STATISTICAL ANALYSIS PLAN

Protocol Number: MEDI-MM36-206

Study Title: A Phase 2 Multi-center, Open-label Study to Assess Pharmacokinetic Parameters and Safety of Topical MM36 (1%) in Pediatric Subjects 2 to < 18 Years of Age with Atopic Dermatitis Under Maximal Use Conditions

Development Phase of Study: 2

Sponsor: Medimetriks Pharmaceuticals, Inc.
Sponsor Contact: Personal Data

Statistical Analysis Plan based on Protocol Version: Amended Protocol 1 20 January 2017

Statistical Analysis Plan Date: May 18, 2017
Statistical Analysis Plan Version: Draft v1

Authored by:

Personal Data

Reviewed by:

Personal Data

Approved by:

Personal Data

Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment with the exception of minor editorial changes, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
AE(s)	Adverse event(s)
ATC	Anatomical therapeutic chemical
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from time zero to the time of last quantifiable plasma concentration
BLQ	Below the limit of quantitation
BSA	Body surface area
C_{max}	Maximum plasma concentration
CV	Coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GM	Geometric mean
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
Max	Maximum
Min	Minimum
n	Number of observations
n_{quant}	Number of quantifiable concentrations
N	Number of subjects (sample size)
PDE	Phosphodiesterase
PK	Pharmacokinetic
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE(s)	Serious adverse event(s)
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SD	Standard deviation
TCIs	Topical calcineurin inhibitors
TEAE(s)	Treatment-emergent adverse event(s)
T_{max}	Time of maximum plasma concentration

WHO-DDE World Health Organization Drug Dictionary

2. INTRODUCTION

MM36 (also known as OPC-271 and OPA-15406) is a novel nonsteroidal phosphodiesterase type 4 (PDE4) inhibitor which selectively inhibits the synthesis of the intracellular second messengers that activate inflammation.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to assess the degree of systemic exposure (active parent compound and metabolites) following 4 weeks of twice daily dosing with MM36 1%, applied topically under maximal-use conditions; ≥ 35% Body Surface Area [BSA] involvement (excluding scalp and venous access areas) in subjects 2 to less than 12 years of age, and ≥ 25%

(excluding scalp and venous access areas) in subjects at least 12 years of age to < 18 years of age with atopic dermatitis.

3.2 Secondary Objectives

The secondary objective of this study is to assess the safety profile of MM36 1% applied topically twice daily for up to 4 weeks in pediatric subjects 2 to < 18 years of age, with atopic dermatitis.

3.3 Exploratory Objectives

This study will also explore the Investigator- and subject-assessed efficacy profile of MM36 1%, applied topically twice daily for up to 4 weeks in pediatric subjects 2 to < 18 years of age, with atopic dermatitis.

4. STUDY DESIGN

4.1 Overall Study Design

This multicenter, open-label study, will evaluate the pharmacokinetics, safety, tolerability, and the exploratory efficacy of MM36 1% ointment when applied twice daily for up to 4 weeks in subjects 2 to < 18 years of age with atopic dermatitis, at the upper range of disease severity. This study will also evaluate the systemic availability of MM36 1% when applied topically under maximal use conditions.

Approximately 45 subjects will be registered for an estimated 32 completed subjects. Following screening (within 30 days prior to the first dose of study drug) and confirmation of study qualification, subjects will be registered and assigned (Day 1) to one of three groups based on the subject's age at Screening. The first dose of study drug will be applied in the study clinic (Day 1) and blood samples will be collected for evaluation of pharmacokinetics (PK) prior to the first application (0 hours) and at 1 hour (± 15 minutes), 4 hours (± 30 minutes) and at 8 hours (± 1 hour) after application of study drug. On Day 15, the study drug will again be applied in the study clinic, and blood samples will be collected for PK prior to dosing and at 1 hour (± 15 minutes), 4 hours (± 30 minutes) and at 8 hours (± 1 hour) after application of study drug.

