP-15497 in human plasma were determined in vitro via an equilibrium dialysis method (Study 038197).

The dialysis time was set to 6 hours (MAP-15484 and MAP-15497) or 8 hours (MAP-15485) and conducted for each analyte at 30, 300, and 3000 ng/mL. The plasma protein binding ratios for MAP-15484, MAP-15485, and MAP-15497 were 98%, >99.9%, and 99.9%, respectively. However, the Applicant did not properly validate the protein binding assay with appropriate positive controls. Therefore, as discussed above, the protein binding ratios of MAP-15485 and MAP-15497 will be conservatively estimated to be 99% (i.e., $f_{u,p}$ of 1%).

17.4.2.3. Inhibition and Induction of CYP Isozymes by Difamilast, MAP-15484, MAP-15485, and MAP-15497

Reversible/Time-Dependent Inhibition (TDI):

The potential for difamilast, MAP-15484, MAP-15485, and MAP-15497 to inhibit various CYP metabolic enzymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, was assessed in human hepatic microsomes in Studies 029108 and 032982 (Table 89). Additionally, TDI of difamilast was evaluated through assessment of percent CYP activity loss with and without pre-incubation with NADPH.

Table 89: In Vitro Assessment of Difamilast, MAP-15484, MAP-15485, and MAP-15497 as Reversible Inhibitors of CYP Enzymes

Isozyme Test Article[a]	K_i (μM)	IC_{50} (μM)[b]	Conclusion	CYP Assay	Positive Controls[c]	Study Report	System
CYP1A2							
Difamilast	1.4	1.9	Not an inhibitor in vivo	Phenacetin *O*-deethylation	α-Naphthoflavone, Furafylline[d]	029180 032980	Human liver microsomes, recombinant CYP1A2
MAP-15484	NC	>30					
MAP-15485	NC	16.7					
MAP-15497	NC	>30					
CYP2A6							
Difamilast	>30	>30	Not an inhibitor in vivo	Coumarin 7-hydroxylation	Pilocarpine, 8-Methoxypsoralen[d]	029180 032980	Human liver microsomes, recombinant CYP2A6
MAP-15484	NC	>30					
MAP-15485	NC	>30					
MAP-15497	NC	>30					
CYP2B6							
Difamilast	7.1	6.0	Not an inhibitor in vivo	Bupropion hydroxylation	Sertraline, Ticlopidine[d]	029180 032980	Human liver microsomes, recombinant CYP2B6
MAP-15484	NC	>30					
MAP-15485	NC	5.7					
MAP-15497	NC	5.6					
CYP2C8							
Difamilast	1.3	2.5	Not an inhibitor in vivo	Paclitaxel 6α-hydroxylation	Quercetin, Gemfibrozil 1-*O*-β-glucuronide[d]	029180 032980	Human liver microsomes, recombinant CYP2C8
MAP-15484	NC	>30					
MAP-15485	NC	1.7					
MAP-15497	NC	4.7					
CYP2C9							
Difamilast	1.4	2.7	Not an inhibitor in vivo	Diclofenac 4'-hydroxylation	Sulfaphenazole, Tienilic acid[d]	029180 032980	Human liver microsomes, recombinant CYP2C9
MAP-15484	NC	>30					
MAP-15485	NC	1.2					
MAP-15497	NC	8.0					
CYP2C19							
Difamilast	2.8	5.4	Not an inhibitor in vivo	*S*-Mephenytoin 4'-hydroxylation	Tranylcypromine, Ticlopidine[d]	029180 032980	Human liver microsomes, recombinant CYP2C19
MAP-15484	NC	>30					
MAP-15485	NC	2.8					
MAP-15497	NC	12.7					
CYP2D6							
Difamilast	8.8	15.7	Not an inhibitor in vivo	(±)-Bufuralol 1'-hydroxylation	Quinidine, Paroxetine[d]	029180 032980	Human liver microsomes, recombinant CYP2D6
MAP-15484	NC	>30					
MAP-15485	NC	10.1					
MAP-15497	NC	23.5					

Isozyme Test Article[a]	K_i (µM)	IC_{50} (µM)[b]	Conclusion	CYP Assay	Positive Controls[c]	Study Report	System
CYP2E1							
Difamilast	>30	>30	Not an inhibitor in vivo	Chlorzoxazone 6-hydroxylation	*N,N*-diethyldithiocarbamate[d]	029180 032980	Human liver microsomes, recombinant CYP2E1
MAP-15484	NC	>30					
MAP-15485	NC	>30					
MAP-15497	NC	>30					
CYP3A4							
Difamilast	>30	>30	Not an inhibitor in vivo	Testosterone 6β-hydroxylation	Ketoconazole, Verapamil[d]	029180 032980	Human liver microsomes, recombinant CYP3A4
MAP-15484	NC	>30					
MAP-15485	NC	5.2					
MAP-15497	NC	7.0					
CYP3A4							
Difamilast	>30	>30	Not an inhibitor in vivo	Midazolam 1'-hydroxylation	Ketoconazole, Verapamil[d]	029180 032980	Human liver microsomes, recombinant CYP3A4
MAP-15484	NC	>30					
MAP-15485	NC	22.8					
MAP-15497	NC	27.1					

