CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219474Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112973

MEETING MINUTES

Medimetriks Pharmaceuticals, Inc.
c/o Prosoft Clinical
Attention: Robert W. Babilon, MS, MBA
Chief Operating Officer
996 Old Eagle School Road, Suite 1106
Wayne, PA 19087

Dear Mr. Babilon:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OPA-15406 ointment.

We also refer to the meeting between representatives of your firm and the FDA on October 31, 2018. The purpose of the meeting was to discuss the development program for OPA-15406 ointment.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Response Document

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 31, 2018, 11 AM
Meeting Location:	WO 22, Rm. 1421
Application Number:	IND 112973
Product Name:	OPQ-15406 ointment
Proposed Indication:	for the topical treatment of mild to moderate atopic dermatitis (b) (4) (b) (4) in patients 2 years of age and older
Sponsor Name:	Medimetriks Pharmaceuticals, Inc.
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Cristina Attinello, MPH

FDA ATTENDEES
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jianyong (Jerry) Wang, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Carin Kim, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DPC) III
Yanhui Lu, PhD, Clinical Pharmacology Reviewer, DCP III
Selena Daniels, PharmD, MS, Team Leader, Clinical Outcomes Assessment (COA)
Wen-Hung Chen, PhD, Social Science Analyst, COA
Lars Johannesen, Clinical Analyst (QT-IRT), ODE I/DCRP
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Donna Heren, VP Regulatory Affairs & Quality Assurance, Medimetriks
Sandra Roth, Clinical representative, Medimetriks
Michelle Aquino, QA/RA representative, Medimetriks
Sharon Levy, CMO for Prosoft Clinical, Medimetriks
Robert Babilon, COO Prosoft Clinical/Regulatory Affairs, Medimetriks

Lynne Georgopoulos, Clinical/Regulatory representative, Medimetriks
John Quiring, Biostatistician, Medimetriks
(b) (4), Biostatistics Consultant, Medimetriks
Angela Smith, Global Medical Affairs, Otsuka US
Satoko Sugaya, Clinical representative, Otsuka Japan
Yoichi Araki, Clinical representative, Otsuka Japan

1.0 BACKGROUND

Regulatory Correspondence History

We have sent the following correspondences:

- May 29, 2018: Advice/Information Request Letter
- March 16, 2018: Advice/Information Request Letter
- January 3, 2018: Advice/Information Request Letter
- March 13, 2017: Advice/Information Request Letter
- December 27, 2016: Advice/Information Request Letter
- October 20, 2014: Advice/Information Request Letter
- August 12, 2014: Advice/Information Request Letter
- November 22, 2013: Final Written Response Letter
- November 9, 2012: Advice/Information Request Letter
- February 6, 2012: Study May Proceed Letter

Purpose of Meeting

To discuss the development plan for OPA-15406 ointment for the treatment of atopic dermatitis

2.0 DISCUSSION

The sponsor submitted a response document, following receipt of our preliminary comments. The response document is appended to these meeting minutes.

2.1. Chemistry, Manufacturing and Controls (CMC)

Question 1:
Does the Agency agree with the plan to bridge the presence of the new and more stable polymorph (b) (4) that will be used in Phase 3 clinical trials and the to-be-marketed formulation, to that of the (b) (4) used in Phase 1 and 2 clinical trials?

FDA Response to Question 1:
Your proposed plan to bridge the new stable polymorph of the API, (b) (4) which is intended for use in the manufacture of the Phase 3 as well as the to-be-marketed product to

the Phase 1 and Phase 2 clinical trial material manufactured using (b) (4) of the API is reasonable. Granted that no precipitation/recrystallization of the API and/or any additional degradation products in the drug product made with (b) (4) are observed during the long-term stability studies within the duration of the proposed drug product shelf-life. Adequacy of the bridging data will be determined during the review of the application.

Question 2:
Does the Agency agree that the proposed physical, chemical, and microbiological tests are acceptable and sufficient for the Primary Batch (Registration) Stability program?

FDA Response to Question 2:
Your proposed plan for the determination of the physical, chemical, and microbiological attributes of the drug product at release and during stability for the three primary batches is considered reasonable based on the information you have provided. However, testing for any additional attribute if needed, will be determined during the review of the application.

2.2. Nonclinical

Question 1:
Does the Agency agree that the safety and tolerability of the formulation excipients have been adequately characterized and no additional nonclinical testing is required?

FDA Response to Question 1:
Yes, we agree.

Question 2:
Does the Agency agree that the completed nonclinical program, and the ongoing carcinogenicity studies, are adequate to support submission of the NDA for difamilast ointment, 1%, and that no additional nonclinical studies are required?

FDA Response to Question 2:
Your nonclinical program appears reasonable to support a NDA submission, with your proposed patient population of 2 years of age and older. The final determination of data adequacy will be made after the review of your NDA package including all the final study reports.

Your juvenile animal toxicity data are not adequate to support a patient population of 3 months to 2 years of age, as in the neonatal rat toxicity study (study no. 030663), the study evaluation only focused on CNS, which is not considered adequate. The study evaluation in the second juvenile rat toxicity study (study no. 030395) was adequate, however, the starting animal age in the study is equivalent to human age of ~2 years. Should you plan to pursue a NDA with a patient population of 3 months of age and older, an additional juvenile rat toxicity study with complete study endpoints is needed.

2.3. Clinical Pharmacology

Question 1:
Does the agency agree that the PK data obtained in multiple Phase 1 and Phase 2 studies and proposed population PK with difamilast and its metabolites in the Phase 3 MEDI-MM36-302 study, together with the PK data on difamilast obtained from study MEDI-MM36-206 under maximal use conditions, should be sufficient to characterize the extent of systemic exposure (difamilast and metabolites MAP-15484, MAP-15497, and MAP-15485) following topical administration of difamilast 1% ointment and support product labeling?

FDA Response to Question 1:
Your proposed approach is reasonable. However, the adequacy of your data for characterizing the systemic exposure of the parent drug and metabolites under maximal use conditions and for supporting product labeling will be a review issue at the time of NDA submission. Clarify if the metabolites (MAP-15484, MAP-15497 and MAP-15485) are pharmacologically active.

Meeting Discussion:
The sponsor stated that they will characterize the pharmacological activities of the metabolites and submit the information to the NDA. The Agency responded that their plan is reasonable.

Question 2:
Does the Agency agree that based on completed in vitro studies conducted to evaluate the drug-drug interaction (DDI) potential of difamilast and confirmation of low systemic absorption following topical administration of difamilast ointment 1% under maximal use conditions (application to at least 25% BSA in subjects 12 years of age and older and at least 35% BSA in subjects 2 to < 12 years), that metabolic based DDIs are unlikely, and no additional nonclinical or clinical studies are required to further characterize the DDI potential of difamilast?

FDA Response to Question 2:
The final decision of whether additional studies are needed or not for evaluation of the DDI potential of your drug product will be made at the NDA submission after fully reviewing your study reports.

Since you don't have conclusive information regarding the systemic exposure of the metabolites of your drug under maximal use conditions yet, we recommend that you revisit this topic once you have that information from your planned PK evaluation in one of your Phase 3 studies.

2.4. Clinical/Biostatistics

General Comments
You are developing a novel phosphodiesterase type 4 (PDE4) inhibitor, difamilast ointment (MM36, OPA-15406), for the proposed indication of the topical treatment of mild to

moderate atopic dermatitis (AD) [redacted]. To date, you have completed 9 clinical trials: 4 trials enrolling healthy volunteers (HV) and 5 trials enrolling subjects with AD. In these 9 trials, a total of 532 subjects received difamilast, including 174 adult HV, 260 adult subjects with AD and 98 pediatric subjects aged 2 to 17 years with AD. There were 211 subjects with AD who received difamilast ointment,1%, the proposed dose for further development: 123 adult subjects and 65 pediatric subjects age 2 to 17 years.