At Screening and Baseline (Day 1), subjects with atopic dermatitis that are 2 to less than 12 years of age (Group 2 and 3) must have a treatable area comprising ≥ 35% BSA involvement

(excluding scalp and venous access areas), and subjects 12 years of age and older (Group 1) must have ≥ 25% BSA involvement (excluding scalp and venous access areas) (i.e., maximal use conditions). The same (or greater, BSA if area involved expands) amount of study drug topically applied at baseline will continue to be applied twice daily, to the same area where study drug was applied on Day 1, even if the % BSA improves over the course of the first 2 weeks (14 days) of treatment. Between Day 15 (after the maximal use application and collection of PK samples) and Day 28, the study drug will only be applied to the involved areas. The last application of study drug will be given the evening before the final visit (Day 29).

The maximum individual study participation is approximately 60 days (screening (Day -30) through final Day 29 (± 1 day) Visit).

4.1.1 Schedule of Visits and Assessments

The schedule of assessments can be found in Section 1 of the protocol.

4.1.2 Method of Assigning Subjects to Treatment Groups

This is a non-randomized one-arm study with subjects split into three groups based on the subject's age at Screening. Group 1 will consist of approximately 16 subjects who are 12 to < 18 years of age. Subjects in Group 1 must have ≥25% BSA involvement. Groups 2 and 3 will each contain approximately 8 subjects, and subjects must have ≥35% BSA involvement. Group 2 will consist of subjects 6 to < 12 years of age and Group 3 will have subjects 2 to < 6 years of age.

Following screening and confirmation of study qualification, subjects will be registered and assigned a kit of study drug. Five labeled tubes will be assembled into a subject box. Each box will be labeled with a single panel label and tamper sealed. Five labeled subject boxes will be assembled into block kits. Each kit will be labeled with a 2-part tear away label and tamper sealed. At Visit 2/Baseline, Visit 3/Week 1, Visit 4/Week 2 and Visit 5/Week 3, subjects will be dispensed tubes of study drug from the assigned kit.

4.1.3 Blinding

Not applicable.

4.2 Determination of Sample Size

The sample size is not driven by inferential statistics. A sample size of 32 subjects is set for qualitative investigation of the pharmacokinetic profile as well as the safety and tolerability and responsiveness (efficacy) of MM36 1% when applied topically twice daily for 4 weeks to pediatric subjects 2 to < 18 years of age.

5. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

There are no changes in the conduct of the study or planned analyses.

6. PHARMACOKINETIC, EFFICACY AND SAFETY ENDPOINTS

6.1 Pharmacokinetic Endpoints

6.1.1 Primary Pharmacokinetic Endpoint

Determination of plasma concentrations, of the parent compound MM36 and its metabolites, after the first topical application of MM36 and after two weeks of twice daily application (steady state).

6.2 Efficacy Endpoints

6.2.1 Primary Efficacy Endpoints

There are no primary efficacy endpoints.

6.2.2 Secondary Efficacy Endpoints

There are no secondary efficacy endpoints.

6.2.3 Additional Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

6.3 Safety Endpoints

6.3.1 Primary Safety Endpoint

There are no primary safety endpoints.

6.3.2 Secondary Safety Endpoints

The secondary safety endpoints are as follows:

- Incidence and severity of application site adverse events (AEs);
- Incidence and severity of all AEs and their relationship to study drug;
- Incidence of clinically meaningful change from baseline in safety laboratory parameters, 12-lead electrocardiograms (ECG), and vital signs;

- Proportion of subjects who discontinue treatment due to an adverse event.

7. STATISTICAL METHODS AND ANALYSIS

7.1 General Methodology

All analyses will be performed by Confidential The standard operating procedures of Confidential will be followed in the creation and quality control of all data displays and analyses.

Efficacy analyses will be performed for the intent-to-treat (ITT) population and safety and PK analyses will be performed using the safety population.

All analyses will be performed using SAS® Version 9.3 or later. Continuous data will be summarized using descriptive statistics (number of values [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]). Additional summary statistics, coefficient of variation (CV%) and geometric mean (GM), will be included for PK data summaries. PK concentration summaries will include CV%, and PK parameter summaries will include both CV% and GM. Categorical data will be summarized using frequency tables (frequencies and percents).