Source. Generated by reviewer based on Study Reports 029180 and 032980
[a] Test articles (i.e., difamilast, MAP-15484, MAP-15485, and MAP-15497) were evaluated at concentrations ranging from 0.3 to 30 µM
[b] Without pre-incubation with NADPH/NADH
[c] Known inhibitors of respective CYP isoforms
[d] Indicates time-dependent inhibitor
Abbreviations: CYP, cytochrome P450; IC_{50}, half-maximal inhibitory concentration; K_i, inhibition constant; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NC, not calculated

Induction:

The induction potential of difamilast, MAP-15484, MAP-15485, and MAP-15497 on messenger ribonucleic acid (mRNA) expression of CYP1A2, 2B6, and 3A4 enzymes was assessed in three lots of cryopreserved human hepatocytes (Table 90). The Applicant also calculated induction parameters (EC_{50} and E_{max}) for difamilast to further characterize induction profile (Table 91). Overall, there appears to be low risk for induction of the tested CYP isoforms by difamilast, MAP-15484, MAP-15485, and MAP-15497 at expected systemic exposure following administration of the proposed dosing regimen.

Table 90: In Vitro Assessment of Difamilast, MAP-15484, MAP-15485, and MAP-15497 as Inducers of CYP Enzymes (mRNA Expression)

Isozyme / Test Article	mRNA Expression (Fold-Change Relative to Vehicle Control)[a] Concentration of Test Article 0.1 µM	1 µM	10 µM	Conclusion	Positive Control[b]	Study Report	System
CYP1A2							
Difamilast	1.3/0.9/1.1	**4.6/2.5/2.4**	**13.3/6.8/9.0**	Potential induction (≥1 µM)	Omeprazole	032888	Cryopreserved human hepatocytes
MAP-15484	0.9/0.7/0.8	1.1/0.9/1.0	1.0/0.6/0.9	Not an inducer			
MAP-15485	1.0/0.6/0.9	1.2/1.0/1.3	**4.4/2.6/2.0**	Potential induction (≥10 µM)			
MAP-15497	0.9/0.6/0.6	1.6/1.3/0.9	**6.6/3.7/3.8**				
CYP2B6							
Difamilast	1.1/0.9/1.3	1.5/1.1/1.5	**5.0/4.6/6.8**	Potential induction (≥10 µM)	Phenobarbital	032888	Cryopreserved human hepatocytes
MAP-15484	0.9/0.7/1.1	1.1/0.9/1.3	0.9/0.7/1.2	Not an inducer			
MAP-15485	0.8/0.8/1.1	0.9/1.0/1.3	1.3/1.0/1.4				
MAP-15497	1.0/1.0/0.8	1.2/0.9/0.9	**2.1**/1.4/1.8	Potential induction (≥1 µM)			
CYP3A4							
Difamilast	0.8/0.5/0.8	**5.0**/1.2/0.9	**74.9/27.1/18.1**	Potential induction (≥1 µM)	Rifampicin	032888	Cryopreserved human hepatocytes
MAP-15484	0.9/0.4/1.0	**2.0**/0.6/1.3	1.9/0.4/0.9	Not an inducer			
MAP-15485	1.3/0.5/1.2	1.5/0.6/1.1	**3.2**/1.1/0.8	Potential induction (≥10 µM)			
MAP-15497	0.9/0.7/0.8	1.8/0.6/0.4	**9.4/2.5/2.0**				

Source. Generated by reviewer based on Study Report 032888
[a] Results reported for three donor lots (DQB/RMH/YNS); Bold indicates ≥2-fold increase in mRNA expression relative to vehicle control (0.1% DMSO)
[b] Known inducers of respective CYP isoforms
Abbreviations: CYP, cytochrome P450; DMSO, dimethyl sulfoxide; mRNA, messenger ribonucleic acid

Table 91: Calculation of CYP Induction Parameters for Difamilast

Isozyme Hepatocyte Donor Lot[a]	$EC_{50,u}$ (µM)	E_{max} (fold)	R Value	Conclusion	Positive Control[b]	Study Report	System
CYP1A2							
DQB	0.5053	5.0115	0.9418				
APA	2.091	10.475	0.9694	Not an inducer	Omeprazole	033432	Cultured Human Hepatocytes
EBS	1.479	14.110	0.9434				
CYP2B6							
DQB	6.602	2.3494	0.9978				
APA	>10	NC	NC	Not an inducer	Phenobarbital	033432	Cultured Human Hepatocytes
EBS	4.250	3.0275	0.9955				
CYP3A4							
DQB	3.482	4.8318	0.9913				
APA	>10	NC	NC	Not an inducer	Rifampicin	033432	Cultured Human Hepatocytes
EBS	>10						

Source. Generated by reviewer based on Study Report 033432
[a] Results reported for three donor lots (DQB/APA/EBS)
[b] Known inducers of respective CYP isoforms
Abbreviations: CYP, cytochrome P450; $EC_{50,u}$, half-maximal effective unbound concentration; E_{max}, maximum induction effect; NC, not calculated

17.4.2.4. Drug Transporters Involved in the Disposition of Difamilast

In vitro assays were conducted to determine whether difamilast is a substrate for P-gp, breast cancer resistance protein (BCRP), OATP1B1, or OATP1B3 using cells expressing each respective transporter isoform (Study 033090). Based on these assessments, it was determined that difamilast is a substrate for BCRP (≥1 µM), but not for P-gp, OATP1B1, or OATP1B3. However, given the low steady-state plasma concentrations observed following topical administration of difamilast, clinically significant changes in systemic exposure due to BCRP inhibition are considered unlikely.

