PROTOCOL MEDI-MM36-206: 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

Compound:	MM36
US IND Number:	112973
Clinical Protocol Number:	MEDI-MM36-206
Phase:	2
Original Protocol Date:	19August 2016
Sponsor:	Medimetriks Pharmaceuticals, Inc. 383 Route 46 West Fairfield, NJ 07004-2402
Medical Monitor:	Personal Data
Clinical Monitoring and Study Management:	Confidential
Serious Adverse Event Reporting:	Confidential
Summary of Incorporated Protocol Amendments:	Amendment No. 1 — Version Date 30 January 2017

GCP Statement

This study will be conducted in accordance with the Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) guidelines on current Good Clinical Practice (GCP), in accordance with the Declaration of Helsinki, and Good Laboratory Practice (GLP) guidelines.

SPONSOR SIGNATURE PAGE

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the clinical trial and complies with applicable regulations and Good Clinical Practice (GCP) standards.

Personal Data

Note: The date of the last signature is the assigned version date of this protocol.

AGREEMENT OF INVESTIGATOR COMPLIANCE

I have read the protocol entitled "MEDI-MM36-206: 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" and

- Agree that Protocol MEDI-MM36-206 contains all of the information necessary to conduct the study;
- Agree to conduct the study in accordance with the protocol and as subsequently amended by the Sponsor (or designee), except when to protect the safety, rights or welfare of study subjects;
- Agree to conduct the study in accordance with applicable federal, state and local laws and regulations, and in accordance with Good Clinical Practice (GCP) and the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, updated October 2013; and
- Agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator	**Site ID**
_____	_____
Print Name	
_____	_____
Signature	Date

ABBREVIATIONS

Abbreviations	Definitions
AD	Atopic Dermatitis
AE	Adverse Event
Ag	Antigen
ALT	Alanine Amino Transferase
AST	Aspartate Transaminase
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to time last (time of last quantifiable plasma concentration) [$AUC_{0\text{-t}}$]
BLQ	Below the limit of quantitation
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
cAMP	cyclic adenosine 3',5'-monophosphate
CBC	Complete blood count
CBP	Childbearing potential
CDC	Center for Disease Control
CK	Creatinine kinase
CLIA	Clinical Laboratory Improvement Act
C_{max}	Maximum plasma concentration
CRF	Case report form
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	US Food & Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HCT	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HPLC−MS/MS	High performance liquid chromatographic method with tandem mass spectrometric detection
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent to treat
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

ABBREVIATIONS

Abbreviations	Definitions
N	Number of observations
NCA	Non-Compartmental Analysis
PDE	Phosphodiesterase
PI	Principal investigator
PK	Pharmacokinetic
POC	Proof of concept
RBC	Red blood cells
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMP	Safety Management Plan
TCI	Topical calcineurin inhibitors
TEAE	Treatment emergent adverse event
T_{max}	Time of maximum plasma concentration
ULN	Upper limit of normal
UV	Ultraviolet
US	United States
WBC	White blood cells
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

PROTOCOL SYNOPSIS

Study Title	Protocol MEDI-MM36-206: 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
Study Number	MEDI-MM36-206
Study Objectives	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 in subjects 2 to less than 12 years of age (excluding scalp and venous access areas), and ≥ 25% in subjects at least 12 years of age to < 18 years of age with atopic dermatitis (excluding scalp and venous access areas). Secondary Objective: 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. Exploratory Objective: Corporate Confidential Information
Study Endpoints	Primary 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). Secondary Endpoints • 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, ECG, and vital signs; • Proportion of subjects who discontinue treatment due to an adverse event. Exploratory Endpoints Corporate Confidential Information

	Corporate Confidential Information

	Corporate Confidential Information
Study Population	Subjects enrolled in this study will be males and females, 2 to < 18 years of age, with a diagnosis of atopic dermatitis, based upon the American Academy of Dermatology atopic dermatitis diagnostic recommendations (2014). Subjects that are 2 to less than 12 years of age will have atopic dermatitis that involves ≥ 35% BSA (excluding scalp and venous access areas). Subjects that are at least 12 years but less than 18 years of age will have ≥ 25% BSA involvement (excluding scalp and venous access areas).
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. Following screening (within 30 days prior to the first application of study drug) and confirmation of study qualification, subjects will be registered and assigned (V2) to one of three treatment groups based on the subject's age at Screening (V1). The first dose of study drug will be applied in the study clinic (V2/Day 1) and blood samples will be collected for pharmacokinetic (PK) evaluation (plasma concentration of MM36) prior to the first application (0 hours) and at 1 hour (± 15 minutes), 4 hours (± 30 minutes) and at 8 hours (± 1 hour) post application. 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) post application. Corporate Confidential Information At Screening (V1) and Baseline (V2), subjects with atopic dermatitis that are 2 to less than 12 years of age must have a treatable area comprising ≥ 35% BSA involvement (excluding scalp and venous access areas), and subjects 12 years of age and older 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 (V6). 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. Details regarding the policies and procedures of the DSMB and intervals and data to be evaluated will be described in the DSMB Charter.
Description of Test Article, Dosage, and Administration	MM36 1% Ointment for topical administration is a white petrolatum based ointment containing MM36 1% weight/weight (w/w), Corporate Confidential Information . Each gram of MM361 % w/w ointment contains 10 mg of active MM36. All subjects will receive active study drug and the dosage will be based on % BSA involvement (intended area to be treated). The study drug will be applied twice daily (approximately 12 hours apart) for up to 4 weeks (28 days).
Study Centers	Up to 12 investigational sites in the United States (U.S.) , Honduras, and Panama will participate.
Main Inclusion Criteria	For a study subject to be evaluated for study participation: 1. Written Informed Consent (including HIPAA) will be obtained prior to the conduct of any study related procedures from the Parent(s)/Legal Guardian(s) to permit participation of a minor in a clinical research study in accordance with federal and local laws. Additionally, assent from a minor child will be obtained in accordance with federal and local laws as well as in compliance with the recommendations of the approving Institutional Review Board (IRB)/Ethics Committee (EC) (Refer to Section 6.1). Study subjects will be eligible for inclusion in the study if they meet all of the following criteria at screening and up to the time of enrollment as applicable: 2. Have a diagnosis of atopic dermatitis, based upon the American Academy of Dermatology atopic dermatitis diagnostic recommendations (2014) (refer to Section 6.5.2). 3. Have atopic dermatitis that involves ≥ 35% BSA (excluding scalp and venous access areas) if 2 to less than 12 years of age or ≥ 25% (excluding scalp and venous access areas) if subject is at least 12 years of age as assessed the by the hand method (one back-of-hand of the subject [palms and fingers] equivalent to 1% of a subject's BSA; refer to Section 6.10) and as confirmed by the Investigator at the Screening visit (V1) and prior to the first dose of study drug (V2). 4. Are male or female between 2 and <18 years of age at the time of Screening visit (V1; when consent for study participation is given). 5. Be in generally good health based on Investigator's assessment (other than AD), with no clinically significant laboratory abnormalities, co-morbidities or psychiatric conditions which, in the opinion of the Investigator, would place the subject at increased risk or would confound the objectives of the study. 6. The Parent(s)/Legal guardian(s) and study subject are willing and able to follow all study-related procedures, including but not limited to application of study drug and pharmacokinetic

	(PK) sampling, and be willing and able to return to the study clinic for study visits. 7. If female of childbearing potential (CBP), must be willing to take a take a pregnancy test at screening and prior to the first dose and the results must be negative. For purposes of this study, a female subject is considered of CBP if she is ≥ 12 years old or has reached menarche, whichever occurred first. Females must either practice abstinence from heterosexual contact or use one of the approved contraceptive options described in the protocol (refer to Section 6.25) from the time of the Screening visit (V1) and for 7 days after the last study visit (V6). Or If male, of reproductive potential, must be willing to practice effective contraception during the study (while receiving study drug from V2 and for 7 days after the last study visit (V6). The Investigator will educate the subject regarding abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy. 8. Willingness to refrain from the use of tanning beds, sunlamps and artificial tanning products, and be willing to avoid excessive unprotected exposure to natural sunlight from Screening (V1) through the end of the study period (V6). Use of topical sunscreen will be permitted providing it has been used consistently (i.e., > 28 days) by the subject and does not contain any prohibited medications/ingredients. 9. Have a baseline Investigator Global Assessment (IGA) score of ≥ 2 (mild) prior to the first dose of study drug (V2).
Main Exclusion Criteria	A study subject will be excluded from the study if they meet any of the following criteria at Screening or Baseline (V2): 1. Have a known allergy or intolerance (hypersensitivity) to the study drug (MM36 or OPA-15406) or any of its components. 2. Pregnant or planning to become pregnant during the study or breastfeeding. 3. Subjects with known difficulty undergoing venipuncture or poor venous access. 4. Subjects with active or acute viral skin infection (e.g., herpes simplex, herpes zoster, chicken pox), and/or clinically infected AD. 5. Subjects with a suspected and/or diagnosed malignancy (including skin) or who have a history of malignancy. 6. Subjects with a history of recurrent bacterial infection, defined as at least 3 major infections resulting in hospitalization and/or requiring intravenous antibiotic treatment within 12 months prior to Screening (V1). 7. Investigator assessed, clinically significant history or physical findings of: cardiac (e.g., rheumatic fever or heart valve replacement), dermatologic (e.g., skin conditions with a skin barrier defect such as but not limited to, Netherton's syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease), endocrinologic (e.g., severe or uncontrolled diabetes), pulmonary, neurologic, psychiatric, hepatic (e.g., HBsAg, anti HCV), renal, hematologic, immunologic/immunocompromised (e.g., lymphoma, acquired immune deficiency syndrome, Wiskott-Aldrich Syndrome, current or prior hepatitis or acquired immunodeficiency syndrome or known carriers of HIV antibodies), or other major disease (e.g., systemic fungal infection) or other severe uncontrolled conditions (e.g., drug or alcohol abuse), that are significant and/or that may pose a health risk to the subject in the study or may have an impact on the study assessments. 8. Clinically significant findings on 12-lead electrocardiogram (ECG) such as, but not limited to, AV

block, or evidence of prolongation of the QRS complex based on gender and age in subjects where an adequate quality ECG could be obtained.