Reported AEs, medical history terms, and prior and concomitant procedures and therapies will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology, Version 19.1. Prior and concomitant medications and skin care products will be classified on the basis of World Health Organization Drug Dictionary (WHO-DDE) terminology, Format B2, Version March 1, 2016.

Data collected at a time point will be summarized regardless of treatment with study drug. Post-treatment assessments for subjects who discontinue treatment but continued to be followed in the study will be included in summaries.

7.2 Adjustments for Covariates

Not applicable to this study.

7.3 Handling of Dropouts or Missing Data

Unless otherwise specified, missing data will not be imputed for analyses.

7.4 Interim Analyses and Data Monitoring

An independent Data Safety Monitoring Board (DSMB) will facilitate the management and identification of potential safety concerns, on a regular basis, that could affect the safety of trial subjects, and will examine whether the information collected during these periodic intervals is consistent with knowledge about the product's safety (e.g., unanticipated adverse events). The

DSMB will also assess whether revisions to the study protocol and/or consent are required, and will evaluate the overall progress of the study.

The DSMB will consist of 3 voting members, and the first DSMB data review meeting will be scheduled after at least 50% or 16 enrolled subjects in the study. Ad hoc meetings may be requested by any member of the DSMB or any other involved party, if deemed necessary. Following each DSMB meeting (planned or ad hoc), the DSMB will make recommendations regarding study continuation, modification or termination based on the observed adverse effects of the treatment under study. Details regarding the policies and procedures of the DSMB and intervals and data to be evaluated will be described in the DSMB Charter.

A pre-specified interim analysis will not be conducted.

7.5 Multicenter Studies

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each study site.

7.6 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

7.7 Examination of Subgroups

Corporate Confidential Information adverse events will be summarized by age group (subjects 2-5 years old and subjects 6-17 years old).

7.8 Analysis Populations

7.8.1 Intent-to-Treat (ITT) Population

All enrolled subjects who took at least one dose of study drug will be included in the ITT population. All efficacy analyses will be presented using the ITT population.

7.8.2 Safety Population

All subjects in the ITT population who have at least one post-baseline safety assessment will be included in the safety population. All safety analyses will be performed using the safety population.

7.9 Statistical Analysis

7.9.1 Baseline Definition

Baseline is defined as the last non-missing assessment prior to first dose of study drug.

7.9.2 Visit Windowing

Data will be summarized based on nominal visit indications with the exception of data captured at early termination and unscheduled visits. Data from early termination and unscheduled visits will be summarized based on mapped visit values. The analysis windows for early termination and unscheduled visits are presented in the following table.

Analysis Windows for Efficacy and Safety Assessments

Scheduled Visit	Target Study Day	Window (Days)
Day 8	8	5 to 11
Day 15	15	12 to 18
Day 22	22	19 to 25
Day 29	29	26 to 32

Data collected at early termination and unscheduled visits prior to study day 5 will not be analyzed, with the exception of those identified as baseline values. Data collected at early termination and unscheduled visits after study day 32 will not be included in analyses.

The definition for the study day included in each study window is defined as below:

Study Day Prior to Day 1 = Visit Date – Day 1 Date

Study Day On or After Day 1 = Visit Date – Day 1 Date + 1

If an assessment's mapped visit is a visit at which the subject has data present, or if no analyses are planned for the assessment at the mapped visit, the data collected at the early termination or unscheduled visit will not be included in analyses.

In the event of multiple values from unscheduled or early termination assessments within an analysis window, the value closest to the scheduled visit target study day will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected.

Data collected at all visits will be included in the data listings.

7.9.3 Subject Disposition

The number of subjects included in each analysis population (ITT and safety), as well as the number of subjects in the safety population with PK data will be summarized. The number of subjects treated, completed, discontinued treatment (including the reason for treatment discontinuation), and discontinued study (including the primary reason for study discontinuation) will be presented.

Subjects who are excluded from an analysis population will be summarized by the reasons for exclusion.