17.4.2.5. Inhibition of Drug Transporters by Difamilast, MAP-15484, MAP-15485, and MAP-15497

The potential of difamilast and its metabolites MAP-15484, MAP-15485, and MAP-15497 to inhibit the transport of known substrates of human uptake and efflux transporters was evaluated in vitro (Table 92). Overall, there appears to be low risk for in vivo inhibition of the tested transporter proteins by difamilast, MAP-15484, MAP-15485, and MAP-15497 at expected systemic exposure following administration of the proposed dosing regimen.

Table 92: In Vitro Assessment of Difamilast, MAP-15484, MAP-15485, and MAP-15497 as Inhibitors of Human Uptake and Efflux Transporters

Isozyme Test Article	IC_{50} (μM)	Conclusion	Probe Substrate	Positive Control[a]	Study Report	System
P-gp (MDR1)[b]						
Difamilast	0.8	Not an inhibitor in vivo	[^{3}H]-Quinidine 0.05 μM [^{14}C]-Mannitol 10 μM	Verapamil	032917	Human P-gp-expressing LLC-PK1 cells
MAP-15484	>30					
MAP-15485	1.1					
MAP-15497	3.7					
BCRP[b]						
Difamilast	0.2	Not an inhibitor in vivo	[^{3}H]-Prazosin 0.01 μM [^{14}C]-Mannitol 10 μM	Ko143	032921	Human BCRP-expressing MDCKII cells
MAP-15484	>30					
MAP-15485	0.3					
MAP-15497	0.3					
OATP1B1[b]						
Difamilast	1.8	Not an inhibitor in vivo	[^{3}H]-Estradiol 17β-D-glucuronide 0.1 μM	Rifampicin	032935	Human OATP1B1-expressing HEK293 cells
MAP-15484	22.1					
MAP-15485	3.3					
MAP-15497	>30					
OATP1B3[b]						
Difamilast	1.2	Not an inhibitor in vivo	[^{3}H]-Estradiol 17β-D-glucuronide 0.1 μM	Rifampicin	032935	Human OATP1B3-expressing HEK293 cells
MAP-15484	18.0					
MAP-15485	2.5					
MAP-15497	2.7					
OAT1[b]						
Difamilast	>30	Not an inhibitor in vivo	[^{3}H]-*p*-Aminohippuric acid 1 μM	Probenecid	032935	Human OAT1-expressing HEK293 cells
MAP-15484	1.6					
MAP-15485	>30					
MAP-15497	>30					
OAT3[b]						
Difamilast	6.1	Not an inhibitor in vivo	[^{3}H]-Estrone-3-sulfate 0.1 μM	Probenecid	032935	Human OAT3-expressing HEK293 cells
MAP-15484	4.9					
MAP-15485	9.6					
MAP-15497	>30					
OCT1[b]						
Difamilast	1.4	Not an inhibitor in vivo	[^{14}C]-Metformin 10 μM	Quinidine	032935	Human OCT1-expressing HEK293 cells
MAP-15484	>30					
MAP-15485	3.7					
MAP-15497	>30					

Isozyme Test Article	IC_{50} (μM)	Conclusion	Probe Substrate	Positive Control[a]	Study Report	System
OCT2[b]						
Difamilast	1.0	Not an inhibitor in vivo	[^{14}C]-Metformin 10 μM	Quinidine	032935	Human OCT2-expressing HEK293 cells
MAP-15484	>30					
MAP-15485	>30					
MAP-15497	>30					
MATE1[c]						
Difamilast	1.0	Not an inhibitor in vivo	[^{14}C]-Metformin 1 μM	Cimetidine	033611	Human MATE1-expressing MDCKII cells
MAP-15484	>30					
MAP-15485	2.3					
MAP-15497	0.8					
MATE2-K[b]						
Difamilast	6.4	Not an inhibitor in vivo	[^{14}C]-Metformin 2 μM	Cimetidine	032935	Human MATE2-K-expressing HEK293 cells
MAP-15484	>30					
MAP-15485	>30					
MAP-15497	2.7					