Phase 1 Trials in Healthy Adult Volunteers

You conducted 2 randomized, double-blind, vehicle-controlled, trials to evaluate the pharmacokinetics (PK) and safety of difamilast ointment (0.1-3%), **Trial 271-11-202** enrolling 64 subjects and **Trial 271-14-001** enrolling 32 Japanese subjects. In addition, you conducted 2 photopatch test trials to evaluate the phototoxic (**Trial 271-12-212:** 34 evaluable subjects) and photoallergic (**Trial 271-12-213:** 60 evaluable subjects**)** potential of difamilast ointment 0.3%, 1%, and 3%. Topical application of difamilast ointment was not associated with phototoxicity or photoallergenicity. However, you did not conduct these dermal safety trials with the to-be-marketed formulation.

Trials in Subjects with Atopic Dermatitis (AD)

271-12-204:

Phase 1b, multi-center, randomized, double-blind, vehicle- and active (tacrolimus) - controlled, proof of concept trial to determine safety, tolerability, PK and efficacy of 4 weeks of treatment with difamilast ointment 0.3%, 1%, 3%, in 90 adults with AD with 5% or ≥ 10% body surface area (BSA) involvement. For subjects receiving difamilast ointment 1% the success rate (score of 0 or 1) on the Investigator Global Assessment (IGA) for AD was 63.6% compared with 26.7% for vehicle at Week 4. The lowest efficacy occurred in the subjects receiving 3% ointment which contained higher levels of [redacted] compared with [redacted] concentrations.) The mean C_{max} on Day1 and 28 among subjects with ≥ 10% BSA (mean BSA 30) in the 1% group was 30.9 and 12.9 ng/mL respectively.

271-12-205:

Phase 2, multi-center, randomized, double-blind, vehicle-controlled, dose-ranging, 3-arm trial to assess the efficacy and safety of topical difamilast ointment, 0.3% and 1%, in 121 subjects age ≥ 10 years with mild to moderate AD and 5% to 40% BSA involvement. At Week 4, 20.9% (9/43) subjects receiving difamilast 1% ointment achieved treatment success compared with 2.7% (1/37) subjects receiving vehicle. The proportion of subjects with treatment success was smaller in subjects receiving difamilast 0.3% ointment.

MEDI-MM36-206:

Phase 2, multi-center, open-label, trial to assess the safety, PK and exploratory efficacy of topical difamilast ointment, 1%, applied twice daily for up to 28 days. This maximal use trial evaluated a total of 32 pediatric subjects age 2 to < 18 years (mean 7.9 years) with moderate to severe atopic dermatitis with 25- 80% affected BSA (mean 43.7%). Mean C_{max} on Day 1 and 15 were 23.1 ng/mL and 16.9 ng/mL, respectively. The maximum C_{max} was 116.0 ng/mL.

271-15-001/271-102-00002:
Phase 2, multi-center, randomized, double-blind, vehicle-controlled, trial(s) to evaluate efficacy, safety, and PK of difamilast ointment 0.3% or 1%, applied twice daily in Japanese subjects with mild to moderate AD. In Trial 271-15-001, 180 adult subjects applied the study product for 8 weeks; in Trial 271-102-00002, 60 adult and pediatric subjects applied the study product for 28 days. These trials confirmed the proposed optimal dose and duration for the proposed Phase 3 trials.

In the development program to date, you identified no safety signals based on review of all treatment emergent adverse events (TEAEs), treatment emergent adverse reactions, TEAEs resulting in trial discontinuation, changes in clinical laboratory results, ECG parameters, and vital sign measurements.

You submitted draft synopses for the following proposed protocols:

MEDI-MM36-301/302
Phase 3, multi-center, randomized, double-blind, vehicle-controlled trial(s) to evaluate the efficacy, safety, and PK of difamilast ointment 1%, applied twice daily for 4 weeks in 970 subjects age 2 years and older with mild to moderate AD. You plan to enroll at least 20% (n=194) in the pediatric age group 2 to <7 years and approximately 10% (n=97) in the adult age group ≥18 years.

MEDI-MM36-303
Phase 3, multi-center, open-label, safety extension trial in subjects age 2 years and older with mild to moderate AD to evaluate the long-term safety of difamilast ointment 1%, applied twice daily for 4-week intervals. You target enrollment of 300 subjects for 26 weeks and 100 subjects for 52 weeks. Eligible subjects will be treated according to their AD severity on IGA on Day 1. Subjects with an IGA of ≥ Mild (2) will be instructed to initiate a 28-day treatment cycle with Difamilast 1% ointment until they achieve an IGA of ≤ 1 (almost clear) and then will be treated for 2 additional months.

MEDI-MM36-101/102
Phase 1, single center, evaluator-blind, controlled, trial(s) to evaluate the potential of difamilast ointment 1% to induce sensitization in 200 healthy adult subjects and irritation in 30 healthy adult subjects.

Question 1:
Does the Agency agree that the completed and planned clinical data package comprising five completed Phase 1 safety, pharmacokinetic, and dermal tolerability studies, six completed Phase 2 clinical studies in patients with mild to moderate atopic dermatitis, the planned Phase 1 dermal irritation/sensitization studies in healthy volunteers, and the planned Phase 3 clinical studies (two pivotal 4-week treatments studies and one open-label 52-week safety study), are adequate to support submission of the NDA for difamilast ointment, 1%, and that no additional clinical studies are required?

FDA Response to Question 1:
Your development program as summarized above appears reasonable to support filing of an NDA for difamilast ointment, 1% for the treatment of AD. However, if the components of your drug product absorb light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible), we recommend that you conduct provocative safety studies to evaluate the potential for phototoxicity and photoallergenicity in a sufficient number of subjects (e.g. 30 and 45 subjects, respectively) with the to-be-marketed formulation.

As you noted in Question 22 and 23, cardiovascular safety in the target populations needs to be addressed.

Question 2:
Does the Agency agree that the dose response, safety, and efficacy of difamilast ointment have been adequately characterized in the clinical Phase 1b and Phase 2 studies, which used relevant primary (IGA) and secondary endpoints (e.g., EASI, POEM, pruritus NRS), to support the selection of the difamilast ointment 1% dosage strength as the optimal effective clinical dose for Phase 3 studies?

FDA Response to Question 2:
From the data provided, it appears that the proposed dose, difamilast, 1%, is reasonable. However, the decision to pursue further development of a given formulation of difamilast ointment lies with you.

Question 3:
Does the Agency agree that 4 weeks of treatment with difamilast 1% topical ointment is an adequate treatment duration to determine efficacy in subjects with mild to moderate AD?

FDA Response to Question 3:
Atopic dermatitis is a disease that recurs and remits. Based on the data from your Phase 2 development program, the timepoint of Week 4 for the evaluation of the efficacy appears reasonable.

Question 4:
Does the Agency agree that the described safety database of approximately 1500 subjects exposed topically to difamilast 1% topical ointment (to-be-marketed dosage strength) applied twice daily for 4 weeks (a treatment cycle) is sufficient to assess the clinical safety of difamilast 1% topical ointment that will be used intermittently and may be used long-term for treatment of AD flares?

FDA Response to Question 4:
At this time, the size of the proposed safety database appears reasonable. However, the adequacy of the data to support approval of difamilast 1% ointment for the treatment of mild to moderate AD will be a review issue.

Question 5:

Does the Agency agree that assessing approximately 300 completed subjects for 6 months and approximately 100 completed subjects for 12 months is sufficient to evaluate the long-term safety and durability of response of difamilast ointment 1% in subjects ≥2 years of age with mild to moderate AD under real world conditions (e.g., intermittent treatment cycles)?

FDA Response to Question 5:
Your proposal appears reasonable.

Question 6:
Does the Agency agree that the 5-point Investigator Global Assessment (IGA) Likert scale (0 [clear], 1 [almost clear], 2 [mild], 3 [moderate] and 4 [severe]), is appropriate to use as the primary efficacy measurement tool?

Table 1: Investigator's Global Assessment of AD Severity

Scale	Grade	Definition
0	Clear	Minor residual hypopigmentation/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting.
1	Almost clear	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe	Deep or bright red erythema with severe induration/papulation and with oozing/crusting

FDA Response to Question 6:
We acknowledge your intent to use the same Investigator's Global Assessment (IGA) of Atopic Dermatitis (AD) Severity scale in the Phase 3 trials as used in the Phase 2 trials for consistency and interpretability of the efficacy data. However, we prefer that the category of "Almost clear" include no induration/papulation.