9. Any abnormal laboratory parameter which in the opinion of the Investigator would place the subject's health at risk for participation. An abnormal test may be repeated once to confirm study eligibility if there is a satisfactory reason to suggest that the initial elevation was either spurious or due to an acute intermittent, now resolved illness (e.g. elevated WBC due to an acute infection).
10. Clinically significant liver dysfunction defined as one or both of the following at Screening (V1). An abnormal test may be repeated once to confirm study eligibility.
    a. Aspartate aminotransferase (AST) > 1.5 x ULN
    b. Alanine aminotransferase (ALT) > 1.5 x ULN
11. Use of the following restricted medications or therapies **prior to** (as specified) and throughout the study period (V6/Day 29):
    a. Within 60 days Prior to Baseline (V2/Day):
        i. Use of a topical or oral PDE4 Inhibitor (i.e. crisaborole) or scheduled use during the study period; or
        ii. Use of any investigational systemic or topical medication or scheduled use during the study period.
    b. Within 28 days Prior to Baseline (V2/Day 1):
        i. Use of systemic immunosuppressive/immunomodulator medication, corticosteroids, antimetabolite medication, or retinoid medication, or scheduled use during the study period. Intra-ocular, intra-nasal, and inhaled corticosteroids may be considered if, in the opinion of the investigator, their use will not impact the assessment of the selected treatment area;
        ii. Phototherapy (ultraviolet light A, narrowband ultraviolet B, and ultraviolet light B); or
        iii. Use of new sunscreen or sunscreen with excluded ingredients, or use during the study period.
    c. Within 14 days Prior to Baseline (V2/Day 1): Use of topical immunomodulators, topical corticosteroids (with exception of 1% hydrocortisone as described in Exclusion 11e) or scheduled use during the study period.
    d. Within 7 days Prior to Baseline (V2/Day 1):
        i. Topical antihistamines;
        ii. Sedating antihistamines, or scheduled use during the study period;
        iii. Non-sedating antihistamines. If stable use within 2 weeks of the study, continued use will be allowed as a concomitant medication and should be continued during the study; or
        iv. Use of topical retinoids, or scheduled use during the study period.
    e. Within 3 days Prior to Baseline (V2/Day 1): Use of topical 1% hydrocortisone, or scheduled use during the study period.
    f. Within 24 Hours Prior to Baseline (V2/Day 1): Use of other prescription or non-prescription non-study topical emollients, occlusive agents, humectants, wet-wraps, coal tar, or bleach baths or scheduled use during the study period.
12. Participation in any other interventional clinical study or trial within 60 days of the Baseline (V2/Day 1) visit, or scheduled participation in another interventional clinical study during the study period.

	13. Children or relatives of the Sponsor, CRO, or the Study Site personnel are excluded from participating in the study.
Statistical Analysis	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. Analysis Population Two populations will be used for analysis: safety and intent-to-treat. The definition of these populations follows: • Safety Population: All enrolled subjects who received at least one dose of study medication and have at least one post-baseline safety assessment constitute the Safety Population. • Intent-to-Treat (ITT) Population: All enrolled subjects who took at least one dose of study medication constitute the Intent-to-Treat Population. PK and safety data will be analyzed based on the safety population. Efficacy data will be analyzed based on the ITT population. Primary and Secondary Analysis Pharmacokinetics Individual plasma concentrations of MM36 and its metabolites (MAP-15484, MAP15497 and MAP-15485) will be summarized descriptively using the arithmetic mean, standard deviation (SD), CV (%), median, minimum and maximum. Individual plasma concentration-time profiles of MM36 will be plotted on both a linear and a semi-logarithmic scale. Mean values will also be presented graphically. The following pharmacokinetic parameters will be analyzed for each subject and for each PK time point at which a sufficient (detectable) concentration of MM36 or its metabolites will be measured to permit their derivation. If there are sufficient concentration data above the level of quantification the following pharmacokinetic parameters will be calculated: • C_{max} = Maximum plasma concentration; • T_{max} = Time of maximum plasma concentration; • AUC0-last = Area under the plasma concentration-time curve from time zero to time last (time of last quantifiable plasma concentration) [AUC0-t]. Safety Safety evaluations will consist of adverse events (AEs), application site reactions, physical examinations, vital signs, ECGs, weight, and laboratory measurements (hematology, chemistry, and urinalysis). Full details will be specified in the SAP. Exploratory Corporate Confidential Information
Study Duration	The maximum individual study participation is approximately 60 days (screening (Day -30) through final Day 29 (± 1 day) Visit).

1 SCHEDULE OF ACTIVITIES

Week/Description	Screening	Week 0	Week 1	Week 2	Week 3	Week 4
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6/ET**
Study Day	**-30 to -2**	**Day 1**	**Day 8 (±1)**	**Day 15 (±1)**	**Day 22 (±1)**	**Day 29 (±1)**
Consent/Assent *Refer to Section 6.1*	X					
Inclusion/Exclusion Criteria *Refer to Sections 5.1and 5.2*	X	X[a]				
Demographics *Refer to Section 6.2*	X					
Height/Weight/BMI and Body Surface Area (BSA) Calculation *Refer to Sections 6.6 and 6.7*	X	X[a,j]		X[a,j]		X[j]
Medical History (General, Surgical, Social and Medications) *Refer to Sections 6.3.1and 6.3.3*	X					
Targeted Medical History – Atopic Dermatitis *Refer to Section 6.3.2*	X					
Physical Examination *Refer to Section 6.4*	X	X[a]	X[c]	X[c]	X[c]	X
Fitzpatrick Skin Type Assessment Refer to Section 6.5	X					
BSA% Involvement *Refer to Section 6.8*	X	X[a]	X[a]	X[a]	X[a]	X
Corporate Confidential Information						
Photography (as applicable) *Refer to Section 6.19*		X[a]	X[a]	X[a]	X[a]	X
Vital Signs *Refer to Section 6.21*	X	X[a]	X[a]	X[a]	X[a]	X

Week/Description	Screening	Week 0	Week 1	Week 2	Week 3	Week 4
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6/ET**
Study Day	**-30 to -2**	**Day 1**	**Day 8 (±1)**	**Day 15 (±1)**	**Day 22 (±1)**	**Day 29 (±1)**
12 Lead Electrocardiogram *Refer to Section 6.22*	X	X		X		X
Safety Laboratory Testing (Hematology, Chemistry and UA) *Refer to Section 6.23.4.2*	X	X[k]				X[k]
Pregnancy Testing – Females of Childbearing Potential only *Refer to Section 6.23.4.1*	X[f]	X[a,b]				X[b]
Pharmacokinetic Sampling Refer to Section 6.23.5		X[g]		X[g]		
Corporate Confidential Information						
Registration *Refer to Section 4.3*		X[a]				
Dispensing Study Drug *Refer to Section 8.3*		X[a]	X	X	X	
Training Subject/Parent/guardian (caregiver) (instructions) and Observation of Dose Application *Refer to Section 8.4*		X[a]	X	X	X	
Dosing and Diary Completion *Refer to Section 8.4*		X----------	----------	----------	----------	----------X[e]
Compliance *Refer to Section 8.5*			X[a]	X[a]	X[a]	X
Concomitant Medications *Refer to Section 6.24*		X[a]	X[a]	X[a]	X[a]	X
Adverse Events and Serious Adverse Events *Refer to Section 0*	X	X	X	X	X	X
Application Site Assessments *Refer to Section 6.18*			X[a]	X[a]	X[a]	X

a Prior to dosing
b For females of childbearing potential, urine pregnancy test will be done locally
c Abbreviated examination of the skin and other areas with previous abnormal findings
d Ongoing adverse events will be followed at 1 to 2 week intervals (unscheduled visit) until resolution or until the event has resolved or improved/stabilized and in the opinion of the Investigator, no longer needs to be followed.
e The last dose of study drug will be applied the evening before this visit
f Serum pregnancy test for females of childbearing potential
g Assessed at 0 hour (pre-dose), 1 hour (± 15 minutes), 4 hours (± 30 minutes), and 8 hours (± 1 hour) after application of the study drug in the study clinic.
h Corporate Confidential Information
i Assessment prior to each application of study drug (approximately every 12 hours) during the first week of dosing
j Weight only
k CBC and chemistry panel only
l Corporate Confidential Information

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2 INTRODUCTION

2.1 Background Information

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

2.2 Rationale

Currently, the pathogenesis of AD is unknown; however, Hanifin et al reported increased PDE activity and decreased intracellular cAMP levels in peripheral blood leukocytes of subjects with AD, which has been associated with higher production of proinflammatory mediators (Hanifin et al., 1985). Cooper et al reported the inhibition of immunoglobulin E synthesis with the PDE inhibitor, Ro 20-1724, in a study using the peripheral blood mononuclear cells of subjects with AD (Cooper et al., 1985). These studies have shown that PDE inhibitors exert an anti-inflammatory action by increasing the intracellular cAMP concentration, inhibiting the production of cytokines and chemical mediators, and inhibiting cellular activity. Due to these effects, PDE inhibitors, particularly Type-4, are thought to be useful for the treatment of allergic inflammatory diseases.

Phosphodiesterases (PDEs) are cyclic nucleotide-degrading enzymes associated with the conversion of cyclic adenosine 3',5'-monophosphate (cAMP) to 5'-adenylic acid. Type-4 phosphodiesterase (PDE4) is widely expressed in a variety of inflammatory cells. PDE4 activity promotes a pro-inflammatory response and increased PDE activity has been associated with increased cytokine production and an abnormally elevated immune response.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 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.

3.1.2 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.

3.2 Exploratory Objectives

3.3 Criteria for Evaluation

3.3.1 Primary Endpoints

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).

3.3.2 Secondary Endpoints

- 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, ECG, and vital signs;
- Proportion of subjects who discontinue treatment due to an adverse event.

3.3.3 Exploratory Endpoints

4 STUDY DESIGN

4.1 General Description

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.

Following screening (within 30 days prior to the first dose of study drug) and confirmation of study qualification, subjects will be registered and assigned (V2) to one of three treatment groups based on the subject's age at Screening (V1). The first dose of study drug will be applied in the study clinic (V2/Day 1) and blood samples will be collected for evaluation of 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 (V1) and Baseline (V2), 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 (V6). Refer to Figure 1.

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. Details regarding the policies and procedures of the DSMB and intervals and data to be evaluated will be described in the DSMB Charter.

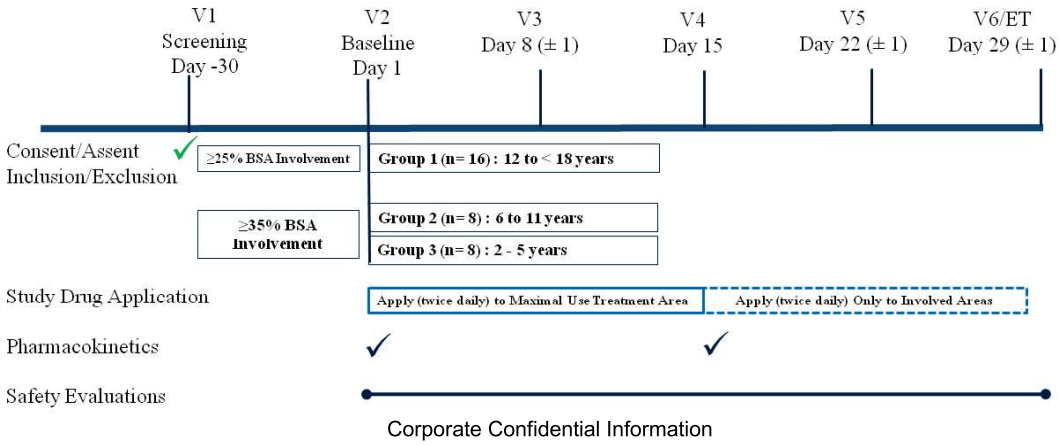

Figure 1 Study Schematic

4.2 Enrollment

A subject is considered enrolled in the study when the subject's parent(s)/legal guardian(s) has provided written informed consent and the child/adolescent has provided assent (as applicable).