7.9.4 Protocol Deviations

Protocol deviations will not be entered into the database and therefore will not be summarized.

7.9.5 Demographic and Baseline Characteristics

All baseline summaries will be done on the ITT and safety populations.

Sex, race, ethnicity, Fitzpatrick skin type, dietary habits, and alcohol, tobacco and drug use will be summarized by counts and percentages. Age, height, and weight will be summarized with descriptive statistics (n, mean, SD, median, min, and max).

Atopic dermatitis history, including family history of atopic dermatitis, location of disease, and diagnoses of allergic rhinitis and asthma, will be summarized by counts and percentages.

Medical histories will be coded using the MedDRA dictionary and will be summarized by MedDRA system organ class and preferred term.

7.9.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to preferred term and anatomical therapeutic chemical (ATC) classification of ingredients using the WHO-DDE.

Counts and percentages will be provided to summarize the use of medications other than the study drug reported throughout the study. The number and percent of subjects reporting medications will be summarized by ATC level 2 term and preferred name. Medications which start prior to first dose will be considered prior medications, and medications which start on or after first dose will be considered concomitant medications. Medications with incomplete start dates which could be prior to first dose or after first dose will be considered concomitant.

Skin care products used during the study and prior and concomitant procedures and therapies will be included in by-subject listings.

7.9.7 Pharmacokinetic Analyses

The pharmacokinetic analysis will be conducted using non-compartmental analysis on plasma concentrations of MM36 and its metabolites (MAP-15484, MAP15497 and MAP-15485) in the subjects in the safety population who have PK data.

Individual plasma concentrations of MM36 and its metabolites will be summarized descriptively at Day 1 and Day 15 using the arithmetic mean, SD, CV%, median, min, and max. Individual plasma concentration-time profiles of MM36 and its metabolites will be plotted on both a linear and a semi-logarithmic scale at each visit. Mean values will also be presented graphically.

Plasma concentrations below the lower limit of quantitation (BLQ) (< 0.2 ng/mL) will not be considered quantifiable concentrations. BLQ values and quantifiable concentrations will be

summarized separately using summary statistics. Any quantifiable concentrations at pre-dose at Day 1 will be set to zero in both concentration summaries, as well as in PK parameter calculations. Plasma concentration-time profiles will display BLQ values as 0 ng/mL on the linear scale, and will omit BLQ values on the semi-logarithmic scale.

The following pharmacokinetic parameters will be analyzed for each subject at Day 1 and Day 15 if there are a sufficient number of quantifiable concentrations of MM36 or its metabolites to permit their derivation.

C_{max}	Maximum plasma concentration C_{max} = BLQ if concentrations are BLQ at all time points
T_{max}	Time of maximum plasma concentration T_{max} will be calculated if at least one quantifiable plasma concentration is detected in the time interval. Individual elapsed sampling times will be used. If the maximum concentration is observed pre-dose, T_{max} will be considered 0 hours.
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the time of last quantifiable plasma concentration $AUC_{0\text{-last}}$ will be calculated if at least two consecutive quantifiable plasma concentrations are detected in the time interval. Area will be computed using the linear trapezoidal rule with individual elapsed sampling times and observed concentratinos. BLQ values will be set to zero before T_{max} and missing after T_{max}.

Descriptive summary statistics (n, arithmetic mean, SD, CV%, median, min, max, and GM) will be reported for PK parameters. Individual plasma concentrations and PK parameter values will be included in by-subject listings.

7.9.8 Efficacy Analyses

7.9.8.1 Primary Efficacy Analysis

There is no primary efficacy analysis.

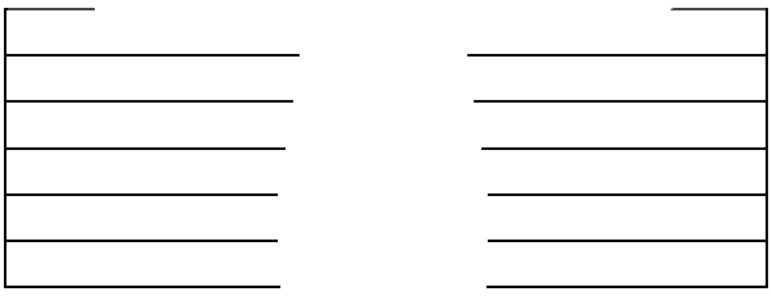
7.9.8.2 Secondary Efficacy Analysis

There is no secondary efficacy analysis.

7.9.8.3 Exploratory Efficacy Analyses

Corporate Confidential Information

7.9.8.3.4.2 Corporate Confidential Information



7.9.9 Safety Analyses

7.9.9.1 Extent of Exposure

The extent of exposure to study drug will be summarized by total number of days of exposure, total number of applications, percent compliance, and total amount of study drug applied. Total number of applications will be determined by the number of entries in the dosing diary. Total number of days of exposure will be computed as follows:

Days of Exposure = Date of Last Application – Date of First Application + 1.

To compute percent compliance, total number of expected applications will be calculated by:

Expected applications = 2*(Study Completion/Discontinuation Date – Date of First Application).

If the total number of expected applications exceeds 58 then it will be set to 58. Percent compliance will be calculated from total number of applications and total number of expected applications as follows:

Percent Compliance = 100*(Total Applications/Expected Applications).

Percent compliance will not be calculated for subjects who are lost to follow-up.

7.9.9.2 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first study drug application. Treatment-emergent AEs will be summarized by system organ class and preferred term and further by severity and relationship to study drug. When summarizing AEs by severity and relationship, each subject will be counted once within a system organ class

or preferred term by using the event with the highest severity and strongest relationship within each classification.

Serious AEs (SAEs) will be summarized by system organ class, preferred term, severity, and relationship to study drug. Application site AEs and any TEAEs reported by ≥ 5% of subjects will be summarized by system organ class and preferred term. Adverse events leading to treatment or study discontinuation will be summarized by system organ class and preferred term.

Listings will be presented for all adverse events as well as for serious adverse events, and adverse events leading to discontinuation from the study.

7.9.9.3 Clinical Laboratory Evalutions

Laboratory test results will be summarized with descriptive statistics at Baseline and Day 29. Additionally, change from baseline values will be summarized at Day 29, and shifts from Baseline to Day 29 in laboratory test results based on normal ranges will be summarized with frequency counts and percentages. Individual laboratory test results, including urine and serum pregnancy test results, will be presented in a by-subject listing.

7.9.9.4 Other Observations Related to Safety

7.9.9.4.1 ECG Measurements

ECGs will be performed in triplicate at Screening, Day 1, Day 15 and Day 29, and the following parameters will be measured for each ECG: heart rate, RR duration, QRS duration, PR duration, QT duration, QT interval corrected for heart rate using Bazett's formula (QTcB), and QT interval corrected for heart rate using Fridericia's formula (QTcF). For each parameter and each visit, the mean of all measurements collected at the visit will be calculated, so each subject will have one value associated with each ECG parameter at each visit.

Descriptive statistics at Baseline, Day 15, and Day 29 will be provided for each ECG parameter. Change from baseline values will be summarized at Day 15 and Day 29.

Individual ECG measurements, as well as means of triplicates, will be presented in a by-subject listing.

7.9.9.4.2 Vital Signs

Temperature, respiratory rate, heart rate, blood pressure, and weight will be summarized at each visit, and change from baseline values will be presented for post-baseline visits. Weight will be summarized at Baseline, Day 15, and Day 29, and all other vital signs will be summarized at Baseline, Day 8, Day 15, Day 22, and Day 29.

Heart rate and blood pressure measurements are collected in triplicate at each visit. Prior to computing summary statistics, the mean of each measurement will be calculated for each subject

at each visit. Summary statistics will be computed from each subject's mean heart rate and blood pressure values at each visit.

Individual vital sign data, as well as means of heart rate and blood pressure triplicates, will be presented in a by-subject listing.

7.9.9.4.3 Physical Examination

Physical examination data will be presented in a by-subject listing.

8. REFERENCES