Question 7:
Does the Agency agree that the primary efficacy endpoint for Phase 3 defining treatment success as achieving a static IGA of clear (0) or almost clear (1), with at least a 2-grade reduction from baseline at the end of 4 weeks of treatment based on a 5-point IGA Likert scale is sufficient to demonstrate efficacy of difamilast 1% topical ointment?

FDA Response to Question 7:
Your proposed primary efficacy endpoint of 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.

Question 8:
Does the Agency agree that a sample size of 970 subjects (~647 active and ~323 vehicle control) providing >90% power, considering an approximate 15% dropout rate, using a two group χ^2 test with a 5% two-sided significance level based on an active treatment response rate of 32% and a vehicle response rate of 21%, is adequate to demonstrate efficacy based on achieving an IGA of 0 (clear) or 1 (almost clear) with a 2-point reduction from baseline at the end of the 4 week treatment period (Day 29) in subjects with mild to moderate AD?

FDA Response to Question 8:
The adequacy of your planned sample size will depend on how reliable the estimates of treatment effect are from your previous trials, and also on how similar the study design and analysis are in your Phase 2 vs. your planned Phase 3 trials.

Question 9:
Does the Agency agree with the plans for stratification by study center, and ensuring that sufficient subjects are enrolled within each age group (≥2 to <7 years of age, ≥7 to <18 years of age and ≥18 years of age)?

FDA Response to Question 9:
We recommend that study enrollment reflect the disease prevalence in the general population to reduce bias in estimating the treatment effect. While the Agency considers randomization stratified by study center to be reasonable, submit full Phase 3 protocols with details concerning the randomization.

Question 10:
Does the Agency agree with the approach to pooling of study centers following an investigation of center-to-center variability?

FDA Response to Question 10:
Your approach for pooling centers that have insufficient number of subjects within geographic region appears reasonable.

Question 11:
Does the Agency agree that an appropriate method of analysis of the primary efficacy endpoint would be testing using a logistic regression model with treatment group and analysis center as factors?

FDA Response to Question 11:
Your proposal appears reasonable. For detailed comments, submit your Phase 3 protocols that include full details of your model.

Question 12:
Does the Agency agree with the plans for imputation of missing primary efficacy data using a last observation carried forward (LOCF) approach with sensitivity analyses including a tipping point analysis and a repeated measures logistic regression model?

FDA Response to Question 12:
Your protocol synopsis specified imputing the missing data due to lack of efficacy or using prohibited medication as a non-responder, yet you stated that the LOCF will be used as the primary imputation method for your primary endpoint. While your proposed approaches for using tipping point analysis and a repeated measures logistic regression model as sensitivity analyses for handling missing data are reasonable, details should be included in the study protocol. Your protocol should clearly specify the primary imputation method for handling missing data as well. Note that for ease of interpretation of study findings, when possible, we recommend using the same method of handling missing data across different endpoints.

Question 13:
Does the Agency agree with the sequential approach to control for multiplicity and with the acceptability of the key secondary endpoints?

FDA Response to Question 13:
Secondary endpoints (b) (4) should be clinically meaningful, limited in number and controlled for multiplicity. Your proposal to sequentially test your single primary and three secondary endpoints will control for multiplicity.

Your proposed secondary endpoints include "time to success on the 5-point IGA of AD Severity scale" and "time to achieving a ≥3-point change from Baseline on the Pruritus WI-NRS". For these time-to-event endpoints, you will need to provide data to support that the thresholds are clinically meaningful and not just statistically significant. See response to Question 16.

Meeting Discussion:
The sponsor clarified that they intend to evaluate success over time on the 5-point IGA of AD severity scale and not time to success. See also Meeting Discussion that follows Question 17.

Question 14:
Does the Agency agree with the proposed methods of analysis for the secondary endpoints?

FDA Response to Question 14:
Provided that the secondary endpoints are agreed upon, the logrank test is an appropriate method to test time-to-event secondary endpoints, and the logistic regression model with analysis center appears reasonable for binary endpoints. Submit full protocols for detailed comments.

Question 15:
Does the Agency have any other comments regarding the secondary endpoints?

FDA Response to Question 15:
See response to Question 13 and comments below.

In principle, a single 11-point numeric rating scale (NRS), such as the WI-NRS, is acceptable to assess itch severity at its worst in patients with AD who are able to self-report. We recommend that you ascertain which patients are developmentally able to validly and reliably self-report among this population and provide justification for this subgroup. We further recommend that you clearly specify who the reporter will be for the planned assessments (e.g., WI-NRS and observer-reported measure) for the respective ages in your clinical trial protocol based on how you define patients who are eligible to self-report.

An observer-reported outcome (ObsRO) assessment will be necessary for children who cannot validly or reliably self-report. An observer is limited to the assessment of observable signs, events, or behaviors that can be reported from the perspective of a parent or caregiver. Because itch intensity is a symptom that can only be experienced and reported by the patients themselves, we do not agree with the proposal for parents/caregivers to assess itch intensity for children who cannot self-report.

To assess clinical benefit of your product for children who cannot validly and reliably self-report, we recommend that you select an existing fit-for-purpose ObsRO instrument (or develop a new instrument if one does not exist) that measures observable signs, behaviors (e.g., attempted scratching or rubbing), and/or verbalizations made by the child related to itch with a recall over the past 24 hours. Review literature and/or conduct qualitative interviews with parents/caregivers to determine what they can report and observe regarding their child's itch experience.

There should be two separate endpoints for different types of COAs (i.e., a PRO endpoint and an ObsRO endpoint) because combining the findings of these different measures into one endpoint across the population makes it difficult to interpret the combined data as they are assessing different concepts (symptoms vs. behaviors).

You may refer to the following references for additional information for measurement in pediatric populations:

(1) Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, Bullinger M. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health. 2013 Jun;16(4):461-79.

(2) Papadopoulos, E. J., Patrick, D. L., Tassinari, M. S., Mulberg, A. E., Epps, C., Pariser, A. R. and Burke, L. B. (2013) Clinical Outcome Assessments for Clinical Trials in Children, in Pediatric Drug Development: Concepts and Applications (eds A. E. Mulberg, D. Murphy, J. Dunne and L. L. Mathis), John Wiley & Sons Ltd., Chichester, UK. doi: 10.1002/9781118312087.ch42

Meeting Discussion:
The sponsor proposed an age cutoff of greater than 6 years for subjects who are able to validly and reliably self-report. The Agency responded that the sponsor should submit evidence to support the proposed age cut-off. (b) (4)

(b) (4)

Question 16:
Does the Agency agree that showing a reduction in the worst itch (WI)-NRS of ≥3 points from baseline among subjects with mild to moderate AD with a baseline WI-NRS of at least 3, is clinically meaningful?

FDA Response to Question 16:
There is insufficient evidence to support that ≥3 points reflects a within-patient meaningful score change in the WI-NRS in your target population. The threshold or range of thresholds for a within-patient meaningful score change should be derived from an anchor-based approach supplemented with both empirical cumulative distribution function and probability density function (many times estimated using kernel density estimation) curves.

We recommend that you derive the meaningful within-patient change score for WI-NRS using anchor-based methods with your Phase 2 data. Patient global assessments of disease severity or change are generally used as anchors. However, other items from clinical outcome assessments may be appropriate for use as an anchor if it measures the concept of interest in the target instrument (WI-NRS). Selected anchors should be plainly understood in context, easier to interpret than the COA itself, and sufficiently correlated to the targeted COA. We recommend that you consider using the itch verbal rating scale as an anchor, and any other applicable scales, used in your Phase 2 trials that measures improvement of itch (e.g., study MEDI-MM36-206).

Once you have generated a threshold(s) for a within-patient meaningful change score in the WI-NRS, you should carefully plan for this analysis. For this analysis to be meaningful, a sufficient proportion of subjects should be in the WI-NRS-evaluable population. Therefore, we recommend that you include an assessment of the WI-NRS at baseline and have sufficient number of subjects with a baseline minimum NRS score that is agreed upon with the Agency.