4.3 Registration

Following verification that the subject meets all inclusion criteria and none of the exclusion criteria (V1), the subject will be scheduled for Visit 2 (Day 1). A subject who continues to meet all inclusion and no exclusion criteria will be registered, and study drug will be dispensed.

4.4 Screen Failure

A subject who has been enrolled but subsequently fails to meet enrollment criteria prior to receipt of study drug will be deemed a screen failure.

4.5 Completion

Each subject will participate in the study up to a maximum of 8 weeks, from the time the informed consent form (ICF) is signed/assent provided (V1) through the final visit (V6/Week 4). A subject is considered to have completed the study after he/she has completed V6/Day 29.

4.6 Early Termination (ET)

A subject or the subject's parent/legal guardian may withdraw the subject from treatment or from the study at any time at their request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

4.6.1 Criteria for Premature Discontinuation

4.6.1.1 Discontinuation from Treatment

A subject must be permanently discontinued from the study drug for any of the following reasons:

- The subject becomes pregnant;
- Allergic or adverse reaction to the study drug;
- Clinically significant adverse event, which in the opinion of the Investigator, or DSMB, would put the subject at unnecessary risk if dosing was continued; or
- The subject's atopic dermatitis worsens and requires alternative or supplemental medication during the study.

If a subject is discontinued from treatment, they should continue to be followed in the study. If subject refuses to stay in the study, then they will be encouraged to complete the V6 (Week 4/ET visit).

4.6.1.2 Discontinuation from Study

A subject must be discontinued from the study drug and from the study for the following reason:

- The subject withdraws consent. From the time consent is withdrawn, no additional data should be collected. However, the Sponsor may retain and continue to use data collected before such withdrawal of consent.

A subject may be discontinued from the study drug or from the study for the following reason:

- The subject requests withdrawal from the study. For the safety of the subject, if withdrawal is requested, the subject should be encouraged to complete the Week 4/ET study procedures.

4.6.1.3 Lost to Follow-up

A subject is considered to have been lost to follow-up if he/she [subject or parent/legal guardian] cannot be contacted by the Investigator (or designee). The Investigator (or designee) will document efforts to attempt to reach the subject twice by telephone and will send a certified letter before considering the subject lost to follow-up. The end of participation for a subject lost to follow-up is documented as the delivery date of the certified letter.

4.6.1.4 Subject Replacement

Subjects who prematurely discontinue and do not have at least three samples collected on either Day 1 or Day 15 post study drug application, may be replaced. The Sponsor may also

replace subjects who prematurely discontinue at their discretion or at the recommendation of the Data Safety Monitoring Board (DSMB).

4.7 Safety Oversight

4.7.1 Data Safety Monitoring Board (DSMB)

An independent DSMB will be assembled and will facilitate the management and identification of potential safety concerns. 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. Details regarding the DSMB will be further described in the study specific DSMB Charter.

4.7.2 Investigator

The Principal Investigator must have access and be available to promptly review the results of all safety assessments (i.e., clinical laboratory testing), electrocardiogram (ECG) results, vital signs and adverse events (AEs) including application site assessment information throughout the study. Safety assessments must be promptly (should be within 48 hours of notification of event) entered into the Electronic Data Capture (EDC) system. Clinical laboratory data will be evaluated by the Principal Investigator and clinical relevance will be assessed for abnormal values and the assessment will be documented on the laboratory report. A copy of the reports will be maintained as part of the source documentation.

5 STUDY SUBJECT SELECTION

5.1 Inclusion Criteria

For a study subject to be evaluated for study participation:

1. Written Informed Consent (including HIPAA) will be obtained (prior to the conduct of any study related procedures) from the Parent(s)/Legal Guardian(s) to permit participation of a minor in a clinical research study in accordance with federal and local laws. Additionally, assent from a minor child will be obtained in accordance with federal and local laws as well as in compliance with the recommendations of the approving Institutional Review Board (IRB/Ethics Committee (EC) (Refer to Section 6.1).

Study subjects will be eligible for inclusion in the study if they meet all of the following criteria at screening and up to the time of enrollment as applicable:

2. Have a diagnosis of atopic dermatitis, based upon the American Academy of Dermatology atopic dermatitis diagnostic recommendations (2014) (refer to Section 6.3.2).

3. Have atopic dermatitis that involves ≥ 35% BSA (excluding scalp and venous access areas) if 2 to less than 12 years of age or ≥ 25% (excluding scalp and venous access areas) if subject is at least 12 years of age as assessed the by the hand method (one back-of-hand of the subject [palms and fingers] equivalent to 1% of a subject's BSA; refer to Section 6.8) and as confirmed by the Investigator at the Screening visit (V1) and prior to the first dose of study drug (V2).

4. Are male or female between 2 and <18 years of age at the time of Screening visit (V1; when consent for study participation is given).

5. Be in generally good health based on Investigator's assessment (other than AD), with no clinically significant laboratory abnormalities, co-morbidities or psychiatric conditions which, in the opinion of the Investigator, would place the subject at increased risk or would confound the objectives of the study.

6. The Parent(s)/Legal guardian(s) and study subject are willing and able to follow all study-related procedures, including but not limited to application of study drug and pharmacokinetic (PK) sampling, and be willing and able to return to the study clinic for study visits.

7. If female of childbearing potential (CBP), must be willing to take a take a pregnancy test at screening and prior to the first dose and the results must be negative. For purposes of this study, a female subject is considered of CBP if she is ≥ 12 years old or has reached menarche, whichever occurred first. Females must either practice abstinence from heterosexual contact or use one of the approved contraceptive options described in the protocol (refer to Section 6.25) from the time of the Screening visit (V1) and for 7 days after the last study visit (V6).

Or

If male, of reproductive potential, must be willing to practice effective contraception during the study (while receiving study drug from V2 and for 7 days after the last study visit (V6).

The Investigator will educate the subject regarding abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

8. Willingness to refrain from the use of tanning beds, sunlamps and artificial tanning products and willing to avoid excessive unprotected exposure to natural sunlight from Screening (V1) through the end of the study period (V6). Use of topical sunscreen will be permitted providing it has been used consistently (i.e., > 28 days) by the subject and does not contain any prohibited medications/ingredients.

9. Have a baseline Investigator Global Assessment (IGA) score of ≥ 2 (mild) prior to the first dose of study drug (V2).

5.2 Exclusion Criteria

Study subjects will be excluded from the study if they meet any of the following criteria at screening and up to the time of enrollment as applicable:

1. Have a known allergy or intolerance (hypersensitivity) to the study drug (MM36 or OPA-15406) or any of its components.

2. Pregnant or planning to become pregnant during the study or breastfeeding.

3. Subjects with known difficulty undergoing venipuncture or poor venous access.

4. Subjects with active or acute viral skin infection (e.g., herpes simplex, herpes zoster, chicken pox), and/or clinically infected AD.

5. Subjects with a suspected and/or diagnosed malignancy (including skin) or who have a history of malignancy.

6. Subjects with a history of recurrent bacterial infection, defined as at least 3 major infections resulting in hospitalization and/or requiring intravenous antibiotic treatment within 12 months prior to Screening (V1).

7. Investigator assessed, clinically significant history or physical findings of: cardiac (e.g., rheumatic fever or heart valve replacement), dermatologic (e.g., skin conditions with a skin barrier defect such as but not limited to, Netherton's syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease), endocrinologic (e.g., severe or uncontrolled diabetes), pulmonary, neurologic, psychiatric, hepatic (e.g., HBsAg, anti HCV), renal, hematologic, immunologic/ immunocompromised (e.g., lymphoma, acquired immune deficiency syndrome,

Wiskott-Aldrich Syndrome, current or prior hepatitis or acquired immunodeficiency syndrome or known carriers of HIV antibodies), or other major disease (e.g., systemic fungal infection) or other severe uncontrolled conditions (e.g., drug or alcohol abuse), that are significant and/or that may pose a health risk to the subject in the study or may have an impact on the study assessments.

8. Clinically significant findings on 12-lead electrocardiogram (ECG) such as, but not limited to, AV block, or evidence of prolongation of the QRS complex based on gender and age in subjects where an adequate quality ECG could be obtained (i.e., ≥ 4 years of age).

9. Any abnormal laboratory parameter which in the opinion of the Investigator would place the subject's health at risk for participation. An abnormal test may be repeated once to confirm study eligibility.

10. Clinically significant liver dysfunction defined as one or both of the following at Screening (V1). An abnormal test may be repeated once to confirm study eligibility.

    a. Aspartate aminotransferase (AST) > 1.5 x ULN

    b. Alanine aminotransferase (ALT) > 1.5 x ULN

11. Use of the following restricted medications or therapies **prior to** (as specified) and throughout the study period (V6/Day 29):

    a. <u>Within 60 days Prior to Baseline (V2/Day 1)</u>:

        i. Use of a topical or oral PDE4 Inhibitor (i.e. crisaborole) or scheduled use during the study period.

        ii. Use of any investigational systemic or topical medication or scheduled use during the study period.

    b. <u>Within 28 days Prior to Baseline (V2/Day 1)</u>:

        i. Use of systemic immunosuppressive/immunomodulator medication, corticosteroids, antimetabolite medication, or retinoid medication, or scheduled use during the study period. Intra-ocular, intra-nasal, and inhaled corticosteroids may be considered if, in the opinion of the investigator, their use will not impact the assessment of the selected treatment area;

        ii. Phototherapy (ultraviolet light A, narrowband ultraviolet B, and ultraviolet light B);

        iii. Use of new sunscreen or sunscreen with excluded ingredients or use during the study period;

c. Within 14 days Prior to Baseline (V2/Day 1): Use of topical immunomodulators, topical corticosteroids (with exception of 1% hydrocortisone as described in Exclusion 10e) or scheduled use during the study period.

d. Within 7 days Prior to Baseline (V2/Day 1):

   i. Topical antihistamines;

   ii. Sedating antihistamines, or scheduled use during the study period;

   iii. Non-sedating antihistamines with stable use within 2 weeks of the study are allowed as a concomitant medication;

   iv. Use of topical retinoids, or scheduled use during the study period.

e. Within 3 days Prior to Baseline (V2/Day 1): Use of topical 1% hydrocortisone, or scheduled use during the study period.

f. Within 24 Hours Prior to Baseline (V2/Day 1): Use of other prescription or non-prescription non-study topical emollients, occlusive agents, humectants, wet-wraps, coal tar, or bleach baths or scheduled use during the study period.