Source. Generated by reviewer based on Study Reports 032917, 032921, 032935, and 033611
[a] Known inhibitors of respective transporter proteins
[b] Test articles (i.e., difamilast, MAP-15484, MAP-15485, and MAP-15497) were evaluated at concentrations ranging from 0.003 to 30 μM
[c] Test articles (i.e., difamilast, MAP-15484, MAP-15485, and MAP-15497) were evaluated at concentrations ranging from 0.1 to 30 μM
Abbreviations: BCRP, breast cancer resistance protein; IC_{50}, half-maximal inhibitory concentration; MATE, multidrug and toxin extrusion; MDR1, multidrug resistance protein 1; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein;

17.4.3. Applicant's PBPK Model to Evaluate Difamilast as Victim Drug

To assess the impact of coadministration of difamilast ointment, 1%, with inhibitors of CYP3A4 and CYP1A2 enzymes on difamilast PK, the Applicant constructed a PBPK model for the purposes of in silico DDI evaluation (Report 271-018-001PBPK). The PBPK model was developed using the SimCYP software (version 16) and was a multi-phase and multi-layer mechanistic transdermal absorption model (MPML MechDermA), which was divided into 5 physiological layers (stratum corneum, epidermis, dermis, subcutaneous tissue, and deep tissue). The model was used to estimate drug distribution between layers and diffusion within each layer. Of note, the contributions of CYP3A4 and CYP1A2 to difamilast elimination were assigned based on in vitro data. Model validation was completed by the Applicant based on PK data from healthy Japanese adults in Study 271-14-001.

Using the PBPK model, the Applicant simulated difamilast PK parameters following administration of difamilast ointment, 1% (50 mg) with and without coadministration of ketoconazole 200 mg BID and fluvoxamine 50 mg once daily, which are potent inhibitors of CYP3A4 and CYP1A2, respectively (Table 93).

Table 93: PBPK Model Simulated Geometric Mean (5th – 95th Percentile) Difamilast PK Parameters Following Administration of Difamilast Ointment, 1% (50 mg) With and Without Coadministration of Ketoconazole (CYP3A4 Inhibitor) and Fluvoxamine (CYP1A2 Inhibitor)

Precipitant Difamilast PK Parameter	Difamilast, 1% Monotherapy (R)	Coadministration with Precipitant (T)	GMR (T/R)
Ketoconazole 200 mg BID AUC_{inf} (ng*h/mL) C_{max} (ng/mL)			(b) (4)
Fluvoxamine 50 mg QD AUC_{inf} (ng*h/mL) C_{max} (ng/mL)			

Source. Adapted from Summary of Clinical Pharmacology Studies (Table 29 and Table 30, pg. 50)
Abbreviations: AUC_{inf}: area under the plasma concentration-time curve from 0 to infinity; BID, twice daily; C_{max}, maximum plasma concentration; CYP, cytochrome P450; GMR, geometric mean ratio; PBPK, physiologically based pharmacokinetic; QD, once daily; R, reference; T, test

Based the PBPK model-predicted exposure, combined use of ketoconazole and fluvoxamine with difamilast ointment, 1%, resulted in a (b) (4)-fold increase, respectively, in difamilast AUC_{inf}, and a (b) (4)-fold increase, respectively, in difamilast C_{max}, as compared to administration of difamilast ointment, 1%, alone. However, following review of the Applicant's PBPK analyses, it was determined that the PBPK model is inadequate for predicting the effects of coadministration of strong inhibitors of CYP3A (i.e., ketoconazole) and CYP1A2 (i.e., fluvoxamine) on difamilast plasma exposure. The following deficiencies were highlighted by the PBPK review team:

- The model could not reproduce the difamilast PK observed following multiple doses of difamilast ointment, 1% (50 mg) for 14 days in Study 271-14-001, with prediction errors exceeding 2-fold.
- The contributions of CYP3A4 and CYP1A2 to difamilast elimination, which are essential for accurately predicting the DDI potential of difamilast as an object drug, cannot be

verified. Clinical DDI data or other clinical data that could verify the contributions of these enzymes are unavailable.

- The dermal absorption model has not been verified in the pediatric population.

Overall, there are insufficient data to characterize the pathway-specific metabolic clearance of difamilast in the target populations and, as a result, the PBPK analyses submitted by the Applicant are insufficient to provide a reliable assessment of clinical DDI risk.

17.4.4. Bioanalytical Method Validation and Performance

The Applicant utilized four bioanalytical assays to support PK assessment of difamilast and its metabolites across the clinical pharmacology program, all of which utilized protein precipitation followed by liquid chromatography with tandem mass spectroscopy (LC-MS/MS) using electrospray positive ionization (ESI). Human plasma concentrations of difamilast and its metabolites were measured using Methods OPAHHP, MN21007, and PRD14-203, while urine concentrations were determined using Method PRD14-205.

For the purposes of this NDA, only Studies MEDI-MM36-206 (maximal use PK study) and MEDI-MM36-302 (QTc sub-study within phase 3 OLE) were considered pivotal clinical pharmacology studies. Therefore, this review focused on the validation and assay performance for Methods OPAHHP and MN21007, which supported Studies 206 and 302, respectively.

17.4.4.1. Bioanalytical Assay Validation (OPAHHP and MN21007)

A tabulated summary of the key assay validation parameters for Methods OPAHHP and MN21007 is provided below in Table 94.

Table 94: Summary of Method Validation Parameters for Bioanalytical Assays Used to Measure Plasma Concentrations of Difamilast, MAP-15485, MAP-15497, and MAP-15484 in Pivotal Clinical Pharmacology Studies

	Bioanalytical Method ID							
Method Parameter	**OPAHPP[a]**				**MN21007**			
Analyte	**Difamilast[b]**	**MAP-15484[b]**	**MAP-15495[b]**	**MAP-15497[b,c]**	**Difamilast[d]**	**MAP-15484[e]**	**MAP-15485[d]**	**MAP-15497[d]**
Analytical Site	(b) (4)				(b) (4)			
Clinical Studies Supported	271-11-202, 271-12-205, 271-12-204, and MEDI-MM36-206				MEDI-MM36-302			
Bioanalytical Methodology	Protein precipitation followed by LC-MS/MS with ESI				Protein precipitation followed by LC-MS/MS with ESI			
Matrix	Sodium heparin human plasma				Sodium heparin human plasma			
Internal Standard (ISTD)	OPA-15521	N/A	N/A	N/A	OPA-15521	MAP-15484-d_7	MAP-15485-d_7	MAP-15497-d_7
Validated Assay Range (LLOQ to ULOQ)	0.200 to 40.0 ng/mL	0.200 to 40.0 ng/mL	0.200 to 40.0 ng/mL	0.200 to 40.0 ng/mL	0.050 to 50.0 ng/mL	0.125 to 125 ng/mL	0.050 to 50.0 ng/mL	0.050 to 50.0 ng/mL
Regression Model	Linear least-squares regression model with $1/X^2$ weighing factor				Linear least-squares regression model with $1/X^2$ weighing factor			
Calibration Curve/Linearity During A&P Runs								
Cum. Bias Range (%RE)	−2.3 to 2.8%	−3.0 to 1.4%	−1.5 to 1.8%	−0.8 to 1.0%	−1.4 to 1.5%	−1.2 to 0.4%	−1.2 to 2.0%	−3.6 to 2.5%
Cum. Precision (%CV)	≤3.8%	≤4.5%	≤5.4%	≤6.1%	≤3.1%	≤2.7%	≤2.5%	≤5.4%
QC Performance During A&P Runs								
Cum. Bias Range (%RE)	−2.5 to 3.6%	−7.0 to −5.0%	11.6 to 14.8%	6.6 to 9.8%	−4.0 to −2.7%	−3.2 to −1.6%	−4.0 to −1.4%	−4.7 to −2.7%
Cum. Precision (%CV)	≤4.1%	≤15.1%	≤13.0%	≤9.5%	≤9.1%	≤9.4%	≤9.4%	≤9.2%
Total Error (%TE)	≤6.7%	≤20.1%	≤26.6%	≤19.0%	≤13.1%	≤12.1%	≤13.4%	≤13.9%
Selectivity	Passed	Passed	Failed	Failed	Passed	Passed	Passed	Passed
Hemolysis Effect	Passed	Passed	Passed	Passed	Passed	Passed	Passed	Passed
Lipemic Effect	Passed	Passed	Passed	Failed	Passed	Passed	Passed	Passed
Specificity/Interference	Passed	Passed	Passed	Passed	Passed	Passed	Passed	Passed
Matrix Effect	Passed	Passed	Failed	Failed	Passed	Passed	Passed	Passed
Dilution Linearity	100-fold	100-fold	100-fold	100-fold	100-fold	100-fold	100-fold	100-fold
Carryover	Passed	Passed	Passed	Passed	Passed	Passed	Passed	Passed

	Bioanalytical Method ID				
Method Parameter	**OPAHPP[a]**				**MN21007**
Established Stability					
Bench-Top Stability	24 h at RT	24 h at RT	6 h at RT	6 h at RT	120 min at RT and ice bath in whole blood; 24 h in ice bath following thaw
Process Stability	163 h at 2-8°C	163 h at 2-8°C	163 h at 2-8°C	163 h at 2-8°C	70 h at 10±5°C in processed extracts
Long-Term Stability	71 days at −10/-30°C; 275 days at −60/-80°C				1058 days at −20°C; 420 days at −70°C
Freeze/Thaw Stability	5 cycles from −10/-30°C to RT; 5 cycles from −60/-80°C to RT		4 cycles from −10/-30°C to RT; 4 cycles from −60/-80°C to RT		5 cycles from −20°C to ice bath; 4 cycles from −70°C to ice bath

Source. Compiled by reviewer from Bioanalytical Reports 8246377, 8357469, MC21B-0022, MC21B-0297, and MC21B-0092
[a] All data reported for analytical runs using plasma procured from (b) (4)
[b] Calibration curve concentrations (8 std. calibrators): 0.200, 0.400, 2.00, 4.00, 8.00, 20.0, 36.0, and 40.0 ng/mL; QC levels: 0.200, 0.600, 5.00, and 32.0 ng/mL
[c] Stability data at −10/-30°C for 31 days failed at LQC concentration due to high %RE (18.0%), although stability was established at −10/-30°C for 71 days
[d] Calibration curve concentrations (10 std. calibrators): 0.050, 0.100, 0.200, 0.400, 1.00, 2.00, 5.00, 10.0, 25.0, and 50.00 ng/mL; QC levels: 0.050, 0.150, 15.0, and 40.0 ng/mL
[e] Calibration curve concentrations (10 std. calibrators): 0.125, 0.250, 0.500, 1.00, 2.50, 5.00, 12.5, 25.0, 62.5, and 125 ng/mL; QC levels: 0.125, 0.375, 37.5, and 100 ng/mL
Abbreviations: A&P, Accuracy and Precision; CV, coefficient of variation; ESI, electrospray ionization; ISTD, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectroscopy; LLOQ, lower limit of quantitation; N/A, not applicable; QC, quality control; RE, relative error; RT, room temperature; TE, total error; ULOQ, upper limit of quantitation

Assessment of Method MN21007 (Study 302 [QTc Sub-Study within Phase 3 OLE]):

No major issues or deficiencies were identified with Method MN21007 and validation was determined to be acceptable in accordance with the M10 Bioanalytical Method Validation and Study Sample Analysis – Guidance for Industry (November 2022).

Assessment of Method OPAHHP (Study 206 [Maximal Use PK Trial]):

Significant issues were identified during the validation procedures for Method OPAHHP, which are described in detail below.

- **Plasma Source-Dependency of Method Validation:** Human plasma matrices were procured from two different commercial vendors for the purposes of method validation, including (b) (4) (formerly (b) (4)) and (b) (4). Based on the validation documents, there were significant and systematic differences in assay performance for selectivity, matrix factor, and hemolysis assessments depending on which plasma source was utilized for testing (Table 95, Table 96).
  - **Selectivity:** Aliquots of individual lots of plasma from both vendors (6 from (b) (4), 6 from (b) (4)) were spiked at low quality control (LQC) concentrations of difamilast, MAP-15484, MAP-15485, MAP-15497, and OPA-15521 (internal standard [ISTD]). For difamilast and MAP-15484, accuracy (%RE) for each sample met acceptance criteria (±15.0%) when using (b) (4) plasma but did not meet criteria with (b) (4) plasma. Selectivity data for MAP-15485 and MAP-15497 failed to meet acceptance criteria using plasma from both vendors, although data was substantially worse when using lots of (b) (4) plasma.
  - **Matrix Effects:** For matrix factor evaluation, blank matrix extracts were spiked post-extraction at LQC concentrations with OPA-15521 (ISTD) and compared to three replicates of pure solutions containing difamilast, MAP-15484, MAP-15485, MAP-15497, and OPA-15521 at equivalent concentrations. The matrix factor for each analyte was calculated as the ratio of the mean peak response with and without matrix ions. ISTD-normalized matrix factors were calculated as the ratio of the matrix factors derived for each analyte to OPA-15521. Data were considered acceptable if precision (%CV) was ≤15.0% for the matrix factor values for OPA-15521 and each analyte (nominal and ISTD-normalized). Acceptance criteria were not met for any of the analytes when using the (b) (4) plasma. Significant ion suppression of both difamilast and OPA-15521 (matrix factors of 0.199 and 0.285, respectively) was observed, the latter of which substantially impacted the calculation of ISTD-normalized matrix factors for each analyte. When using plasma from (b) (4), acceptance criteria were met for difamilast and MAP-15484, but not for MAP-15485 or MAP-15497.
  - **Hemolysis Effect:** To evaluate hemolysis, six replicates of LQC samples were analyzed following preparation in blank matrix containing 2% lysed whole blood. Results were considered acceptable if the mean concentration of the spiked samples had a precision (%CV) and accuracy (%RE) of ≤15.0% and ±15.0%, respectively. This

evaluation was completed using plasma obtained from (b) (4) (Run ID 2) and then repeated using (b) (4) plasma (Run ID 10). Acceptance criteria were met for difamilast using both (b) (4) and (b) (4) plasma, while the metabolites (MAP-15484, MAP-15485, and MAP-15497) were only acceptable while using (b) (4) plasma.

Table 95: Summary of Selectivity, Matrix Effect, and Hemolysis Data Using (b) (4) Plasma (Method OPAHHP)

Validation Parameter	(b) (4) Plasma			
Performance	Difamilast	MAP-15484	MAP-15485	MAP-15497
Selectivity	Failed	Failed	Failed	Failed
Bias (%RE)	−33.5%	213.3%	251.7%	236.7%
Precision (%CV)	12.3%	23.1%	26.1%	26.6%
Matrix effect	Failed	Failed	Failed	Failed
Bias (%RE)	−80.1%	2.7%	9.3%	22.3%
MF (%CV)[a]	0.199 (58.3%)	1.03 (4.3%)	1.09 (5.1%)	1.22 (5.2%)
ISTD-Normalized MF (%CV)[b]	0.672 (16.1%)	3.90 (23.7%)	4.19 (26.3%)	4.67 (25.7%)
Hemolysis effect	Passed	Failed	Failed	Failed
Bias (%RE)	−13.2%	59.5%	70.0%	47.2%
Precision (%CV)	2.3%	9.1%	3.6%	4.3%

Source. Compiled by reviewer from Bioanalytical Reports 8246377 (Table 7.2-7.5 [pg. 33-36], Table 7.6-7.9 [pg. 37-44], Table 7.72-7.75 [pg. 119-122])
[a] MF = Post-extraction spike peak area / Mean pure solution peak area; MF >1 indicates ionization enhancement, whereas MF <1 indicates ionization suppression
[b] ISTD-Normalized MF = Matrix Factor of the Analyte / Matrix Factor of the ISTD
Abbreviations: CV, coefficient of variation; ISTD, internal standard (OPA-15521); MF, Matrix Factor; RE, relative error

Table 96: Summary of Selectivity, Matrix Effect, and Hemolysis Data Using (b) (4) Plasma (Method OPAHHP)

Validation Parameter	(b) (4) Plasma			
Performance	Difamilast	MAP-15484	MAP-15485	MAP-15497
Selectivity	Passed	Passed	Failed	Failed
Bias (%RE)	3.0%	−0.5%	16.0%	7.0%
Precision (%CV)	3.3%	14.2%	18.2%	23.5%
Matrix effect	Passed	Passed	Failed	Failed
Bias (%RE)	−7.5%	5.6%	19.1%	28.9%
MF (%CV)[a]	0.926 (8.8%)	1.06 (3.5%)	1.19 (11.5%)	1.29 (14.6%)
ISTD-Normalized MF (%CV)[b]	1.02 (2.3%)	1.18 (13.2%)	1.34 (21.5%)	1.45 (24.8%)
Hemolysis effect	Passed	Passed	Passed	Passed
Bias (%RE)	1.2%	4.0%	−0.8%	−2.3%
Precision (%CV)	0.9%	2.1%	2.3%	2.4%

Source. Compiled by reviewer from Bioanalytical Reports 8246377 (Table 7.2-7.5 [pg. 33-36], Table 7.6-7.9 [pg. 37-44], Table 7.72-7.75 [pg. 119-122])
[a] MF = Post-extraction spike peak area / Mean pure solution peak area; MF >1 indicates ionization enhancement, whereas MF <1 indicates ionization suppression
[b] ISTD-Normalized MF = Matrix Factor of the Analyte / Matrix Factor of the ISTD
Abbreviations: CV, coefficient of variation; ISTD, internal standard (OPA-15521); MF, Matrix Factor; RE, relative error

- **Inadequate Performance of QC Samples During A&P Runs:** Accuracy and precision (A&P) were established over a total of four runs (Run IDs 3, 4, 5, and 10). Although overall (inter-run) A&P were established for all analytes, there were significant inconsistencies with intra-run QC performance for the metabolites. Most notably, all four QC levels for MAP-15485 and MAP-15497 failed to meet acceptance criteria in Run 5 due to an unacceptable overestimation bias, necessitating the generation of data from

a fourth A&P batch. This represents an important protocol deviation, since A&P could not be established over three consecutive batches for these metabolites. Additionally, the LLOQ and medium QC (MQC) levels for MAP-15484 failed to meet acceptance criteria during Run 10 due to an unacceptable underestimation bias.

- **Lack of Multiple Internal Standards:** A critical limitation in the analytical method design is the lack of matched internal standards for all analytes, which likely contributed to the variability observed in metabolite quantitation. Per the validation report, difamilast measurements were more consistent than metabolite measurements because only a single internal standard (OPA-15521, a stable isotope-labeled analog of difamilast) was used during validation. Synthesizing additional isotope-labeled internal standards for MAP-15484, MAP-15485, and MAP-15497 may have improved accuracy and assisted with compensation of the significant matrix effects noted above.

Overall, the bioanalytical method OPAHHP appears suitable for the quantitation of difamilast in human plasma. However, there are significant issues affecting the reliability of this assay for quantitation of plasma concentrations of MAP-15484, MAP-15485, and MAP-15497, including unacceptable selectivity data, substantial matrix effects, and poor QC performance. The failure to utilize matched isotope-labeled internal standards for each metabolite likely contributed to these deficiencies and to the overall variability of the assay. Additionally, matrix effect assessment for each analyte was incomplete, as analysis was conducted only at the LQC level, whereas current guidance recommends assessment at both LQC and HQC concentrations. Therefore, based on these considerations, this assay is not suitable for the quantitation of MAP-15484, MAP-15485, and MAP-15497 and data reported for these metabolites from clinical studies 271-11-202, 271-12-205, 271-12-204, and MEDI-MM36-206 is not considered reliable.

17.4.4.2. Bioanalytical Assay Performance in Studies MEDI-MM36-206 and MEDI-MM36-302

The in-study bioanalysis results for quantitation of difamilast, MAP-15484, MAP-15485, and MAP-15497 in Studies 206 and 302 are summarized below in Table 97 and Table 98, respectively.

- ***Study 206:*** Overall method performance for quantitation of difamilast appears robust and met all acceptance criteria. However, all three metabolites failed ISR assessment, with re-analysis passing rates of only 10%, 10%, and 0%, respectively. When considered in tandem with the deficiencies highlighted above regarding the validation of Method OPAHHP, the reported metabolite PK data derived from this clinical trial are considered unreliable.
- ***Study 302:*** No concerns were identified and method performance met all acceptance criteria for each analyte. A reduced number of MAP-15484 samples were selected for ISR due to the high prevalence of BLQ samples. All ISR samples met acceptance criteria except for a single sample for MAP-15485, which was attributed to carryover. Overall, PK data derived from this study are considered reliable.

Table 97: Method Performance for PK Analysis in Study MEDI-MM36-206 (Method OPAHPP)

Assay Performance Metric	Analyte			
A&P Criteria	Difamilast	MAP-15484	MAP-15485	MAP-15497
Run acceptance rate	72.7% (8/11)	63.6% (7/11)	72.7% (8/11)	72.7% (8/11)
Standard curve performance	Acceptable	Acceptable	Acceptable	Acceptable
Cum. bias range (%RE)	−3.8 to 2.8%	−4.3 to 3.0%	−4.7 to 6.3%	−3.6 to 6.3%
Cum. precision (%CV)	≤4.1%	≤6.4%	≤8.7%	≤5.9%
QC performance	Acceptable	Acceptable	Acceptable	Acceptable
Cum. bias range (%RE)	−4.7 to −1.0%	-3.8 to −0.6%	−2.8 to 1.5%	−2.8 to 6.0%
Cum. precision (%CV)	≤4.2%	≤8.7%	≤6.4%	≤10.3%
Total error (%TE)	≤8.4%	≤12.5%	≤8.8%	≤16.3%
Method reproducibility	Acceptable	Failed	Failed	Failed
Total no. samples	242	242	242	242
No. samples BLQ	29	70	44	44
ISR passing rate	100% (60/60)	10% (6/60)	10% (6/60)	0% (0/60)
Sample Analysis/Stability	Acceptable	Acceptable	Acceptable	Acceptable

Source. Compiled by reviewer from Bioanalytical Report 8353505
Abbreviations: A&P, Accuracy and Precision; BLQ, below the limit of quantitation; CV, coefficient of variation; ISR, incurred sample reanalysis; PK, pharmacokinetic; QC, quality control; RE, relative error; TE, total error

Table 98: Method Performance for Plasma PK Analysis in Study MEDI-MM36-302 (Method MN21007)

Assay Performance Metric	Analyte			
A&P Criteria	Difamilast	MAP-15484[a]	MAP-15485	MAP-15497
Run acceptance rate	81.8% (9/11)	81.8% (9/11)	81.8% (9/11)	81.8% (9/11)
Standard curve performance	Acceptable	Acceptable	Acceptable	Acceptable
Cum. bias range (%RE)	−3.6 to 3.8%	−1.6 to 3.2%	−2.2 to 3.0%	−4.8 to 4.6%
Cum. precision (%CV)	≤6.4%	≤4.7%	≤7.3%	≤7.7%
QC Performance[a]	Acceptable	Acceptable	Acceptable	Acceptable
Cum. bias range (%RE)	−3.8 to −1.3%	−1.6 to −0.5%	−0.5 to 0.0%	−4.0 to −0.7%
Cum. precision (%CV)	≤4.8%	≤4.3%	≤4.1%	≤4.6%
Total error (%TE)	≤8.1%	≤5.0%	≤4.1%	≤8.0%
Method reproducibility	Acceptable	Acceptable	Acceptable	Acceptable
Total no. samples	363	363	363	363
No. samples BLQ	118	332	212	203
ISR passing rate	100% (37/37)	100% (9/9)	97.3% (36/37)	97.3% (36/37)
Sample analysis/stability	Acceptable	Acceptable	Acceptable	Acceptable

Source. Compiled by reviewer from Bioanalytical Report MC21B-0194
[a] A reduced number of MAP-15484 samples were selected for ISR due to the prevalence of BLQ results
Abbreviations: A&P, Accuracy and Precision; BLQ, below the limit of quantitation; CV, coefficient of variation; ISR, incurred sample reanalysis; PK, pharmacokinetic; QC, quality control; RE, relative error; TE, total error

17.5. Additional Clinical Outcome Assessment Analyses

None

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

/s/

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Renqin DUAN
02/10/2026 09:47:45 AM

JIANYONG WANG
02/10/2026 09:51:37 AM
on behalf of myself and Dr. Carmen Booker

YUNZHAO REN on behalf of JAMES D MEASE
02/10/2026 09:56:28 AM

ANAND BALAKRISHNAN on behalf of CHINMAY SHUKLA
02/10/2026 10:50:22 AM

KAPIL D VERMA
02/10/2026 10:52:07 AM

GORDANA DIGLISIC
02/10/2026 12:45:21 PM

MATTHEW W GUERRA
02/10/2026 12:46:40 PM

NIKOLAY P NIKOLOV
02/10/2026 12:57:57 PM