(b) (4)

Question 17:

(b) (4)

(b) (4)

FDA Response to Question 17:
Please see response to Question 16.

Meeting Discussion:

(b) (4)

(b) (4)

(b) (4) To maintain the integrity of the trials, the endpoints and the statistical strategy to control Type I error rate need to be prespecified, and that such specification should be done as early as possible. The Agency noted that analysis for determining threshold for within patient meaningful change in the WI-NRS should be done for the overall disease severity (IGA $\geq$ 2) as well as for the sub-population with mild disease only (IGA = 2). The sponsor should consider an enrollment criterion for the WI-NRS and ensure that a sufficient number of subjects meet the threshold level at enrollment.

The sponsor inquired about the process and timeframe to reach agreement on the proposed validation of the WI-NRS in children under 12 years and on the adequacy of Phase 2 data. The Agency replied that a submission(s) to the IND would be the most appropriate way to receive feedback. The Agency commented that in certain circumstances, a Meeting Request could be submitted, if appropriate.

Question 18:
Does the Agency agree to the general approach to validation of the WI-NRS for assessment of itch severity in patients with AD?

FDA Response to Question 18:
The performance of an itch NRS has been well-documented in literature in adolescents and adults. No further validation of the WI-NRS is needed in adults and pediatric patients who can validly and reliably self-report. Cognitive interviews to test the WI-NRS in children

under 12 years may be helpful to ensure these ages are able to interpret and understand how to complete the WI-NRS.

We recommend that you conduct additional analyses to determine a within-patient meaningful score change in the WI-NRS. See responses to Questions 15 and 16.

Question 19:
Does the Agency agree that the approach to validation of the WI-NRS is acceptable for adults and children ≥2 years of age with AD?

FDA Response to Question 19:
Please see responses to Questions 15 and 18.

Question 20:
Does the Agency have any comments regarding the exploratory endpoints?

FDA Response to Question 20:
You propose to evaluate 11 exploratory endpoints which include the absolute change from Baseline in individual signs and symptoms of AD, the proportion of subjects achieving EASI 75 at Days 8 and 29 and the absolute change from Baseline on the EASI score at Days 8 and 29. As exploratory endpoints were not included in the multiplicity adjustment plan to control the Type I error rate, they are considered exploratory in nature (b) (4)
(b) (4)

(b) (4)

There are some limitations with the proposed clinical outcome assessments, which are described below. (b) (4)
(b) (4)

Comments regarding the POEM:

- The POEM instructs patients to leave items blank if they do not experience a particular symptom, which makes the instrument more susceptible to missing data. Inclusion of a 'Not Applicable' response option might be more ideal to understand why the item was not completed.
- The POEM has a 7-day recall period, which may be susceptible to recall error.
- The POEM appears to use a total score combining multiple concepts (symptoms, signs and impacts), which may make it difficult to describe clinical benefit (b) (4)
(b) (4) We generally recommend measuring disease symptoms and impacts separately to the extent possible.
- The POEM includes atopic dermatitis signs (i.e., "bleeding," "oozing clear fluid," "cracking," "flaking," and "felt dry or rough" are observable signs. You may want to

consider which signs are more appropriate for clinicians to assess and exclude from this measure if possible.

- The POEM uses numerical cutoff values for the response options to assess the frequency of the concept being measured. It is unclear how these cutoffs were determined. Additionally, there is not an option for greater than 6 days (i.e., it skips from 5-6 days to everyday).
- The POEM assesses sleep quality, which may be an important concept to assess in this patient population. However, the concept of sleep disturbance may be challenging to measure as it may be affected by other external factors and not modifiable by treatment.

Comments regarding the DLQI/CDLQI:

- The DLQI/CDLQI contains questions that measure broad concepts related to general skin conditions (e.g., going shopping, making your home messy) which may lack clinical relevance and be insensitive to treatment effect among atopic dermatitis patients.
- The DLQI/CDLQI includes multi-barreled questions (questions measuring more than one concept; e.g., Questions 1-3, 5, 7, 8 and 10) which can be problematic from a measurement standpoint.
- Some of the impacts included in the DLQI/CDLQI may not be relevant for AD (e.g., going shopping, making your home messy). This instrument may need to be supplemented with another instrument to measure the impacts of AD symptoms on patients' daily life functioning in order to provide meaningful information on the clinical benefit of the product. We are open to consider any proposals the sponsor may offer.

Question 21:
Does the Agency agree that given the minimal systemic exposure following topical application of difamilast 1% ointment under maximal use conditions, Medimetriks can assess risk for suicidal behavior/ideation through systematic collection of AEs in the case report form where the event is described, and onset, duration, severity, and causality assessed by the Investigator, with conclusions regarding causality for an event being based on a comprehensive assessment and results presented descriptively rather than using the Columbia-Suicide Rating Scale (C-SSRS) to assess the potential for depression and suicidal ideation?

FDA Response to Question 21:
We do not agree. 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. We note that there is an increased

baseline risk of suicide in this treatment population[1] and the prescribing information for another PDE-4 inhibitor, roflumilast, contains a warning for psychiatric events including suicidality and depression. The fact that your product is a topical ointment does not obviate these concerns. For example, in the case of crisaborole, another topical PDE-4 inhibitor, a potential suicide-related safety signal was detected, but its evaluation was limited by lack of formal psychiatric symptom monitoring in clinical trials[2].

Depression and suicidal ideation (SI) and attempts (SA) are often missed in clinical practice and clinical trials. Suicide fatality, SA, and SI, have approximately order of magnitude successive prevalence ratios to one another; i.e., for each suicide fatality in the U.S. annually, there are over 10 non-fatal suicide attempts and over 100 instances of serious suicidal ideation[3]. Thus, the roughly equal numbers for fatal-SA, non-fatal SA, and SI in the safety data for crisaborole and for roflumilast[4], provide evidence that the clinical assessment of SA and SI (AE collection) was inadequately sensitive in those studies.

Use of validated instrument-based assessments of depression and SI/SA should improve sensitivity at baseline and accuracy of change-from-baseline assessments, which would allow more reliable estimates of any treatment-related effects. Further, the use of standardized instruments will reduce inter-clinician differences in performance of safety assessments, and thus are preferable for safety signal detection in these domains. Finally, we note that the C-SSRS assesses SI and SA, but not depression. Therefore, we recommend that you include a standardized assessment for depression, such as the PHQ-9.

Question 22:

Does the Agency agree that the nonclinical assessments (cardiovascular safety pharmacology assessment in dogs and hERG channel and action potential assessment in vitro), and the clinical assessment of QT liability in children 2 to 17 years of age with AD, administered difamilast 1% topical ointment twice daily for 14 days under maximal use conditions with the to-be-marketed formulation, is sufficient to characterize the QT liability of difamilast 1% topical ointment?

FDA Response to Question 22:

No, we do not agree. Your maximal use PK study (MEDI-MM36-206) does not have a placebo control arm and it is not clear whether the timing of ECGs was appropriate to characterize the QTc effects over the dosing interval (at Tmax and any possible delayed effects). Thus, this trial cannot be used as a substitute for a TQT study (ICH E14 Q&A (R3)) and we recommend that you conduct a TQT study as per ICH E14 guidelines.

[1] Singhal, A., J. Ross, O. Seminog, K. Hawton and M. J. Goldacre (2014). "Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage." J R Soc Med 107(5): 194-204.
[2] (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207695Orig1s000MedR.pdf)
[3] Ahrnsbrak, R., J. Bose, S. Hedden, R. Lipari and E. Park-Lee (2017). "Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health." Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration: Rockville, MD, USA.
[4] (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000SumR.pdf)

If it is not feasible to achieve higher exposures in healthy volunteers, you may consider conducting the study in adult population with atopic dermatitis.

Meeting Discussion:
The Agency requested clarification regarding the apparent missing ECG data in the response document provided by the sponsor. The sponsor clarified that the data is available but was not included in their response. The sponsor asked if they could submit this data to the Agency for review, and the Agency concurred.