12. Participation in any other interventional clinical study or trial within 60 days of the Baseline (V2/Day 1) visit, or scheduled participation in another interventional clinical study during the study period.

13. Children or relatives of the Sponsor, CRO, or the Study Site personnel are excluded from participating in the study.

6 DESCRIPTION OF STUDY PROCEDURES

A description of study procedures listed in the Schedule of Activities is provided within the content of this protocol. Refer to the **Schedule of Activities** 1 for additional information on the frequency of each procedure.

6.1 Informed Consent

6.1.1 Written Parental/Legal Guardian Consent

Adequate provisions must be made for soliciting the permission of the child/adolescent's (less than 18 years of age) parent(s) or legally authorized representative/guardian. The process for obtaining oral and/or written consent for children and adolescents is similar to that of obtaining consent for adults. An effective informed consent process involves at minimum these elements:

- Conducting the process in a manner and location that ensures privacy;
- Giving adequate information about the study in a language understandable to the parent/legal guardian and child/adolescent;
- Providing adequate opportunity for the parent/legal guardian and child/adolescent to consider all options;
- Responding to the parent(s)/legal guardian(s) and child/adolescent's questions;
- Ensuring the parent/legal guardian and child/adolescent has understood the information provided;
- Obtaining the parent/legal guardian and child/adolescent voluntary agreement to participate, and
- Continuing to provide information as the parent(s)/legal guardian(s), child/adolescent, or research requires.

6.1.2 Minimum Federal Requirements for Consent

The minimum United States (U.S.) federal requirements for consent indicated below should be met. However, the Investigator or the Institutional Review Board (IRB)/Ethics Committee (EC) may determine that more stringent requirements are appropriate.

Regulatory Category of Permitted Research with Children	**Permissions Required**
Minimal Risk (45 CFR 46.404, 21 CFR 50.51)	One parent/legal guardian may be sufficient
Greater than Minimal Risk, Direct Benefit to Subject (45 CFR 46.405, 21 CFR 50.52)	One parent/legal guardian may be sufficient but IRB must determine whether one or two is required
Greater than Minimal Risk, No Direct Benefit to Subject, but Likely to Yield Generalizable Knowledge about Subject's Condition (45 CFR 46.406 21, CFR 50.53)	Both parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.
Greater than Minimal Risk, No Direct Benefit to Subject, but Results May Alleviate Serious Problems of Children's Health or Welfare (45 CFR 46.407 21	Both parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for

Regulatory Category of Permitted Research with Children	Permissions Required
CFR 50.54)	the custody of the child.

6.1.3 When Parents/Legal guardians Disagree

If there are two parents/legal guardians available to give permission but they disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. This applies to all permissible categories, even if only one parent's signature is required, when both parents are involved in the decision, they must agree for the child to be enrolled. If a parent who was not involved or available for the original consent later becomes involved or available, the two parents must then agree.

6.1.4 Assent

The Investigator should carefully consider and propose adequate provisions for obtaining assent of children and adolescents prior to their participating in research. The approving IRB/EC application should address whether the intended subject population of children would be capable of understanding the nature of their participation in the research, and if so, whether or how assent will be obtained. In determining whether a child is capable of assenting, their age, maturity, and psychological state should be taken into account. In general assent is usually obtained from a child $\geq$ 7 years of age, however the determination may be made for all children and adolescents to be involved in research under a particular protocol, or for each child, as appropriate. An assent process that takes into account the child's experience and level of understanding, assures an element of cooperation and a feeling of inclusion on the part of the child, and also illustrates the Investigator's respect for the rights and dignity of the child in the context of research. The child should be provided with essential information and asked whether or not they wish to participate in the research study.

6.1.5 Documenting the Consent/Assent Process

Consent/Assent MUST be obtained and documented PRIOR to initiation of any study procedures. Additionally, the consent form approved for use by the IRB/EC will either contain language regarding subject confidentiality, the Health Insurance Portability and Accountability Act (HIPAA) or a separate form will also be signed as required by local law (as applicable). The PI or his/her approved designee must explain the nature of the study and associated risks to the parent(s)/legal guardian and study subject. The date/time that the informed consent is signed, a brief description of the consent/assent process (e.g., questions asked by the subject), and the name of the individual who obtained consent will be recorded in the source record. A copy of the signed informed consent should be provided to the parent(s)/legal guardian. Depending on the approving IRB and local requirements, an assent form may be included as part of the consent and may or may not be required to be signed by the child. Investigators must adhere to their local requirements for proper documentation of consent/assent. A summary of assent procedures for execution of this study must be maintained in the Investigator Essential Regulatory File. It is the responsibility of the PI to ensure that any individual delegated the responsibility for obtaining consent/assent are

familiar and adhere to the applicable consent/assent requirements. Refer to protocol section 13.3 for other general provisions.

6.2 Demographics

Study subject demographic information will be recorded at Screening (V1). Demographic information will include date of birth, gender (at the time of birth), race, and ethnicity. Findings will be documented in the source documentation and the eCRF.

6.3 Histories

6.3.1 General Medical/Surgical and Social History

Relevant medical and surgical history will be recorded at Screening (V1) and will include medical diagnoses, major surgical procedures within the last 3 years. Social history (tobacco, drug, and alcohol use) as well as dietary habits (e.g., unrestricted, vegetarian, gluten-free, vegan, other) and allergies (food, medications and environmental) will also be recorded at screening. Findings will be documented in the source documentation and the eCRF.

6.3.2 History - Atopic Dermatitis

Diagnostic criteria adopted by the American Academy of Allergy, Asthma, and Immunology (Eichenfield, et al, 2014) are defined below will be assessed at Screening (V1) for confirmation of study eligibility and will be documented in the source documents and recorded in the eCRF.

Essential features — must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
  - Typical morphology and age specific patterns*
  - Chronic or relapsing history

*Patterns include:

1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions

Important features — seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
  - Personal and/or family history
  - Immunoglobulin E reactivity
- Xerosis

Associated features — These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- Atypical vascular responses (eg facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/ pityriasis alba/ hyperlinear palms/ ichthyosis
- Ocular/periorbital changes
- Perifollicular accentuation/ lichenification/ prurigo lesions

Exclusionary conditions — It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

6.3.3 Medication History

Medications taken within the last 2 months (60 days) prior to screening will be recorded in the source document and on the eCRF. Also refer to Section 6.23.5 concomitant medications for additional information.

6.4 Physical Examination

The physical examination will also include an examination of general appearance, skin, eyes, ears, nose, throat, neck/thyroid, lungs, heart, upper/lower extremities, lymph nodes, abdomen, musculoskeletal system and basic neurological assessment. Additional systems will be evaluated as needed. Physical exam findings must be recorded in the source documentation and include the date and name of the individual conducting the examination. Physical examinations must be performed by an individual licensed to conduct standard physical examinations.

Significant findings that are present prior to dosing with the study drug will be recorded in the eCRF as adverse events. Clinically significant findings present after dosing will be recorded as an adverse event in the eCRF.

6.5 Fitzpatrick Skin Type Assessment

The Fitzpatrick Skin assessment (Fitzpatrick, 1988) will be conducted at Screening (V1) and the information will be recorded in the source document and in the eCRF.

FITZPATRICK SKIN TEST

Score	0	1	2	3	4	Your Score
Your natural eye color?	Light blue, Gray, Light Green	Blue, Gray or Green	Dark Blue or Hazel	Dark Brown	Brownish Black	
Natural color of your hair?	Sandy or Red	Blonde	Chestnut/ Dark Blonde	Dark Brown	Black	
Color of your non-exposed skin?	Reddish	Very Pale	Pale with Beige Tint	Light Brown	Dark Brown	
Do you have freckles on non-exposed areas?	Many	Several	Few	Incidental	None	

Genetic Disposition Score _____

Score	0	1	2	3	4	Your Score
What happens when you stay in the sun too long?	Painful redness, blistering, peeling	Blistering followed by peeling	Burns sometimes followed by peeling	Rarely burn	Never had burns	
To what degree do you turn brown?	Hardly or not at all	Light color tan	Reasonable tan	Tans easily	Turns dark brown quickly	
Do you turn brown within several hours after sun exposure?	Never	Seldom	Sometimes	Often	Always	
How does your face react to the sun?	Very sensitive	Sensitive	Normal	Very resistant	Never had a problem	

Sun Reaction Score _____

Score	0	1	2	3	4	Your Score
When was the last time you exposed your body to the sun, tanning bed or self-tanning cream	More than 3 months ago	2-3 months ago	1-2 months ago	Less than a month ago	Less than 2 weeks ago	
How frequently do you expose the area to be treated	Never	Hardly ever	Sometimes	Often	Always	

Tanning Habits Score _____

Total Combined Score _____

If your total score is:	Then your Fitzpatrick skin type is:	Response to UVA
0-7	I	Never tans, always burns
8-16	II	Tans with difficulty, usually burns
17-25	III	Average tanning, sometimes burns
25-30	IV	Easily tans, rarely burns
over 30	V-VI	Very easy to tan, very rarely burns

6.6 Height/Weight and Body Mass Index (BMI) Calculation

Height (cm) and weight (kg) should be obtained with shoes off and only light clothing. Scales should be calibrated and the same scale should be used for each weight assessment. Body Mass Index (BMI) will be calculated by dividing the weight (kg) by the height squared (cm) and will be obtained at Screening (V1).

6.7 Body Surface Area (BSA) Calculation

The Mosteller Formula (Mosteller, 1987) will be utilized to assess the overall BSA of each subject in this study utilizing height and weight collected at Screening (V1).

$$\text{BSA } (m^2) = \sqrt{\frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3600}}$$

The average BSA of individual subjects in this study will vary based on each subject's height and weight; however, the following general estimates, can be made regarding the average CDC (50th percentile) (Kuczmarski et al., 2000) expected overall BSA.

Age	Estimated (based on 50th percentile) Overall BSA m^2
2	0.5
3	0.6
4-5	0.7
6	0.8
7-8	1.0
9-10	1.1
11	1.2
12-13	1.3
14-17	1.6

6.8 Body Surface Area (BSA)% Involvement

The BSA% involvement is the numerical area of active atopic dermatitis disease assessed by the Investigator at Screening (V1) and confirmed at Baseline (V2). One back-of-hand of the subject (palms and fingers) is equivalent to approximately 1% of a subject's BSA. All eligible subjects 2 to less than 12 years of age must have a BSA% involvement (affected area/treatable area) of ≥ 35% (excluding scalp and venous access areas) and subjects ≥ 12 years of age must have a BSA% involvement of ≥ 25% (excluding scalp and venous access areas). The BSA% affected score may increase or decrease in area (i.e., size/shape) during the duration of the study and should be recorded in the source document and the eCRF. The BSA% involvement should be calculated by a qualified physician.

6.9 Selected Treatment Area and BSA% to be Treated

6.9.1 Maximal Use Treatment Area

The selected treatment area is defined as the collective areas selected for treatment in the study and it must be identified by the Investigator. At Baseline (V2) subjects 2 to less than 12 years of age must have BSA% involvement (affected area) of ≥ 35% (excluding scalp and venous access areas) and subjects ≥ 12 years of age must have a BSA% involvement of ≥ 25% BSA% (excluding scalp and venous access areas). Once the selected treatment area is set at Baseline, it may increase in area during the duration of the study (for expanded disease), but will not decrease in area during the first 2 weeks (14 days) of treatment (through collection of the Day 15 PK samples).

6.9.2 Treatment for Improvement in Selected Treatment Area

In order to assess the pharmacokinetic profile of MM36 1% (w/w) under maximal use conditions, all originally involved BSA treated with study drug at Baseline will continue to be treated with MM36 1% ointment even if the area has cleared until after the PK samples have been collected on Day 15. On Day 15, the proportion of the treatment area will be defined as either involved or normal (cleared) skin and will be recorded in the source and eCRF.

6.9.3 Treatment for Worsening Selected Treatment Area

If the selected treatment area worsens, the Investigator will evaluate whether this worsening warrants withdrawal of the subject from study treatment. Worsening is defined as a post-baseline selected treatment area which requires additional study medication application due to an enlarged area of the BSA% involvement. If the worsening does not warrant discontinuation, the investigator will re-evaluate the selected treatment area and assess the new BSA% treated and increase the ointment dispensing, as appropriate, to cover the increased BSA% affected.

The source document body diagram will require updating and a new copy will be provided to the subject/parent/guardian (caregiver) along with updated dosing/application instructions (refer to Appendix A).

6.10 Dosing Diary

The subject/parent/guardian (caregiver) will be provided with an electronic dosing diary to record the time and amount of each study drug application. The importance of adherence to the study schedule will be reinforced at each study visit.

6.11 Corporate Confidential Information

6.18 Application Site Assessment

The study drug application sites will be evaluated at each visit, preferably by the same assessor. The study drug should not be applied prior to the study visit to ensure accurate visualization of the areas of involvement. Skin irritation will be recorded as an adverse event and followed until resolution (or stabilization, as applicable). Should a skin irritation event occur, patch testing is recommended to be performed, if feasible, to rule out an allergic/hypersensitivity event.

6.20 Photography

Photographs of the lesions will be taken at the times presented in the schedule of Assessments. Selected sites will take standardized color photographs of the subject's lesions. Photographic equipment and photography standards and procedures will be outlined in the photographic manual. All selected sites will be properly trained and instructions will be detailed in the Photographic Manual that will be provided.

6.21 Vital Signs

6.21.1 Temperature and Respiratory Rate

Temperature (oral or oral equivalent) and respiratory rate will be recorded once at each scheduled time point. Findings will be recorded in the source documentation and in the eCRF.

6.21.2 Seated Blood Pressure and Heart Rate

Blood pressure should be measured on the SAME arm (location should be documented) and with an appropriately sized (e.g., pediatric cuff) blood pressure cuff (that should be the same sized cuff throughout the study) for accurate comparison of readings over time. Position is critical for accurate BP measurements. Therefore, when the BP is measured, the arm (cuff) should be at the level of the heart. When seated, feet should be flat on the floor (if possible) with back supported and arm supported at the level of the heart (e.g., resting on a table). Blood pressure (systolic/diastolic) and heart rate will be assessed after the study subject has rested in a seated position for at least five (5) minutes. Blood pressure readings and heart rate readings will be measured in triplicate (approximately 1 minute apart) and the results will be recorded in the source document and eCRF along with the time they were taken.

It is important that vital signs be taken either before a meal, or at least 30 minutes after a meal or consuming caffeine. If the subject is a smoker, the subject must not be permitted to smoke within 30 minutes prior to scheduled study activities.

6.22 Electrocardiogram (ECG)

All investigative sites will be provided with an identical make/model calibrated portable ECG machine. Site personnel must assess the quality of the ECG while the subject is still at the investigative site in the event that additional ECGs need to be performed (i.e., if artifact is present). QT intervals will be reported uncorrected as well as corrected for heart rate according to the Fridericia Formula (QTcF).

For young children, the parent/parent/guardian (caregiver) should practice, prior to the study visit, lying still (starting with 5 seconds and work up to lying still for 1 minute [time to capture the ECG reading]). Suggest use of a timer to help the child understand how long to hold still. If possible, have the subject rest quietly for at least 10 minutes. Collection of the ECG should be considered for all subjects and this data will be read by a central core lab. Refer to ECG manual for additional details regarding data collection and transmission.

6.23 Laboratory Testing

6.23.1 Testing Facilities

Blood samples for screening and routine safety laboratory testing will be analyzed by a centralized laboratory that is certified under the Clinical Laboratory Improvement Act (CLIA).

6.23.2 Blood Volumes

Total blood volume (TBV) is related to body weight. The TBV of a child is about 75-80 mL/kg. Existing guidelines for blood sample volume limits (ranging from 1–5% of total blood volume within 24 hours and up to 10% of total blood volume over 8 weeks) are consistent with the limited evidence available on "minimal risk" to children (Howie, 2010).

In this study, the smallest volume of blood will be collected for analysis of safety and PK. A total of approximately 29.5 mL will be collected over the study period.

Blood samples are scheduled to be collected ten (10) times over the course of the study. Additional blood samples may be collected for evaluation of safety as clinically indicated.

6.23.3 Sample Identification

Blood samples will be labeled with the subject ID and initials and sample collection date/time and sample type. The Sponsor will not have any information that would identify the study subject.

6.23.4 Screening and Safety Laboratory Testing

6.23.4.1 Pregnancy Testing

A pregnancy test is required for all female subjects ≥ 12 years of age or has reached menarche, whichever occurs first. A serum pregnancy test will be collected at Screening (V1) and must be negative. A urine pregnancy test will also be repeated at V2/Day 1. Additionally, a urine pregnancy test (local) will be done on the last study visit (V6/Day 29).

6.23.4.2 Routine Safety Laboratory Testing

The following safety laboratory panel will be analyzed by a central reference laboratory.

Test Group	Parameter
Serum Chemistry (**approximately 2.5 mL sample required for testing**)	Alanine Amino Transferase (ALT)
	Aspartate Transaminase (AST)
	Albumin
	Alkaline phosphatase
	Amylase
	Anion gap
	Bilirubin (total, direct and indirect)
	Blood urea nitrogen (BUN)
	Calcium
	Carbon dioxide
	Chloride
	Creatinine, serum
	Creatinine kinase (CK)
	Gamma glutamyltransferase (GGT)
	glucose
	Lactate dehydrogenase (LDH)
	Lipase
	Magnesium
	Phosphorous
	Potassium
	Sodium
	Total protein
Hematology (**approximately 2 mL sample required for testing**)	Complete blood count [red blood cells (RBC), hematocrit (HCT), hemoglobin (Hgb), white blood cells (WBC), platelets] (reported as % and absolute values)
	Differential (Automated)
Urinalysis/Microscopy	Appearance Bilirubin Blood Color Glucose Ketones Microscopic examination [bacteria, casts, red blood cells (RBC), white blood cells (WBC), crystals] pH Protein Protein/creatinine ratio and Urobilinogen]

6.23.5 Pharmacokinetics

At each collection time point, 2 mL of blood will be collected in a sodium heparin collection tube. Samples are stable at room temperature for up to 2 hours after sample collection. Transfer an equal amount of plasma into each of two (2) pre-labeled polypropylene tubes (label one as Set A and one as Set B) and immediately store in a freezer at -70˚C (± 10) until shipment is initiated. If a -70˚C if not available, samples may be stored up to 2 months at -20˚C (± 10). Refer to the Laboratory Procedure Manual for instructions regarding sample processing and other additional information.

Samples will be analyzed for MM36 and its metabolites (MAP-15484, MAP15497 and MAP-15485) using a high performance liquid chromatographic method with tandem mass

spectrometric detection (HPLC−MS/MS). The detection range for MM36 and its metabolites is 0.2 to 40 ng/mL.

6.24 Concomitant Medications

6.24.1 General

Use of chronic medications or as-needed medications (e.g., acetaminophen) will be permitted during the screening and active study period (unless otherwise restricted, refer to Section 6.24.2) and should be recorded in the source document and on the eCRF. Any changes in concomitant medication usage will be recorded in the source documents and on the eCRF. If the reason for change is related to an adverse event, the event should be recorded in the source documents and as an adverse event in the eCRF.

Study medication and procedures which are not detailed in Table 2 will be allowed while the subject is in Screening (V1) and for the 4-week duration of the study (through V6), at the discretion of the Investigator, as long as they will not confound assessments of the treatment area.

The following concomitant medications, although not an exhaustive list of allowable medications, can be considered for use during the study treatment period, as long as reviewed/cleared by the investigator and have been at stable doses at the time of Screening and will be maintained at stable doses throughout the study period:

- Intra-ocular or intra-nasal corticosteroids
- Intra-ocular or intra-nasal antihistamines
- Inhaled corticosteroids/bronchodilators

Additional post-treatment (i.e., end-of-study) therapy, including medication to treat adverse events or atopic dermatitis, can be prescribed to the subject as needed, at the discretion of the investigator.

6.24.2 Concomitant Medication Restrictions

The following medications will not be permitted during the study period:

Medications (prescription and non-prescription) that are prohibited prior to Baseline (Visit 2) and during study treatment are detailed in **Table 2**. The study treatment period is defined as Baseline (V2/Day 1) through to Week 4 (V6/Day 29) even though the last study medication dosing will be the evening (Day 28) prior to V6/Day 29.