When you submit your QT study report, include the following items:

a. Statistical analysis plan
b. Clinical study protocol
c. Investigator's Brochure
d. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
e. Annotated CRF
f. A data definition file which describes the contents of the electronic data sets
g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
h. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
i. Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.
j. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study

In addition, this data will inform the need for cardiac safety monitoring in the Phase 3 trials.

Question 23:
Does the Agency agree that serial electrocardiogram (ECG) monitoring, in Phase 3 studies, would not be necessary in children 2 to 17 years of age?

FDA Response to Question 23:
The data from trial MEDI-MM36-206, indicates that highest systemic exposure is expected to occur in the pediatric population (maximal individual value 116 ng/mL). Therefore, we recommend that you conduct routine cardiac safety monitoring in your pivotal Phase 3 trials (e.g. electrocardiograms at baseline, at T_{max} after the first dose, steady state and end of treatment).

Question 24:
Does the Agency agree that it would be reasonable to request a waiver from conducting a pediatric assessment with difamilast 1% topical ointment for the treatment of mild to moderate AD, in neonates and infants 0 to < 3 months of age, when the initial Pediatric Study Plan (iPSP) is submitted to the Agency within 60 days of the EOP2 meeting?

FDA Response to Question 24:
Your proposal to request a partial waiver from conduct of a pediatric assessment of difamilast ointment 1% in neonates and infants 0 to < 3 months of age appears reasonable. Provide in your initial Pediatric Study Plan a regulatory justification with a discussion based on epidemiologic data. Refer to Guidance for Industry "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans."

Question 25:
Does the Agency agree that it would be reasonable to delay the initiation of the open-label study to assess the safety, PK (sparse sampling) and pharmacodynamic response of difamilast 1% topical ointment, in infants 3 months to < 2 years of age, until after the safety and effectiveness of difamilast 1% topical ointment has been established in Phase 3 clinical studies in adults, adolescents and children ≥ 2 years of age?

FDA Response to Question 25:
In general, the appropriate timing for assessments of a proposed product in this population will depend on the safety profile/treatment effect established in other pediatric age groups and the need for additional nonclinical data to support that evaluation. See response to Question 2.

Question 26:
Does the Agency agree that a request to defer the pediatric assessment in infants 3 months to < 2 years of age, would be appropriate at the time of submission of the NDA as studies in infants may take longer to enroll?

FDA Response to Question 26:
See Responses to Question 2 and Question 25.

Additional Comments-Based on your Phase 3 Protocol Synopses

- In your Phase 3 development program, we recommend that your safety evaluation include an active assessment of local safety using an appropriate scale. We encourage

you to explore the potential for irritation and sensitization of your product under the conditions of use and propose further assessments (patch testing/photopatch testing) for subjects who experience reactions suggestive of irritation, sensitization, phototoxicity or photoallergenicity.

- The proposed treatment strategy in your safety extension trial (MEDI-MM36-303) is not entirely clear from the synopsis. However, we recommend that subjects who achieve treatment success (IGA score of ≤ 1 (clear/almost clear) with a 2-grade improvement) do not receive 2 additional months of treatment.

Additional Comments-Clinical Outcome Assessments

- Additional considerations specific to pediatric populations should be taken into account when selecting an appropriate clinical outcome assessment, including: 1) selecting a well-defined and reliable instrument(s) that is developmentally appropriate for the entire age range included in your clinical trial population; and 2) using an instrument that is content and psychometrically valid for assessment in the patient population of interest.

- You have proposed electronic data capturing for your planned studies. We recommend you perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device. We also recommend you implement a back-up plan (e.g., web- or paper-based) prior to using the devices in your clinical trials, in case of any electronic device malfunctions.

  We recommend electronic data capture using a device with a reminder or alarm function, when appropriate and feasible, as this tends to facilitate operation, minimize the extent of missing data, and allows for the collection of other important information (e.g., timestamps for data input). You may refer to the FDA guidance for industry on electronic source data.[5]

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[5] guidance for industry, *Electronic Source Data in Clinical Investigations* (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf)

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such **with SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This

meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master** File (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments

7. For changes to protocols only, also include the following information:
   - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
   - Other significant changes
   - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

2.3. Clinical Pharmacology

Question 1:

Does the agency agree that the PK data obtained in multiple Phase 1 and Phase 2 studies and proposed population PK with difamilast and its metabolites in the Phase 3 MEDI-MM36-302 study, together with the PK data on difamilast obtained from study MEDI-MM36-206 under maximal use conditions, should be sufficient to characterize the extent of systemic exposure (difamilast and metabolites MAP-15484, MAP-15497, and MAP-15485) following topical administration of difamilast 1% ointment and support product labeling?

FDA Response to Question 1:

Your proposed approach is reasonable. However, the adequacy of your data for characterizing the systemic exposure of the parent drug and metabolites under maximal use conditions and for supporting product labeling will be a review issue at the time of NDA submission. Clarify if the metabolites (MAP-15484, MAP-15497 and MAP-15485) are pharmacologically active.

Sponsor Response

Thank you for the response. Could the FDA provide the rationale for this request regarding pharmacological activity of the metabolites and the required timing for the submission of this information?

2.4. Clinical/Biostatistics

Question 6:

Does the Agency agree that the 5-point Investigator Global Assessment (IGA) Likert scale (0 [clear], 1 [almost clear], 2 [mild], 3 [moderate] and 4 [severe]), is appropriate to use as the primary efficacy measurement tool?

Table 1: Investigator's Global Assessment of AD Severity

Scale	Grade	Definition
0	Clear	Minor residual hypopigmentation/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting.
1	Almost clear	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe	Deep or bright red erythema with severe induration/papulation and with oozing/crusting

FDA Response to Question 6:

We acknowledge your intent to use the same Investigator's Global Assessment (IGA) of Atopic Dermatitis (AD) Severity scale in the Phase 3 trials as used in the Phase 2 trials for consistency and interpretability of the efficacy data. However, we prefer that the category of "Almost clear" include no induration/papulation.

Sponsor Response

The Sponsor notes the Agency's preference for a revision to the Investigator's Global Assessment of AD Severity. The IGA scale is used for the COA primary endpoint. This same scale has been used by the Sponsor in the now-completed Phase 2 study for the determination of the appropriate dose for Phase 3 studies (see Agency response line 251 for proposed dose) and is identical to the scale used for determination of efficacy of other products in this class (eg, crisaborole). The Sponsor's power calculations for Phase 3 studies are based on performance of the product using the Sponsor version of the IGA. The IGA is a static assessment scale encompassing the evaluation considering all AD affected skin.

The Agency has suggested a change to the anchor language for Grade 1, almost clear. It is important for anchor language to have clinical relevance and provide distinction from adjacent grades. The anchor language for the IGA grades address three features: skin color/pigmentation, induration/papulation and oozing/crusting. Grades 0, 1 and 2 all require the absence of skin

oozing/crusting, leaving only two features for the clinician to distinguish among the grades. In the Sponsor and FDA proposed IGA the anchor language for skin color/pigmentation is distinct for three Grades 0, 1 and 2. The Sponsor submits that it is important to retain distinct language for the induration/papulation, the only other feature for distinguishing Grade 1 from the adjacent grades.

Therefore the sponsor requests that the FDA agree that it is acceptable to maintain the Grade 1 description as: "Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting". Does the Agency agree?

2.4. Clinical/Biostatistics

Question 11:

Does the Agency agree that an appropriate method of analysis of the primary efficacy endpoint would be testing using a logistic regression model with treatment group and analysis center as factors?

FDA Response to Question 11:

Your proposal appears reasonable. For detailed comments, submit your Phase 3 protocols that include full details of your model.

Sponsor Response

We appreciate the Agency's response and agree that reviews of the Phase 3 protocols will be valuable. Could the Agency comment on the expected process and timeframe for comments to the Phase 3 protocols following submission to the IND?

2.4. Clinical/Biostatistics

Question 13:

Does the Agency agree with the sequential approach to control for multiplicity and with the acceptability of the key secondary endpoints?

FDA Response to Question 13:

Secondary endpoints (b) (4) should be clinically meaningful, limited in number and controlled for multiplicity. Your proposal to sequentially test your single primary and three secondary endpoints will control for multiplicity.

Your proposed secondary endpoints include "time to success on the 5-point IGA of AD Severity scale" and "time to achieving a ≥3-point change from Baseline on the Pruritus WI- NRS". For these time-to-event endpoints, you will need to provide data to support that the thresholds are clinically meaningful and not just statistically significant. See response to Question 16.

Sponsor Response

Sponsor would like additional discussion as to the Agency's position on the clinical meaningfulness of the proposed secondary endpoints. Please note that the time to success on the 5-point IGA of AD Severity scale' refers to a success threshold which has already been agreed to be clinically meaningful (success as defined in the primary objective). Therefore, please clarify whether additional data is required to support the clinical meaningfulness of the secondary endpoint of time to success (based on change in the IGA scale).

It is understood that the clinical meaningfulness of a 3-point or greater change in Pruritus WI-NRS threshold will require supportive clinical data.

2.4. Clinical/Biostatistics

Question 15:
Does the Agency have any other comments regarding the secondary endpoints?

FDA Response to Question 15:
See response to Question 13 and comments below.

In principle, a single 11-point numeric rating scale (NRS), such as the WI-NRS, is acceptable to assess itch severity at its worst in patients with AD who are able to self-report. We recommend that you ascertain which patients are developmentally able to validly and reliably self-report among this population and provide justification for this subgroup. We further recommend that you clearly specify who the reporter will be for the planned assessments (e.g., WI-NRS and observer-reported measure) for the respective ages in your clinical trial protocol based on how you define patients who are eligible to self-report.

An observer-reported outcome (ObsRO) assessment will be necessary for children who cannot validly or reliably self-report. An observer is limited to the assessment of observable signs, events, or behaviors that can be reported from the perspective of a parent or caregiver. Because itch intensity is a symptom that can only be experienced and reported by the patients themselves, we do not agree with the proposal for parents/caregivers to assess itch intensity for children who cannot self-report.

To assess clinical benefit of your product for children who cannot validly and reliably self-report, we recommend that you select an existing fit-for-purpose ObsRO instrument (or develop a new instrument if one does not exist) that measures observable signs, behaviors (e.g., attempted scratching or rubbing), and/or verbalizations made by the child related to itch with a recall over the past 24 hours. Review literature and/or conduct qualitative interviews with parents/caregivers to determine what they can report and observe regarding their child's itch experience.

There should be two separate endpoints for different types of COAs (i.e., a PRO endpoint and an ObsRO endpoint) because combining the findings of these different measures into one endpoint across the population makes it difficult to interpret the combined data as they are assessing different concepts (symptoms vs. behaviors).

You may refer to the following references for additional information for measurement in pediatric populations:

(1) Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, Bullinger M. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health. 2013 Jun;16(4):461-79.

(2) Papadopoulos, E. J., Patrick, D. L., Tassinari, M. S., Mulberg, A. E., Epps, C., Pariser, A. R. and Burke, L. B. (2013) Clinical Outcome Assessments for Clinical Trials in Children, in Pediatric Drug Development: Concepts and Applications (eds A. E. Mulberg, D. Murphy, J.

Dunne and L. L. Mathis), John Wiley & Sons Ltd., Chichester, UK. doi: 10.1002/9781118312087.ch42

Sponsor Response

Based on the Agency's comments regarding ObsRo assessments, the sponsor proposes to assess the secondary itch assessments only in patients who are developmentally able to validly and reliably self-report, and therefore an observer-reported outcome (ObsRO) assessment will not be utilized. Does the Agency agree with this approach?

2.4. Clinical/Biostatistics

Question 16:

Does the Agency agree that showing a reduction in the worst itch (WI)-NRS of ≥3 points from baseline among subjects with mild to moderate AD with a baseline WI-NRS of at least 3, is clinically meaningful?

FDA Response to Question 16:

There is insufficient evidence to support that ≥3 points reflects a within-patient meaningful score change in the WI-NRS in your target population. The threshold or range of thresholds for a within-patient meaningful score change should be derived from an anchor-based approach supplemented with both empirical cumulative distribution function and probability density function (many times estimated using kernel density estimation) curves.

We recommend that you derive the meaningful within-patient change score for WI-NRS using anchor-based methods with your Phase 2 data. Patient global assessments of disease severity or change are generally used as anchors. However, other items from clinical outcome assessments may be appropriate for use as an anchor if it measures the concept of interest in the target instrument (WI-NRS). Selected anchors should be plainly understood in context, easier to interpret than the COA itself, and sufficiently correlated to the targeted COA. We recommend that you consider using the itch verbal rating scale as an anchor, and any other applicable scales, used in your Phase 2 trials that measures improvement of itch (e.g., study MEDI-MM36-206).

Once you have generated a threshold(s) for a within-patient meaningful change score in the WI-NRS, you should carefully plan for this analysis. For this analysis to be meaningful, sufficient proportion of subjects should be in the WI-NRS-evaluable population. Therefore, we recommend that you include an assessment of the WI-NRS at baseline and have sufficient number of subjects with a baseline minimum NRS score that is agreed upon with the Agency.

(b) (4)

Question 17:

(b) (4)

FDA Response to Question 17:

Please see response to Question 16.

Sponsor Response to Questions 16 and 17

Sponsor agrees with the approach suggested by the Agency to ascertain clinical meaningfulness of a 3-point or greater change in Pruritus WI-NRS using anchor-based methods with the Phase 2 data. Once the data is available for submission, could the Agency clarify the process and timeframe to reach agreement on the adequacy of this data for its intended purposes?

2.4. Clinical/Biostatistics

Question 18:

Does the Agency agree to the general approach to validation of the WI-NRS for assessment of itch severity in patients with AD?

FDA Response to Question 18:

The performance of an itch NRS has been well-documented in literature in adolescents and adults. No further validation of the WI-NRS is needed in adults and pediatric patients who can validly and reliably self-report. Cognitive interviews to test the WI-NRS in children under 12 years may be helpful to ensure these ages are able to interpret and understand how to complete the WI-NRS.

We recommend that you conduct additional analyses to determine a within-patient meaningful score change in the WI-NRS. See responses to Questions 15 and 16.

Question 19:

Does the Agency agree that the approach to validation of the WI-NRS is acceptable for adults and children ≥2 years of age with AD?

FDA Response to Question 19:

Please see responses to Questions 15 and 18.

Sponsor Response – Questions 18-19

Sponsor agrees in principle with the approach to validate the WI-NRS as suggested by the Agency for the under 12 years age group, to ensure these ages are able to interpret and understand how to complete the WI-NRS. Could the Agency clarify the process and timeframe to reach agreement on the proposed validation of the WI-NRS in children under 12 years?

2.4. Clinical/Biostatistics

Question 22:

Does the Agency agree that the nonclinical assessments (cardiovascular safety pharmacology assessment in dogs and hERG channel and action potential assessment in vitro), and the clinical assessment of QT liability in children 2 to 17 years of age with AD, administered difamilast 1% topical ointment twice daily for 14 days under maximal use conditions with the to-be-marketed formulation, is sufficient to characterize the QT liability of difamilast 1% topical ointment?

FDA Response to Question 22:

No, we do not agree. Your maximal use PK study (MEDI-MM36-206) does not have a placebo control arm and it is not clear whether the timing of ECGs was appropriate to characterize the QTc effects over the dosing interval (at Tmax and any possible delayed effects). Thus, this trial cannot be used as a substitute for a TQT study (ICH E14 Q&A (R3)) and we recommend that you conduct a TQT study as per ICH E14 guidelines.

If it is not feasible to achieve higher exposures in healthy volunteers, you may consider conducting the study in adult population with atopic dermatitis.

Sponsor Response

As part of the safety evaluation of difamilast, non-clinical and clinical cardiac safety assessments have been performed to characterize the potential for QTc prolongation and pro-arrhythmic activity *in vitro* and *in vivo* (Cardiac Safety Analysis Report; Report No. MM36-CS320, submitted in SN0100 on 11SEP2018 with the EOP2 Briefing Package). To date, these assessments have included 1) hERG binding studies in vitro, 2) the effect of difamilast on action potential duration in isolated guinea-pig papillary muscles ex vivo 3) in vivo telemetry (ECG) assessments in conscious dogs and 4) clinical ECG assessments in healthy adult volunteers and adult/pediatric AD patients following topical administration, including subjects enrolled in a Maximal Use (MUSE) PK study and adults with AD in Phase 1 and Phase 2 safety and PK studies.

Medimetriks acknowledges the Agency's comment that Study MEDI-MM36-206 is not sufficient to use as a substitute for a TQT study as described in ICH E14 Q&A (R3). You have recommended that a TQT be conducted per ICH E14 guidelines. Topical application (intended route of administration) of difamilast 1% topical Ointment, to healthy volunteers would not achieve supratherapeutic levels as intake skin exhibits low permeability to topically applied drugs.

It was suggested that a study could be conducted in adults with atopic dermatitis (AD).

Medimetriks has conducted a single and multiple ascending dose study (271-12-204; previously reported to the Agency under SN0031 on June 23, 2014 and further described in the Cardiac Safety Analysis Report (Report No. MM36-CS320) submitted in SN0100 on 11SEP2018 with the EOP2 Briefing Package), in which patients with AD were exposure to 0.3%, 1%, and 3%

difamilast or vehicle control (applied BID to 5% of BSA for 28 consecutive days) and exposed to 1% and 3% (applied BID to at least 10% of BSA for 28 consecutive days) in part 2 of the study.

On Day 1 and Day 28, blood samples for determination of difamilast and metabolites concentrations were collected prior to the first of the BID doses and at 2, 3, 4, 8, and 12 hours after the first of the BID doses. On Day 2 and Day 29, blood samples for PK analysis were collected approximately 24 hours after the first BID dose administered on the previous day (Day 1 or Day 28, respectively). On Day 14, a single trough (pre-dose) blood sample was collected. In Part 2, blood samples for determination of difamilast and metabolites concentrations were collected On Day 1 and Day 28, prior to the first of the BID doses and at 2, 4, and 8 hours after the first of the BID doses (refer to Table 1). Electrocardiograms were collected at screening, Day 1 pre-dose and at 2 and 4 hours post-dose prior to the PK sample collection (approximate Cmax), and Day 28 pre-dose. Twelve-lead ECGs were recorded with the subject supine and at rest for at least 10 minutes. Heart rate, PR interval, RR interval, QRS duration, QT interval, corrected QT interval (QTc), and any machine-read abnormalities in ECG results were recorded. Screening ECG data was captured in the electronic CRF; all other ECG data was captured electronically by the central ECG laboratory (refer to Table 2).

Results from this study showed no clinically significant ECG abnormalities noted in this study. Incidences of categorical changes in ECG evaluations were reported for 3 subjects:

- Subject (b) (6) (3% treatment group) had a change from baseline to Week 4 of an increase of the QTcB interval between 30 msec and 60 msec.
- Subject (b) (6) 5 (3% treatment group) had a change from baseline to Week 4 of an increase of the QTcB interval between 30 msec and 60 msec.
- Subject (b) (6) (3% treatment group) had changes from baseline to Week 4 of increases of the QTcB and QTcF intervals between 30 msec and 60 msec

One subject (Subject (b) (6)) in the 3% treatment group, had an increase in QTcF of 26 msec on Day 1 at 2 hours postdose (refer to Table 2), although the QT interval remained within the normal range. The corresponding plasma concentration was not sufficient (NS) at 2 hours, 15.8 ng/mL at 3 hours, 1.43 ng/mL at 4 hours and 3.33 at 8 hours post-dose.

Table 1 Pharmacokinetic Parameters from Study 271-12-204

Table 5.2-3 Mean (SD) Pharmacokinetic Parameters of OPA-15406 after Twice Daily Topical Administration of OPA-15406 Ointment (0.3%, 1%, and 3% [weight to weight]) to Adult Subjects with Atopic Dermatitis - Trial 271-12-204

		OPA-15406 Cohort								
		0.3%			1%			3%		
Part	Day	C_{max} (ng/mL)	$AUC_{0\text{-}12h}$ (ng·h/mL)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}12h}$[a] (ng·h/mL)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}12h}$[a] (ng·h/mL)	T_{max} (h)
1	1	0.686 (0.799)	9.4 (7.59)	4.04 (0.145)	2.15 (2.65)	14.0 (10.3)	6.10 (2.72)	3.83 (4.78)	22.5 (21.2)	7.27 (3.65)
	28	0.624 (0.453)	6.77 (4.91)	4.38 (3.97)	3.69 (3.51)	23.2 (15.8)	2.80 (2.86)	5.75 (7.47)	42.4 (36.3)	4.82 (4.54)
2	1	Not applicable			30.9 (33.7)	121 (142)	4.97 (2.43)	8.14 (5.96)	36.1 (28.0)	5.73 (2.48)
	28	Not applicable			12.9 (15.1)	73.5 (90.0)	5.94 (2.75)	22.3 (25.2)	115 (104)	5.75 (2.59)
2[b]	1	Not applicable			5.26 (6.20)	17.9 (14.6)	4.97 (2.43)	1.56 (0.878)	7.65 (4.10)	5.73 (2.48)
	28	Not applicable			2.14 (1.90)	11.2 (9.94)	5.94 (2.75)	4.71 (6.39)	23.1 (25.3)	5.75 (2.59)

$AUC_{0\text{-}12h}$ = area under the concentration-time curve from time 0 to 12 hours postdose; SD = standard deviation.

[a]For Part 2, this is $AUC_{0\text{-}8h}$ (area under the concentration-time curve from time 0 to 8 hours postdose).

[b]The values here are for C_{max}_N and $AUC_{0\text{-}8h}$_N, which represent C_{max} and $AUC_{0\text{-}8h}$ normalized by the amount of OPA-15406 ointment administered.

Source: OPA-15406 Investigator's Brochure Edition 7

Table 2 QTcF Findings for Protocol ECG 271-12-204

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	TREATMENT GROUP	VISIT	HOUR	ORIGINAL VALUE N[2]	MEAN	MED	SD	MIN	MAX	CHANGE FROM BASELINE n[3]	BASELINE MEAN	MEAN	MED	SD	MIN	MAX
QTC INTERVAL, FRIDERICIA (MSEC)	VEHICLE	BASELINE[1]		14	401.4	400.5	19.4	362.0	439.0							
		DAY 1	2 H POST-DOSE	1	404.0	404.0		404.0	404.0	1	409.0	-5.0	-5.0		-5.0	-5.0
		DAY 1	4 H POST-DOSE	1	414.0	414.0		414.0	414.0	1	409.0	5.0	5.0		5.0	5.0
		WEEK 1		1	407.0	407.0		407.0	407.0	0						
		WEEK 4		15	404.1	405.0	19.2	379.0	454.0	14	401.4	1.1	2.0	11.3	-15.0	17.0
		LAST VISIT[1]		14	402.6	403.0	18.9	379.0	454.0	14	401.4	1.1	2.0	11.3	-15.0	17.0
	OPA-15406 0.3%	BASELINE[1]		13	415.5	418.0	21.1	379.0	440.0							
		WEEK 1		2	409.5	409.5	31.8	387.0	432.0	0						
		WEEK 4		15	416.2	421.0	24.8	381.0	456.0	13	415.5	2.9	2.0	6.3	-4.0	16.0
		LAST VISIT[1]		13	418.4	421.0	24.9	381.0	456.0	13	415.5	2.9	2.0	6.3	-4.0	16.0
	OPA-15406 1%	BASELINE[1]		20	407.9	402.5	22.2	373.0	444.0							
		DAY 1	2 H POST-DOSE	4	383.8	388.5	18.9	359.0	399.0	4	389.5	-5.8	3.5	20.2	-36.0	6.0
		DAY 1	4 H POST-DOSE	3	383.7	382.0	18.6	366.0	403.0	3	388.3	-4.7	6.0	21.1	-29.0	9.0
QTC INTERVAL, FRIDERICIA (MSEC)	OPA-15406 1%	WEEK 1		3	395.0	390.0	10.4	388.0	407.0	1	418.0	-11.0	-11.0		-11.0	-11.0
		WEEK 4		21	405.4	405.0	18.6	372.0	435.0	19	408.7	-2.0	-1.0	13.6	-29.0	26.0
		LAST VISIT[1]		20	406.3	405.5	18.7	372.0	435.0	20	407.9	-1.7	-1.0	13.3	-29.0	26.0
	OPA-15406 3%	BASELINE[1]		23	406.1	414.0	21.3	365.0	448.0							
		DAY 1	2 H POST-DOSE	1	411.0	411.0		411.0	411.0	1	385.0	26.0	26.0		26.0	26.0
		DAY 1	4 H POST-DOSE	1	397.0	397.0		397.0	397.0	1	385.0	12.0	12.0		12.0	12.0
		WEEK 1		4	415.0	415.5	13.3	402.0	427.0	4	415.0	0.0	1.0	8.2	-9.0	7.0
		WEEK 4		22	406.3	406.5	18.9	360.0	442.0	22	405.4	1.0	1.5	14.7	-27.0	30.0
		LAST VISIT[1]		22	406.3	406.5	18.9	360.0	442.0	22	405.4	1.0	1.5	14.7	-27.0	30.0

[1]BASELINE = LAST PRE-DOSE EVALUATION; LAST VISIT = LAST SCHEDULED POST-BASELINE EVALUATION INCLUDING EARLY TERMINATION EVALUATION.
[2]N = TOTAL NUMBER OF SUBJECTS WITH AT LEAST ONE OBSERVATION OF THE GIVEN PARAMETER.
[3]n = TOTAL NUMBER OF SUBJECTS WITH BOTH BASELINE AND AT LEAST ONE OBSERVATION OF THE GIVEN PARAMETER.

		VEHICLE			OPA-15406 0.3%			OPA-15406 1%			OPA-15406 3%		
CLASSIFICATION	CATEGORY[1]	N[2]	n[3]	(%)	N[2]	n[3]	(%)	N[2]	n[3]	(%)	N[2]	n[3]	(%)
QTcF	NEW ONSET (>= 450 MSEC) IN MALE	14	0	(0.0)	13	0	(0.0)	20	0	(0.0)	22	0	(0.0)
	NEW ONSET (>= 470 MSEC) IN FEMALE	14	0	(0.0)	13	0	(0.0)	20	0	(0.0)	22	0	(0.0)
	NEW ONSET (>= 450 MSEC) AND >= 10% INCREASE	14	0	(0.0)	13	0	(0.0)	20	0	(0.0)	22	0	(0.0)
	INCREASE 30 - 60 MSEC	14	0	(0.0)	13	0	(0.0)	20	0	(0.0)	22	1	(4.5)
	INCREASE > 60 MSEC	14	0	(0.0)	13	0	(0.0)	20	0	(0.0)	22	0	(0.0)

[1]CRITERIA FOR CATEGORICAL CHANGES IN ECG EVALUATIONS ARE DEFINED IN CT-12.4.
[2]N IS THE TOTAL NUMBER OF SUBJECTS WITH AT LEAST ONE POST-BASELINE NUMERIC RESULT FOR THE GIVEN ECG PARAMETER.
[3]n IS THE NUMBER OF SUBJECTS WITH ECG ABNORMALITY.

The Sponsor would like to discuss with the Agency whether this Phase 1 dose ranging vehicle controlled study of difamilast dosed at concentrations ranging from 0.3% up to 3% BID for 28 days data would be sufficient to for assessing potential risks of QT prolongation (TQT study) in adults with AD, as ICH E14 Q&A (R3), advocates that concentration-response analysis, in which all available data across all doses used to characterize the potential for a drug to influence QTc is an important component of the totality of evidence assessment of the risk of QT prolongation.

2.4. Clinical/Biostatistics

Question 23: Does the Agency agree that serial electrocardiogram (ECG) monitoring, in Phase 3 studies, would not be necessary in children 2 to 17 years of age?

FDA Response to Question 23: The data from trial MEDI-MM36-206, indicates that highest systemic exposure is expected to occur in the pediatric population (maximal individual value 116 ng/mL). Therefore, we recommend that you conduct routine cardiac safety monitoring in your pivotal Phase 3 trials.

Sponsor Response

In study MEDI -MM36-206, blood samples were collected for PK evaluation of difamilast on Days 1 and 15 prior to application of study drug (0 hours) and at 1 hour, 4 hours, and 8 hours post-application of study drug. Over the course of the maximal use treatment period

(Days 1-15), low absorption levels were detected, with a lower mean C_{max} observed at Day 15 relative to Day 1 (16.9 and 23.1 ng/mL, respectively). The median t_{max} occurred at 4 hours post application on both Day 1 and Day 15. Overall, there was no evidence of accumulation (AUC_t = 107 and 86.2 ng•hr/mL at Days 1 and 15, respectively) (refer to Table 3).

Subject (b) (6) was a 15 year-old male (62 kg) with moderate AD (IGA 3) with 26% BSA area involvement at baseline. The subject was enrolled in MEDI-MM36-206 and treated with difamilast 1% topical Ointment 1% twice daily for 28 days. On Day 1 the difamilast plasma concentration was 55 ng/mL at 1 hour post application, 79.5 ng/mL at 4 hours post application and 15.4 ng/mL at 8 hours post application. On Day 15 the difamilast plasma concentration at1 hour post application was 0.9 ng/mL, 116 ng/mL at 4 hours post application and 12.6 ng/mL at 8 hours post application of 3.96 grams of 1% difamilast ointment. Through Day 15 the subject received 31 applications with total dose of 119.6 grams. The IGA remained a 3 through Day 15 as well. There were no AE reported for this subject. It is unclear why this subject had appreciably higher plasma concentrations at 4 hours post application compared to other subjects enrolled in this study or the adult studies.

Table 3 Pharmacokinetic Parameters from Study MEDI-MM36-206

Table 14.3.0.1.1: Summary of Plasma Concentrations
(Safety Population with PK Data)
(Page 1 of 4)

	MM36 1% (N=31)			
	Day 1			
	Pre-Dose	1 Hour Post-Dose	4 Hours Post-Dose	8 Hours Post-Dose
MM36 Concentration (ng/mL)				
n	31	31	31	30
n_{quant}	0	30	31	30
Mean	0.00	14.1	17.8	12.1
SD	0.00	21.6	16.8	11.7
CV%		154	94.7	97.1
Median	0.00	3.94	12.1	9.43
Min. to Max.	0.00 to 0.00	0.00 to 76.8	1.61 to 79.5	1.67 to 59.2
	Day 15			
	Pre-Dose	1 Hour Post-Dose	4 Hours Post-Dose	8 Hours Post-Dose
MM36 Concentration (ng/mL)				
n	29	29	29	29
n_{quant}	29	29	29	29
Mean	5.16	7.77	15.9	9.45
SD	3.53	5.38	22.1	8.10
CV%	68.5	69.2	139	85.7
Median	4.06	5.98	8.28	6.06
Min. to Max.	0.369 to 15.5	0.938 to 24.1	2.07 to 116	1.94 to 31.6

Note: n_{quant} = Number of subjects with quantifiable levels of the analyte detected
Lower Limit of Quantitation = 0.2 ng/mL
Plasma concentrations below the lower limit of quantification are included as 0 ng/mL in summary statistic computations.

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Table 4 QTcF Findings for Protocol MEDI-MM36-206

	MM36 1% (N=31)		
	Baseline	Day 15	Day 29
QTcF Duration (msec)			
n	31	30	28
Mean	390.14	388.42	386.85
SD	19.306	18.927	17.880
Median	390.00	385.83	388.67
Min. to Max.	349.0 to 426.3	357.0 to 435.0	350.7 to 423.3
Change from Baseline			
n		30	28
Mean		-1.72	-3.58
SD		13.724	13.563
Median		-4.33	-3.83
Min. to Max.		-24.3 to 36.0	-30.7 to 31.7

Although the mean C_{max} in pediatrics is higher than the mean C_{max} observed in adults with AD, there is still a safety margin > 190 fold above the maximum free plasma concentrations triggering hERG activity.

Therefore the Sponsor would like to discuss further the approach to cardiac safety monitoring in Phase 3.

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/

KENDALL A MARCUS
11/14/2018