Table 2 Table of Restricted Medications

List of Prohibited Medications/Products
For 60 days prior to Baseline (V2) through the Week 4 visit (V6)
Approved PDE4 Inhibitor, or Investigational systemic or topical medication within 60 days of Baseline (V2). Examples include, but are not limited to: MM36 (1%) (OPA-15406) and other topical PDE4 inhibitors such as crisaborole (also known as AN-2728 or AN2728).
For 28 days prior to Baseline (V2/Day 1) through the Week 4 visit (V6)
1. Systemic immunosuppressive/immunomodulatory medications or oral corticosteroids. Examples include, but are not limited to: glucocorticoids, cytostatics, antibodies, and drugs acting on immunophilins. • Glucocorticoids, such as: hydrocortisone, cortisol, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclomethasone, fludrocortisone acetate, and deoxycorticosterone acetate • Cytotoxic antibiotics, such as: actinomycin, bleomycin, plicamycin and mitomycin • Antimetabolites, such as: methotrexate, azathioprine, mercaptopurine, fluorouracil • Alkylating agents, such as: mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide,busulfan • Mycophenolate: mycophenolate mofetil • Drugs acting on immunophilins, such as: calcineurin inhibitors, cyclosporine, tacrolimus, sirolimus
2. Systemic antimetabolite medication. Examples include, but are not limited to: methotrexate, hydroxyurea, and thioguanine.
3. Systemic oral retinoid medication. Examples include, but are not limited to: acitretin, isotretinoin, tazarotene, bexarotene.
4. Phototherapy (ultraviolet light A, narrowband ultraviolet B, and ultraviolet light B).
5. New sunscreen or sunscreen with excluded ingredients.
For 14 days prior to Baseline (V2/Day 1) through the Week 4 visit (V6)
1. Topical immunomodulators. Examples include, but are not limited to: pimecrolimus and tacrolimus.
2. Use of topical corticosteroids, with exception of 1% hydrocortisone, as described below. Examples include, but are not limited to: betamethasone, clobetasol, desoximetasone, flurandrenolide, fluticasone, triamcinolone, and hydrocortisone of > 1% potency.
For 7 days prior to Baseline (V2/Day 1) through the Week 4 visit (V6)
1. Topical antihistamines. Examples include, but are not limited to: hydroxyzine, desloratadine, cyproheptadine, carbinoxamine, levocetirizine, fexofenadine, diphenhydramine, brompheniramine, loratadine, clemastine, chlorpheniramine, and cetirizine.
2. Sedating systemic antihistamines. Examples include, but are not limited to: chlorpheniramine, diphenhydramine, and promethazine.
3. Non-sedating antihistamines. Examples include acrivastine, bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, and mizolastine. **NOTE**: Will be allowed if taking at stables doses for at least 14 days prior to V2/Day 1 and remain at stable doses throughout the study.
4. Topical retinoids. Examples include, but are not limited to: tretinoin, tazarotene, adapalene.
For 3 days prior to Baseline (V2/Day 1) through the Week 4 visit (V6)
1. Use of topical 1% hydrocortisone.
For 24 hours prior to Baseline (V2/Day 1) through the Week 4 visit (V6)
1. Other prescription or non-prescription topical emollients, occlusive agents or humectants. Examples include, but are not limited to: non-medicated prescription topicals (Neosalus®, EpiCream®), nonprescription emollients (eg, Eucerin®, CeraVe®, Cetaphil®).
2. Bleach baths, wet wraps or other similar treatments.

6.25 Prevention of Pregnancy during the Study

6.25.1 Instructions for Female Subjects of Childbearing Potential

Women who are pregnant or breastfeeding will not be allowed to participate in this study. Females must either practice abstinence from heterosexual sexual contact or use one of the approved highly effective methods to prevent contraception that are described below. These methods should be followed from the time of consent/assent through the last dose of study drug. The Investigator will educate the subject regarding abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

Acceptable Method Option 1: Any one of the following methods may be used: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD), tubal ligation: or partner's vasectomy.

Acceptable Method Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane (e.g., polyurethane: PLUS, one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

Unacceptable Methods: Periodic abstinence (e.g., calendar, ovulation) or withdrawal.

6.25.2 Instructions to Males of Reproductive Potential

Due to unknown risks and potential harm to the unborn fetus, male subjects of reproductive potential (capable of impregnating their partner) who are sexually active with women of childbearing potential must use a reliable method of birth control while participating in this study. Refer to the acceptable methods listed above.

6.26 Lifestyle Guidelines

6.26.1 Restricted/Limited Exposure to Artificial/Natural Sunlight or Artificial Tanning Agents

Subjects must not use tanning beds, sunlamps, or artificial topical tanning materials, while participating in the study. Subjects should also avoid excessive unprotected exposure to sunlight from Screening (V1) through the final visit (V6), in order to reduce the risk of sunburn during the treatment period as this may confound the treatment area assessment, from Screening and for the 4-week duration of the study.

6.26.2 Use of Sunscreen

Use of sunscreens is permitted providing that the sunscreen has been used consistently (> 28 days) by the subject and does not have any prohibited medications/ingredients and is reviewed by the investigator at Screening V1). Sunscreen should be applied at least 20 minutes following study ointment application.

6.26.3 Bathing and Swimming

Subjects should be advised to avoid bathing or swimming, for at least 20 minutes after application of study ointment. Additionally, if subject sweats excessively, they should not wipe ointment off of skin for at least 20 minutes following study ointment application.

7 STUDY VISITS

The procedures and assessments to be performed at each visit are indicated in the Schedule of Activities. The timing of each visit (while on treatment) is relative to V2 when study registration occurs. An estimated time for the conduct of each visit is provided as a guide only to the study site personnel and study subject (parent/guardian/caregiver) for planning purposes. Note: it will not be considered a departure from the protocol if the visit length is shorter or longer than anticipated.

7.1 Screening (Visit 1)

The screening visit can occur up to 30 days prior to the first dose. It is estimated that this visit will take approximately 2 hours to complete.

- Informed Consent Process
    - The parent(s)/legal guardian (s) must provide written informed consent prior to any study procedure being done; and
    - If able, the subject must provide assent to participate in the study.

- Interview
    - Evaluate Inclusion/Exclusion Criteria;
    - Review and record demographic information;
    - Review and record prior medications (those taken within the last 60 days and current medications);
    - Review prior medical and surgical histories;
    - Review atopic dermatitis history; and
    - Corporate Confidential Information

- Assessments
    - Measure and record height, weight and calculate BMI and BSA;
    - Obtain and record vital signs;
    - Perform a 12-Lead ECG;
    - Perform a complete physical examination and Fitzpatrick Skin Type Assessment;
    - Assess BSA for affected AD and record on body grid; and
    - Corporate Confidential Information

- Sample Collection
    - Collect blood samples for safety laboratory testing and pregnancy testing (as applicable), and
    - Collect urine sample for UA.

- Instructions
    - Inform Parent/guardian (caregiver)/subject that they will be contacted within approximately 1 week regarding study qualification and will be scheduled for Visit 2 (as applicable).

7.2 Baseline (Visit 2/Day 1)

It is estimated that this visit will take approximately 8 hours to complete. Following verification of study eligibility (meets all inclusion and none of the exclusion criteria), the subject will be registered in the study.

- Interview
    - Review and record prior medications (those taken since the last visit);
    - Evaluate Inclusion/Exclusion Criteria (update);
    - Update AEs since last visit;
    - Corporate Confidential Information

- Assessments Prior to First Application
    - Measure and record weight;
    - Obtain and record vital signs;
    - Perform a 12-Lead ECG;
    - Perform a complete physical examination;
    - Assess BSA for affected AD and record on body grid;
    - Corporate Confidential Information
    - Photograph AD sites as applicable.

- Sample Collection
    - Prior to first application:
        - Collect blood samples for safety laboratory testing and PK; and
        - Collect urine sample for urine pregnancy testing (as applicable).
    - Post application:

        - Collect a blood sample for PK at 1 hour (± 15 minutes), 4 hours (± 30 minutes) and 8 hours (± 1 hour) post application.

- Instructions
    - Dosing and Application Training
        - Based on the BSA involved, the appropriate number of tubes of study drug will be dispensed along with a scale and dosing cups.
        - The parent/guardian (caregiver) and/or subject will be trained by the study site personnel on measuring and applying the study drug and recording the information in the electronic dosing diary.
        - The parent/guardian (caregiver) or subject will apply the study drug to the affected areas twice daily (approximately 12 hours apart).

- Corporate Confidential Information

7.3 Visit 3/Day 8 (±1)

It is estimated that this visit will take approximately 1.5 hours to complete.

- Interview
    - Update medications (those taken since the last visit);
    - Assess for AEs; and
    - Corporate Confidential Information

- Assessments
    - Assess application sites;
    - Perform abbreviated physical exam (only as applicable for evaluation of AEs);
    - Obtain and record vital signs;
    - Assess BSA for affected AD and record on body grid;
    - Corporate Confidential Information
    - Photograph AD sites as applicable; and
    - Compliance check (weight check of study drug and review diary completion).

- Instructions
    - Dispense study drug;
    - Review dosing procedure and have the parent/guardian (caregiver)/subject apply the study drug to the affected areas; and
    - Schedule Return visit for 1 week (Day 15) and remind parent/guardian (caregiver) not to apply study drug in the morning before the visit and to bring all used and unused study dug to next visit.

7.4 Visit 4/Day 15 (±1)

It is estimated that this visit will take approximately 8 hours to complete.

- Interview
    - Update medications (those taken since the last visit);
    - Assess for AEs; and
    - Corporate Confidential Information

- Assessments
    - Assess application sites;
    - Perform abbreviated physical exam (only as applicable for evaluation of AEs);
    - Obtain weight;
    - Obtain and record vital signs;
    - Assess BSA for affected AD and record on body grid;
    - Photograph AD sites as applicable;
    - Corporate Confidential Information
    - Compliance check (weight check of study drug and review diary completion).

- Sample Collection
    - Collect a blood sample for PK prior to application at the study clinic and again at 1 hour (± 15 minutes), 4 hours (± 30 minutes) and 8 hours (± 1 hour) post application.

- Instructions
    - Dispense study drug;
    - Review dosing procedure and have the parent/guardian (caregiver)/subject apply the study drug to the affected areas; and

- Schedule Return visit for 1 week (Day 22) and remind parent/guardian (caregiver) and subject not to apply study drug in the morning before the visit and to bring all used and unused study dug to next visit.

7.5 Visit 5/Day 22 (±1)

It is estimated that this visit will take approximately 1.5 hours to complete.

- Interview
  - Update medications (those taken since the last visit);
  - Assess for AEs;
  - Corporate Confidential Information

- Assessments
  - Assess application sites;
  - Perform abbreviated physical exam (only as applicable for evaluation of AEs);
  - Obtain and record vital signs;
  - Assess BSA for affected AD and record on body grid;
  - Photograph AD sites as applicable;
  - Corporate Confidential Information
  - Compliance check (weight check of study drug and review diary completion).

- Instructions
  - Dispense study drug; and
  - Review dosing procedure and have the parent/guardian (caregiver)/subject apply the study drug to the affected areas.

Schedule Return visit for 1 week (Day 29) and remind parent/guardian (caregiver) that the last dose of study drug should be applied the night before the final visit (Day 28). They should also be reminded to bring all used and unused study drug and the scale, to final visit.

7.6 Visit 6/Day 29 (±1) or Early Termination (ET)

It is estimated that this visit will take approximately 1.5 hours to complete.

- Interview
  - Update medications (those taken since the last visit);
  - Corporate Confidential Information

- Assess for AEs.

- Assessments
  - Assess application sites;
  - Perform physical examination;
  - Obtain weight;
  - Obtain and record vital signs;
  - Perform a 12-Lead ECG;
  - Assess BSA for affected AD and record on body grid;
  - Photograph AD sites as applicable;
  - Corporate Confidential Information
  - Compliance check (weight check of study drug and review diary completion). Collect all used and unused study drug and scale.

- Sample Collection
  - Collect blood samples for safety laboratory testing.
  - Collect urine sample for urine pregnancy testing (as applicable).

7.7 Unscheduled Visit(s)

An unscheduled visit will be scheduled every 7 to 14 days in order to follow-up on unresolved adverse events that were still present at the final visit (V6). Additionally, the Study subject may be asked to return for additional visits to follow clinically significant abnormal laboratory results.

7.8 Unscheduled Procedures

It may be necessary to collect unscheduled procedures as clinically indicated for evaluation of subject safety. Procedures completed at an unscheduled visit will be driven by the reason for the unscheduled visit. Should a skin irritation event occur, a patch testing can be performed, if feasible, to rule out an allergic/hypersensitivity event.

8 STUDY DOSING

8.1 Formulation, Packaging and Labelling

8.1.1 Formulation

MM36 1% is a white petrolatum based ointment. A list of all components in MM36 1%, is presented in Table 3. Each gram of MM361 % w/w ointment contains 10 mg of active MM36.

Table 3 Components of MM36 1%

Components Ointment
MM36 1% w/w

Corporate Confidential Information

8.1.2 Packaging

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.

8.2 Storage

Study drug will be stored at the clinical site in a secured (limited access to authorized site personnel only) storage area. The investigational drug product will be stored at controlled room temperature (15°C to 25°C).

8.3 Dispensing

As reported in Nelson et al, 2006, "an average of 9.9 g/m2 (equivalent of 1.0 mg/cm2) of a topical agent (by weight) are required by a disciplined operator to achieve a thin, even layer of ointment on a patient" (pp. 224). Therefore, to determine the number of grams (by weight) per day, the Investigator/designee will use the following formula:

Step 1 Formula to Calculate Grams (by weight) of MM36 1% to Use Per Dose:

Overall BSA (m^2)	**X**	Total (BSA %) of <u>All</u> areas of involvement that will be treated	**X**	10 grams/m^2	=	Grams of ointment per application

Example: A six-year-old boy with 32% BSA involved areas of AD

0.7 m^2	***X***	*32% (or 0.32)*	***X***	*10 grams/m^2*	=	***2.24** grams/ application*

Step 2 Formula to Calculate Grams Needed to Dose BID for 1 Week (7 Days):

Grams of ointment needed per Application	**X**	Number of applications Per day	=	Total grams of ointment needed per day	**X**	Number of Treatment Days	=	Total Grams Needed

Example continued:

2.24 grams	***X***	*2*	=	*4.48 grams*	***X***	*7*	=	*31.36 grams*

Step 3 Formula to Calculate Number of MM36 Tubes of Study Drug (27 grams per each) Needed for 1 Week (7 Days) of Treatment:

Total Grams Needed	÷	27 grams (weight per 1 tube of study drug)	=	Number of Tubes to be dispensed

Example continued:

31.36 grams	÷	*27 grams (weight per 1 tube of study drug)*	=	*1.16 tubes (dispense 2 tubes)*

The table below (Table 4) is provided as general guide to determine the amount of study drug to be dispensed based on a subject's BSA and their intended area of application. Exact calculation will be done on an individual basis. The Investigator or designee will enter the subject's overall BSA, BSA% involvement and intended number of treatments (until the next visit) into the dosing module in the eCRF. The number of tubes to be dispensed will be calculated.

Table 4 Estimated Dispensing Table

Age Range	Estimated[a] BSA m^2 Of the Average 50th Percentile for Males and Females	Approx[b] Grams of Ointment Needed for Application to Every 1% BSA Involvement	Grams (weight) of Ointment Required Per Application to a Minimum Involved Area of 25%	Grams of Ointment Required Per Application to a Minimum Involved Area of 35%
2- 3	≥ 0.5 to < 0.7	0.07	1.75	2.45
4 – 6	≥ 0.7 to < 1.0	0.10	2.5	3.5
7 – 11	≥ 1.0 to < 1.3	0.13	3.25	4.55
12 – 13	≥ 1.3 to < 1.6	0.15	3.75	5.25
14 – 17	≥ 1.6 to < 1.9	0.20	5.0	7

[a] Kuczmarski et al, 2000
[b] Nelson, 2006

The subject/subject's parent/guardian (caregiver) will be provided a calibrated scale and measuring cups to dispense the calculated dose for each application. Procedure will be

discussed with the subject or parent/guardian (caregiver) at the site and documented that proper training occurred prior to first application (refer to Appendix A).

8.4 Dosing

The subject (parent/guardian (caregiver) will be instructed on proper application of the study drug and will apply the initial application on Day 1 at the study site. The proper dose dispensing procedure and use of the study drug will be demonstrated and observed by study staff to ensure subject (parent/guardian (caregiver) understand the instructions.

- For each dosing period, the subject, under the supervision of the parent/guardian (caregiver), or the parent/guardian (caregiver), will dispense the required amount of ointment (by weight) using the measuring cup(s) provided.
- The subject should wash his/her hands both before and after applying study ointment. If applied by the parent/guardian (caregiver), they should also wash hands before and after applying study ointment, but will also wear non-latex gloves (provided by the Sponsor).
- The subject (parent/guardian (caregiver) will apply a thin layer of ointment to affected areas twice daily (approximately 12 hours apart) for 28 consecutive days.
- It is recommended that the ointment be applied after showering/bathing. The skin should be dry prior to application. Important: Subjects should not swim or bathe or wipe application area for a minimum of 20 minutes after application of ointment.
- The ointment should be rubbed in gently and completely, avoiding contact with the eyes.
- Subject's (parent/guardian (caregiver) will be instructed not to administer the study drug in the morning on the day of the study visit to avoid any effect of the study drug on the assessments.
- An adult (≥18 years of age) parent/guardian (caregiver) will verify if the study drug was weighed appropriately and applied as directed. Application details will be recorded in the electronic diary.

8.5 Compliance

The parent/guardian (caregiver)/subject will record the amount of drug used at each application and application location in the electronic diary. All used and unused study drug will be returned at all protocol-specified visits for study drug inventory and assessment of subject adherence.

The weight of the study drug will be measured before it is dispensed and after it is returned at Visit 3/Week 1, Visit 4/Week 2, Visit 5/Week 3 and Visit 6/Week 4. Each dispensing and return of study drug as well as the weight of study drug will be documented in the eCRF.
The dispensing and return of all study drug will be recorded on the study drug dispensing log. The subject number/initials and the initials and date of the person dispensing and receiving the returned medication will be documented on this form.

8.6 Study Drug Accountability

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to inspection by regulatory authorities at any time. Study drug will be received and dispensed by the designed study staff and returned to the Sponsor (unused study at completion of the study. All study drug will be accounted for on the study drug inventory/accountability log and will include:

- Subject ID and initials
- Date/time dispensed
- Amount dispensed
- Amount remaining in inventory

Damaged or lost study drug will also be accounted for and recorded in the drug accountability records.

At completion of the study, the Investigator (or designee) is responsible for returning all unused study drug and used study drug containers to the Sponsor or representative, and must verify that no supplies remain in the investigator's possession.

8.7 Blinding

Not applicable as this is an open-label study.

8.8 Breaking the Study Blind

Not applicable.

9 PROTOCOL VIOLATIONS

A protocol violation occurs when the study subject, Investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, study subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Dosing error

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a study subject or if data analysis will be censored.

When a protocol violation occurs, it will be discussed with the Investigator, and the details will be documented and reviewed by the Sponsor representative and the Investigator. A copy of such documentation will be filed in the site's regulatory binder and in the Sponsor's files.

10 ADVERSE EVENTS

10.1 Definition of an Adverse Event

An adverse event is any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

10.2 General Guidelines

All observed or volunteered adverse events regardless of suspected causal relationship to the study drug are to be recorded on the appropriate eCRF from the time consent/assent is obtained through the end of the study as described in the following sections.

For all adverse events, the Investigator (Principal Investigator or Sub-Investigator) must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the Sponsor or designee. For all adverse events, sufficient information should be obtained by the Investigator to determine the causality of the adverse event. The Investigator (Principal or physician Sub-Investigator) is required to assess causality. For adverse events with a causal relationship to the study drug, follow-up by the Investigator (Principal or physician Sub-Investigator) is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator (Principal or physician Sub-Investigator) and Medical Monitor concurs with that assessment.

10.3 Reporting Period

Serious adverse events require immediate notification to the Sponsor or designee, beginning from the time that the informed consent is signed, which is obtained prior to participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving study drug, through and including the day of the last dose of study drug or longer as applicable. Any serious adverse event occurring any time within the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

- Adverse events (serious and non-serious) should be recorded on the eCRF from the time the study subject has signed informed consent (assent) through last study visit, unless otherwise specified.
- Any changes in the subject's status between enrollment (signing informed consent) up to the time of the first dose of study drug will be recorded as a pre-treatment adverse event and severity will be assessed.

- Any adverse event occurring after the first dose of study drug will be considered a treatment emergent adverse event (TEAE).

10.4 Assessment of Severity

- Mild – An event that is usually transient in nature and generally not interfering with normal activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal activities.
- Severe – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

10.5 Relationship of an Adverse Event to Study Drug

The investigator is to classify the relationship of an AE to the investigational product using good clinical judgment and the following definitions:

Relationship	Description
Not Related	The AE is clearly explained by another cause not related to the study product;
Probably Not Related	A potential relationship between study product and the AE could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than the study agent;
Possibly Related	The AE and administration of study product are temporally related, but the AE can be explained equally well by causes other than the study product;
Probably Related	The AE and use of study product are temporally related, and the AE is more likely explained by study product than by other causes;
Definitely Related	The AE and use of study product are related in time, and a direct association can be demonstrated.

The following factors should also be considered:

- The temporal sequence from study medication administration: The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the study subject may have.
- Concomitant medication: The other medications the study subject is taking or the treatment the study subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study medication: Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study medication: The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.
- In the case of skin irritation, the results of any patch testing should be considered.

10.6 Suspected Adverse Reaction

An adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event

10.7 Unexpected Adverse Events

An adverse event or suspected adverse reactions is considered "unexpected" if it is not listed in the investigator brochure (IB) or it is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere, as applicable. Unexpected, as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the IB or other applicable documentation as occurring with a class of drug or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.8 Serious Adverse Event Definition

An adverse event or suspected adverse event reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;

  NOTE: An adverse event or suspected adverse event is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the study subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations;

  NOTE: Any hospital admission will be considered an inpatient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for a pre-planned procedure or social or situational

reasons (i.e., no place to stay, lives too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Other important medical event (event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above).

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

10.9 Reporting

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

All adverse events occurring from the time consent/assent is obtained through the end of the study will be reported on the adverse event page(s) of the eCRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the eCRFs as well as on the form for collection of serious adverse event information.

10.9.1 Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, the Sponsor or designee is to be notified (see below) within 24 hours of awareness of the event by the Investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to the Sponsor or designee, must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Pregnancy cases. A site designee will complete the Serious Adverse Event (SAE) Reporting Form and send the report(s), within 24 hours of learning of an initial SAE to

with supporting documentation, if applicable.

Medical Monitor	Serious Adverse Event (SAE) Reporting
Personal Data	Corporate Confidential Information

In the rare event that the Investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient trial study subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the Investigator is obligated to pursue and provide information to the Sponsor or designee, in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor or designee to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a study subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative. The Investigator must continue to follow the study subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the study subject dies. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit it to the Sponsor or Designee Safety Coordinator.

10.9.2 Non-Serious Adverse Event Reporting Requirements and Ongoing Safety Review

Non-serious adverse events are to be reported in the eCRF which will be reviewed by the Sponsor or designee Medical Monitor on an ongoing basis.

10.10 Pregnancy Reporting

If a study subject becomes pregnant during the study, the Investigator should report the pregnancy to the Sponsor, or its representative, within 24 hours of being notified.
The Pregnancy Report form must be completed by the site and sent within 24 hours of learning of a pregnancy to Corporate Confidential Information with supporting documentation, if applicable.

The study subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE. Otherwise, a Pregnancy Outcome Report should be completed.

11 DATA ANALYSIS AND STATISTICAL METHODS

11.1 Sample Size Determination

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.

11.2 Analysis Populations

Two populations will be used for analysis: safety and intent-to-treat. The definition of these populations follows:

- Safety Population: All enrolled subjects who received at least one dose of study medication and have at least one post-baseline safety assessment constitute the Safety Population.
- Intent-to-Treat (ITT) Population: All enrolled subjects who took at least one dose of study medication constitute the Intent-to-Treat Population.

Safety and PK data will be analyzed based on the safety population. Efficacy data will be analyzed based on the ITT population.

11.3 Statistical Analysis

11.3.1 General Statistical Methodology

- All statistical processing will be performed using SAS® unless otherwise stated.
- Continuous data will be summarized using descriptive statistics (number of values, mean, standard deviation, median, minimum and maximum). Categorical data will be summarized using frequency tables (frequencies and percent).
- A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to locking the database. The SAP will contain any modifications to the analysis plan presented below.

11.3.2 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history including history of acute dermatitis, and prior and concomitant medications will be summarized using descriptive statistics.

11.3.3 Treatment Compliance

The Parent/guardian (caregiver)/Subject will record all applications made or missed in the electronic diary. Subject compliance during the overall treatment period and by visit will be summarized.

11.3.4 Drug Exposure

Amount of study drug (weight) and the number of days with study drug application will be summarized.

11.4 Primary Analysis

11.4.1 Pharmacokinetics

Individual plasma concentrations of MM36 and its metabolites (MAP-15484, MAP15497 and MAP-15485) will be summarized descriptively using the arithmetic mean, standard deviation (SD), CV (%), median, minimum and maximum. Individual plasma concentration-time profiles of MM36 will be plotted on both a linear and a semi-logarithmic scale. Mean values will also be presented graphically. The following pharmacokinetic parameters will be analyzed for each subject and for each PK time point at which a sufficient (detectable) concentration of MM36 or its metabolites will be measured to permit their derivation. If there are sufficient concentration data above the level of quantitation the following pharmacokinetic parameters will be calculated:

- C_{max} = Maximum plasma concentration
- T_{max} = Time of maximum plasma concentration
- $AUC_{0\text{-last}}$ = Area under the plasma concentration-time curve from time zero to time last (time of last quantifiable plasma concentration) [$AUC_{0\text{-t}}$]

The pharmacokinetic analysis will be implemented in SAS®, and conducted using Non-Compartmental Analysis (NCA) on plasma concentrations of MM36 in the subjects who will receive MM36 1% ointment and had evaluable plasma concentration-time profiles. PK parameters will be listed for all individuals. Descriptive summary statistics (number of observations (N), arithmetic mean, standard deviation (SD), CV%, median, minimum, maximum and geometric mean) will be reported for PK parameters. Individual elapse sampling time will be used in the pharmacokinetic analysis. C_{max} and t_{max} will be obtained directly from the experimental observations. $AUC_{(0\text{-t})}$ will be calculated using the linear trapezoidal rule.

BLQ (< 0.2 ng/mL) samples will be set to zero for the summary of the statistics for concentration values. For the purpose of the NCA, BLQ set to zero before t_{max} and missing after t_{max}. Any quantifiable concentrations at pre-dose at Day 1 will be set to zero.

11.5 Secondary Analysis

11.5.1 Safety

Safety evaluations will consist of adverse events (AEs), application site reactions, physical examinations, vital signs, ECGs, weight, and laboratory measurements (hematology, chemistry, and urinalysis). Full details will be specified in the SAP. A general description of the planned analysis is as follows:

- Descriptive statistics and frequency tables will be prepared as appropriate for physical examinations, vital signs, weight, ECG (HR, QTcF, PR, and QRS) and laboratory measurements (hematology, chemistry, and urinalysis).
- Adverse Events
    - AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); the version will be identified in the clinical study report.
    - AEs that occurred during the screening period will be listed separately and will not be included in the AE tabulations.
    - All other AEs that start on or after first dose will be considered TEAEs. Summaries will be presented by system organ class and preferred term, and further by severity and relationship to study drug. Application site AEs and any TEAEs reported by ≥ 5% of subjects will also be tabulated.
    - The proportion of subjects who discontinue treatment due to an adverse event will be presented.
- Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary and will be presented in data listings.

11.6 Exploratory Analysis

11.7 Interim

A pre-specified interim analysis will not be conducted.

12 DATA COLLECTION, RETENTION AND MONITORING

12.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each study subject treated with the test article. The Investigator is responsible for ensuring that data is properly entered into the electronic devices (diaries and site electronic devices) as this will serve as source documentation for certain scales, measures, dosing for the study. Study personnel at each site will enter data from source documents corresponding to a study subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

Study subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, study subject number and initials.

If a correction is required for an eCRF, the time and date stamps will track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on study subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. Copies of final completed eCRFs will be provided on a compact disk (CD) or other similar media for archiving at the study site following database lock and at or prior to study closure.

12.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

12.2.1 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the electronic data capture (EDC) system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

12.2.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords

will be strictly confidential. Data should be entered onto the eCRF approximately no later than 72 hours after the visit has taken place.

12.2.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of the Medical Dictionary for Regulatory Activities (MedDRA) for medical history and adverse events; and
- World Health Organization Drug Dictionary (WHODD) for prior and concomitant medications.

12.2.4 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the uploaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.
The CRFs must be reviewed and electronically signed by the Investigator who signed the protocol.

12.3 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

12.4 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each study subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that study subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient and subject files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

12.5 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor (or designee) according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

12.6 Subject Confidentiality

In order to maintain study subject confidentiality, only a site number, study subject number and initials will identify all study subjects on CRFs, blood samples, and other documentation submitted to the Sponsor. Additional study subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

12.7 Retained Blood Samples

Blood samples collected during the study for pharmacokinetic analysis may be retained for future testing as necessary. Study subject's confidentiality will be maintained and only the site and study subject number and initials will identify the sample. No other linked or identifying information is maintained by the Sponsor.

13 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312 Subpart D).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

13.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor or Sponsor designee. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to study subjects/patients. A protocol amendment intended to eliminate an apparent immediate hazard to study subjects/patients may be implemented immediately, provided the IRBs are notified within five working days.

13.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject/patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects/patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information

that may affect adversely the safety of the subjects/patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

13.3 Informed Consent Form – General Provisions

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations. Also refer to Protocol Section 6.1.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each study subject or the subject's legally authorized representative prior to entering the study subject into the trial and conducting any Screening visits. Information should be given in both oral and written form and study subjects (or their legally authorized representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the study subject will also be obtained. If a study subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the study subject. A copy of the signed consent form (and assent) will be given to the study subject or legal representative of the study subject and the original will be maintained with the study subject's records.

13.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating Investigators. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

14 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the referenced investigational drug at any time.

If the study is prematurely terminated or discontinued, the Sponsor, or designee, will promptly notify the Investigator. After notification, the Investigator must contact all participating study subjects within 5 business days. As directed by the Sponsor all study materials must be collected and all CRFs completed to the greatest extent possible.

15 REFERENCES

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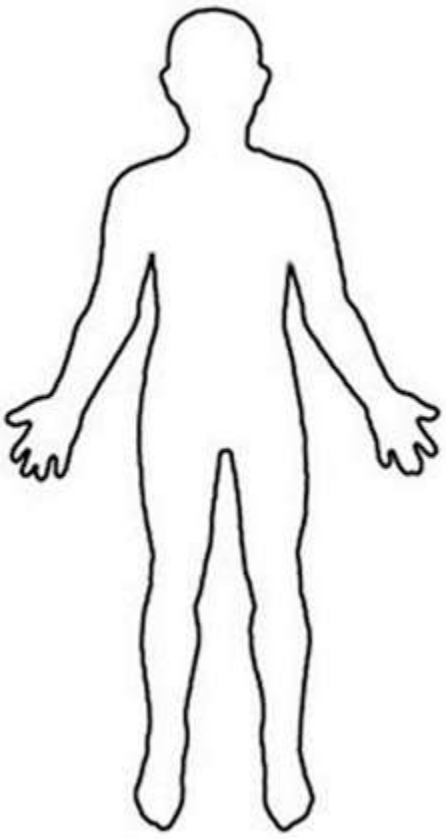
APPENDIX A – DOSING INSTRUCTIONS



Apply _____ grams on the affected areas noted below and on the diagram by your doctor:

(**Site:** Please circle areas affected below and on diagram)

Head/Neck

Trunk

Upper Limbs

Lower Limbs

Acceptable Range for Dosing:_____to_____

- At each study visit, you/your child will be given enough tubes of study drug until the next visit.
- Be sure to wash your hands before and after applying study drug.
- Using the measuring cups and scale, measure out the amount of ointment to be applied.
- If you squeeze out too much of the ointment in the medicine cup, record the initial weight and scoop off the excess ointment and discard it (throw it away). Reweigh the ointment again to make sure that the dose is within the acceptable range for dosing (bottom of page 1). Please record the details of the change in the chart on the next page.
- Apply the study drug twice daily; once in the morning and once in the evening for 4 weeks.
- If the study drug is applied by a parent/caregiver, they will need to wear the protective gloves provided.
- It is recommended that the ointment be applied after showering/bathing. The skin should be dry. Important: Subjects should not swim or bath or wipe application area for a minimum of 20 minutes after application of ointment.
- The ointment should be rubbed in gently and completely, avoiding contact with the eyes.
- A parent/caregiver must confirm how much of the study drug was applied and note this on the dosing diary (provided).
- On the morning of a study visit:
    - Do not apply the study drug so that the application areas can be checked by the study doctor/nurse.
    - You/your child will be asked to apply the study drug in the study clinic so that a study team member can see how you are using the study drug.
    - Bring the dosing diary and ALL used and unused tubes of study drug to the clinic.

The Next Study Visit is Scheduled for: _____ at _____

If you accidentally squeezed out too much medication into the cup, please fill out this section.

Please record the weights BEFORE and AFTER you scoop off the extra ointment in the chart below.

Date of Dose	AM/PM Dose	BEFORE weight of study ointment	AFTER weight of study ointment	Discarded by: