A TWO PART, PHASE I/II, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, VEHICLE-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF TOPICALLY APPLIED AMTX-100 *CF* IN ADULT PATIENTS WITH MILD TO MODERATE ATOPIC DERMATITIS

Protocol Number:	**AMTX100-AD-01 (NCT04313400)**
Version Number:	**Final Version 4.0**
Version Date	**12Jul2023**
Development Phase:	**Phase I/II**
Investigational Compound:	**AMTX-100 *CF3***
Control:	**Vehicle (Placebo)**
Sponsor:	Amytrx Therapeutics, Inc.
Protocol Prepared By:	Amarex Clinical Research, LLC. 20201 Century Blvd, 4th floor Germantown, MD 20874 USA

Confidentiality Statement

This protocol is provided for conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

PROTOCOL APPROVAL SIGNATURES

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

[redacted]		
Project Lead	Signature	Date
[redacted]		
Safety and Pharmacovigilance	Signature	Date
[redacted]		
Biometrics	Signature	Date
[redacted]		
Medical Writing	Signature	Date
[redacted]		
Sponsor Representative	Signature	Date

INVESTIGATOR SIGNATURE PAGE

I have read the protocol specified above and agree to participate in and comply with the procedures, as detailed herein for the conduct of this clinical trial. I also agree to comply with the applicable US Food and Drug Administration (FDA) regulations and Institutional Review Board (IRB) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature	Date
Print Name	
Site Number	

STUDY SPONSOR INFORMATION

Amytrx Therapeutics, Inc.

Primary Contact: [redacted]
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LIST OF ABBREVIATIONS

TERM	DEFINITION
%	Percent
AD	Atopic Dermatitis
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Amarex	Amarex Clinical Research, LLC.
ANCOVA	Analysis of Covariance
AP-1	Activator Protein 1
API	Active Pharmaceutical Ingredients
AST	Aspartate Aminotransferase
BID	Twice a Day
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
ChREBP	Carbohydrate-responsive element-binding protein
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
cSN50	Cyclic SN50
CTCAE	Common Terminology criteria for Adverse events
CV	Curriculum vitae
DLQI	Dermatology Life Quality Index
DLT	Dose-Limiting Toxicity
DSMB	Data Safety and Monitoring Board
DSMC	Data Safety Monitoring Committee
EASI	Eczema Area Severity Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practices
GLP	Good Lab Practices
GMP	Good Manufacturing Practices
HED	Human Equivalent Dose
HIPAA	Health Insurance Portability and Accountability Act
HPBL	Human Peripheral Blood Lymphocyte
HR	Heart Rate

TERM	DEFINITION
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IGA	Investigator's Global Assessment
IL	Interleukin
Imp	Importin
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intra Uterine Device
IV	Intravenous
IWRS	Interactive Web Based Response System
kDa	Kilo Dalton
Kg	Kilograms
LPN	Licensed Practical Nurse
LVN	Licensed Vocational Nurse
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCP	Monocyte Chemoattractant Protein
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
MRSD	Maximum Recommended Starting Dose
Msec	Milliseconds
MTD	Maximum Tolerable Dose
NBUVB	Narrowband UVB
NFAT	Nuclear factor of activated T-cells
NFκB	Nuclear Factor kappa B
NLS	nuclear localization sequence
NOAEL	no-observed-adverse-effect level
NRS	Pruritus Numeric Rating Scale
NTM	nuclear transport modifier
PBL	Plastic Barrier Laminate
PDE-4	Phosphodiesterase-4
PEG	Polyethylene Glycol
PP	Per Protocol
Pruritus NRS	Pruritus Numeric Rating Scale
PT	Preferred Term
RBC	Red Blood Cells
RR	Respiration Rate

TERM	DEFINITION
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SOC	System Organ Class
SOP	Standard Operating Procedures
SREBP	Sterol Regulatory Element Binding Protein
SRTF	Stress-Responsive Transcription Factor
STAT1	Signal Transducer and Activator of Transcription 1
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroids
TEA	Triethylamine
TEAE	Treatment Emergent Adverse Event
TF	Transcription Factor
TNFα	Tumor Necrosis Factor Alpha
USA	United States of America
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
vIGA-AD™	Validated Investigator Global Assessment scale for Atopic Dermatitis
WBC	White Blood Cells
WHO	World Health Organization

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Amytrx Therapeutics, Inc.	
Name of Study Product: AMTX-100 *CF3* Topical Cream **Comparator Product:** Placebo (Vehicle)	
Protocol Number: AMTX100-AD-01	**Indication:** Mild to Moderate Atopic Dermatitis in Adults
Title of Study: A Two-part, Phase I/II, Multi-center, Double-Blind, Randomized, Vehicle-controlled Study of the Safety and Efficacy of topically applied AMTX-100 *CF* in adult patients with Mild to Moderate Atopic Dermatitis	
Background/ Rationale: Atopic Dermatitis (AD) is a chronic, pruritic inflammatory skin disease of unknown origin that usually starts in early infancy, but also affects a substantial number of adults. AD affects 15-30% of children and 2-10% of adults globally, and its prevalence rate is rising. AD typically presents with pruritus, xerosis, lichenification, and eczematous lesions. Excoriations and crusting are common and some patients exhibit prurigo nodularis–like lesions. The eczematous changes and its morphology are seen in different locations depending on the age of the patient. In adults, lesions are more diffuse with an underlying background of erythema. The face is commonly involved and is dry and scaly. The mainstays of treatment are moisturization (frequent lukewarm baths, and using petrolatum or Aquaphor, etc.), along with topical steroids. For more severe cases, other treatment options such as immunomodulators (ex. tacrolimus, and pimecrolimus), biologicals (ex. dupilumab and omalizumab), topical phosphodiesterase-4 (PDE-4) inhibitors (ex. crisaborole), probiotics and phototherapy are also used. All of these options for AD management, and many of these treatment regimens are considered expensive and with various side effects in chronic use. Thus, patients with AD are in need of new treatment options that are efficacious and safe in long term use. AMTX-100 *CF3* drug product is formulated as a water-based, topical cream incorporating a 28-amino acid synthetic polypeptide (AMTX-100) as the active pharmaceutical ingredient (API). AMTX-100 is a chimeric, cell-penetrating, bifunctional nuclear transport modifier (NTM), that is engineered to modulate nuclear transport of transcription factors (NF-κB, NFAT, AP-1 and STAT1) involved in activation of gene expression of key mediators of inflammation (TNFα, IL-1β, IL-6, IL-17, MCP-1, etc.) and metabolic syndrome (ChREBP and SREBP) by importin α/β complex and importin β, respectively. This further leads to a reduction in pro-inflammatory cytokine/chemokine production and lipid metabolic products. Several nonclinical safety studies have been conducted with AMTX-100 and AMTX-100 *CF3* to evaluate their toxicological profile and additional studies are currently ongoing. Substantial scientific literature is also available on the anti-inflammatory mechanisms of AMTX-100. The current study is designed to evaluate the safety, tolerability and efficacy of topically applied AMTX-100 *CF3* in adult patients with mild to moderate AD.	
Study Center(s): **Phase I (Part 1)**: Up to 5 centers within the USA **Phase II (Part 2)**: Up to 20 centers within the USA	

Name of Sponsor/Company:

Amytrx Therapeutics, Inc.

Name of Study Product: AMTX-100 *CF3* Topical Cream

Comparator Product: Placebo (Vehicle)

Protocol Number:	**Indication:**
AMTX100-AD-01	Mild to Moderate Atopic Dermatitis in Adults

Planned Number of Subjects:

Phase I (Part 1):
Approximately twenty-five (25) subjects with various treatable Body Surface Area (BSA) involvement of Mild to Moderate Atopic Dermatitis will be enrolled in the study and treated with 1.1% w/w AMTX-100 *CF*.

Phase II (Part 2):
Approximately sixty (60) subjects with Mild to Moderate Atopic Dermatitis with various treatable BSA involvement of Mild to Moderate Atopic Dermatitis will be randomized to be treated with 1.1% w/w AMTX-100 *CF3* or Vehicle (Placebo) in the study.

Study Development Phase:

Phase I/II

Indication for Use:

AMTX-100 *CF3* is intended for improvement of symptoms associated with mild to moderate Atopic Dermatitis in adults.

Objectives:

This is an adaptive, Phase I/II study in 2 parts: Part 1 (to determine the Maximum Tolerable Dose (MTD) by maximum BSA percentage treated) and Part 2 (evaluating efficacy of 1.1% w/w AMTX-100 *CF3* versus placebo (vehicle).

Phase I (Part 1) Objectives:

The primary objective of Part 1 of this study is to determine the MTD of topically applied AMTX-100 *CF* (in 1.1% w/w concentration) in adult patients with mild to moderate Atopic Dermatitis (AD) while escalating the treatable BSA involved in sequential cohorts.

The secondary objective of Part 1 of this study is to evaluate the safety, tolerability and efficacy of topically applied AMTX-100 *CF* (in 1.1% w/w concentration) in improving symptoms associated with mild to moderate Atopic Dermatitis in adults.

Phase II (Part 2) Objectives:

The primary objective of Part 2 of this study is to evaluate efficacy of 1.1% w/w AMTX-100 *CF3* versus placebo (0 % w/w) (vehicle)

The secondary objective of Part 2 of this study is to evaluate the safety, and tolerability of 1.1% w/w AMTX-100 *CF3* compared to placebo (0 % w/w).

[redacted]

Study Endpoints:

<u>Phase I (Part 1) Study Outcome Measures</u>

Primary Outcome Measure:

Name of Sponsor/Company: Amytrx Therapeutics, Inc.	
Name of Study Product: AMTX-100 *CF3* Topical Cream **Comparator Product:** Placebo (Vehicle)	
Protocol Number: AMTX100-AD-01	**Indication:** Mild to Moderate Atopic Dermatitis in Adults

- Maximum Tolerable Dose (MTD) by maximum percentage of BSA treated, by evaluation of dose-limiting toxicity (DLT) of AMTX-100 *CF* (1.1% w/w concentration) based on the safety profile

Safety Outcome Measures:

- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of withdrawals from the study due to TEAEs
- Changes in study treatment application site reaction assessment
- Changes and shifts in laboratory measurements over time
- Changes in vital signs over time

[redacted]

Phase II (Part 2) Study Outcome Measures

Primary Efficacy Outcome Measure

- Proportion of responder subjects at Day 28, defined as subjects with both Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) score of 0 (clear) or 1 (almost clear) (on a 5-point scale) and a reduction of ≥ 2 points from baseline

Note: Subjects who have received rescue treatments will be considered non-responders

[redacted]

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[redacted]

Safety Outcome Measures

- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of withdrawals from the study due to TEAEs
- Changes from baseline in study treatment application site reaction assessment

Name of Sponsor/Company: Amytrx Therapeutics, Inc.	
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- Changes and shifts in laboratory measurements over time
- Changes in vital signs over time

Study Population:

Phase I (Part 1):

Male and female subjects who are 18 years and older, who have been diagnosed with mild to moderate AD for at least 6 months prior to study enrollment.

Phase II (Part 2):

Male and female subjects who are 18 years and older, who have been diagnosed with mild to moderate AD for at least 6 months prior to study enrollment, and with AD affecting 5% to 30% of the total BSA at the time of enrollment.

Trial Design:

This is an adaptive, Phase I/II study in 2 parts: Part 1 (Maximum Tolerable Dose (MTD) Finding by maximum percentage of BSA treated) and Part 2 (evaluating efficacy of AMTX-100 *CF3* 1.1% w/w versus placebo (vehicle)).

Phase I (Part 1) Study Design

Part 1 of this study is an open-label, dose escalation study of the safety and tolerability of topically applied AMTX-100 *CF* in adult patients with mild to moderate AD. Part 1 of this study is designed to determine the MTD of AMTX-100 *CF* (1.1% w/w concentration) for the highest treated percentage of the BSA affected with AD. The MTD is defined as 1 cohort dose level below the dose, in which dose limiting toxicities (DLTs) as defined below were observed. In total, five (5) cohort dose levels will be tested sequentially by escalating applications of AMTX-100 *CF* 1.1% to higher percentages of BSA affected with AD at each cohort. Each enrolled subject will receive the assigned dose of open-label AMTX-100 *CF*1.1% w/w to be applied twice daily to all treatable lesions of AD (excluding the scalp, face, eyes, eyelids, neck, hands, palms, feet, groin, genitals or in the axillae) for 7 consecutive days (14 applications in total), regardless of whether the lesions become clinically clear during the 7 day treatment period.

Five (5) cohorts will be sequentially enrolled in the Part 1 of the study. Each cohort will include five (5) subjects with eligible, treatable percentages of BSA affected with AD per below:

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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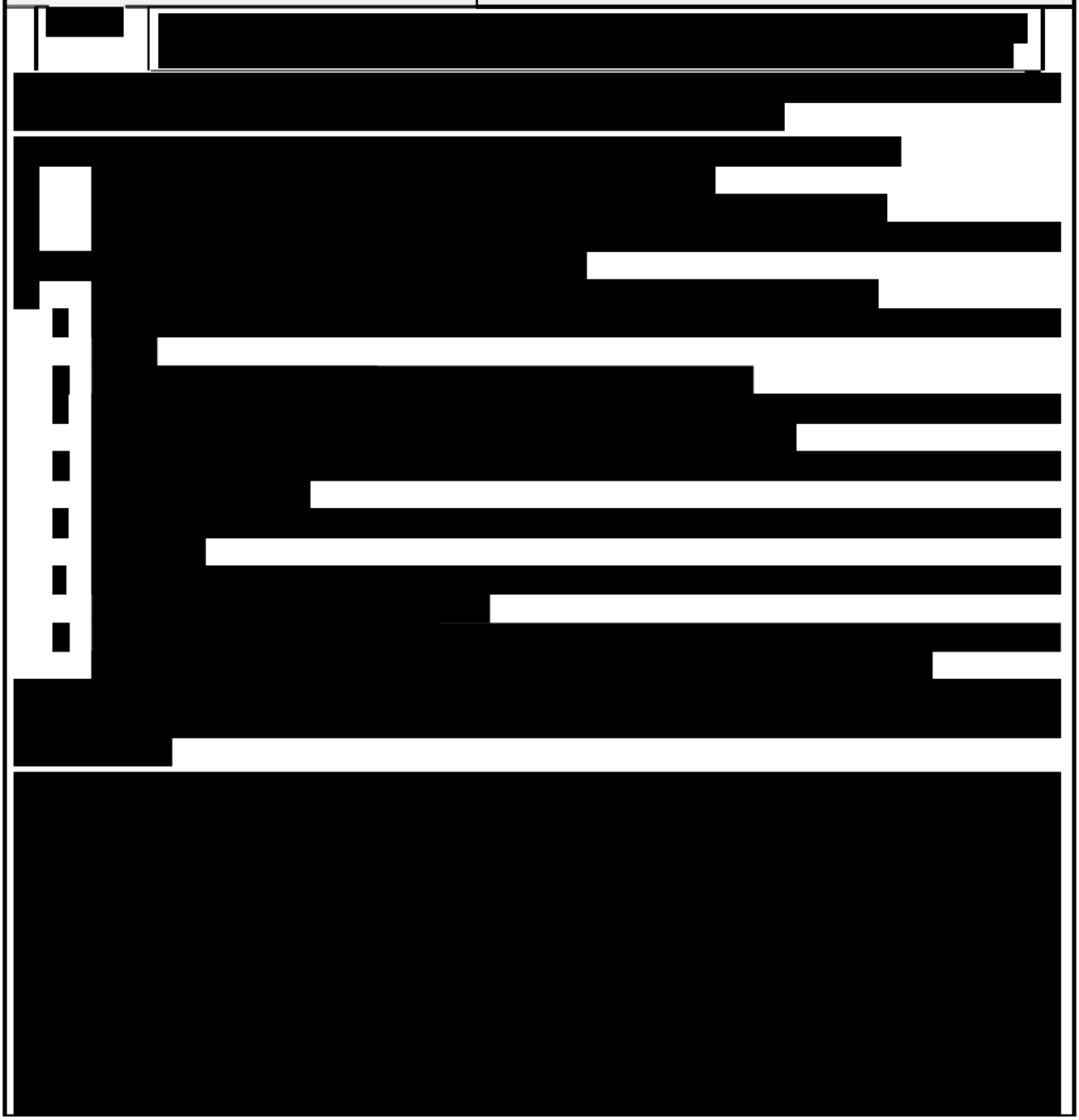

Name of Sponsor/Company: Amytrx Therapeutics, Inc.	
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Protocol Number: AMTX100-AD-01	**Indication:** Mild to Moderate Atopic Dermatitis in Adults

[redacted]

Phase II (Part 2) Study Design

Phase II (Part 2) of this study is a multi-center, double-blind, randomized, vehicle-controlled study of the safety and efficacy of topically applied AMTX-100 *CF3* in adult patients with Mild to Moderate AD. Sixty (60) subjects will be enrolled in two groups of AMTX-100 *CF3* 1.1% w/w and placebo (vehicle). The subjects will be randomized in a 1:1 ratio, thus thirty (30) subjects will be randomized to Group A (AMTX-100 *CF3* 1.1% w/w) and thirty (30) subjects will

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be randomized to Group B (placebo (vehicle 0% w/w)). Each enrolled subject, after screening and randomization, will receive AMTX-100 *CF3* 1.1% w/w or placebo (vehicle) to be applied twice daily to all treatable AD lesions regardless of whether the AD lesions become clinically clear or not (excluding the scalp, face, eyes, eyelids, hands, palms, feet, groin, genitals or in the axillae) for 28 consecutive days.

The dosing regimens for each group are as follows:

Group	Description
Group A	AMTX-100 *CF3* dose concentration of 1.1% w/w, topically applied twice a day for 28 consecutive days to all treatable AD affected areas
Group B	Placebo (Vehicle) (0% w/w), topically applied twice a day for 28 consecutive days to all treatable AD affected areas

[redacted]

[redacted]

[redacted]

Name of Sponsor/Company:
Amytrx Therapeutics, Inc.

Name of Study Product: AMTX-100 *CF3* Topical Cream
Comparator Product: Placebo (Vehicle)

Protocol Number:	**Indication:**
AMTX100-AD-01	Mild to Moderate Atopic Dermatitis in Adults

[redacted]

Projected Study Timelines

Phase I (Part 1) Study Timelines

Duration of Screening Period: up to 3 weeks

Duration of the Treatment Period: 7 days (1 week)

Safety Follow-up phase: 2 weeks

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Total Study Duration: Up to 6 weeks

Phase II (Part 2) Study Timelines

Duration of Screening Period: up to 4 weeks

Duration of the Randomized, Double-blind Treatment Period: 28 days (4 weeks)

Safety Follow-up phase: 2 weeks

Total Study Duration: Up to 10 weeks

Phase I (Part 1) Subject Eligibility

Inclusion Criteria:

Subjects are required to meet ALL of the following criteria for enrollment into the Phase I (Part 1) of the study:

1. Male or female subjects who are 18 years or older
2. If female and not infertile (defined below), the subject must agree for the duration of the study to use one of the following forms of contraception 1) systemic hormonal treatment 2) an intrauterine device (IUD) which was implanted at least 2 months prior to screening or 3) "double-barrier" contraception (condom, diaphragm and spermicide are each considered a barrier). Females are considered to be infertile if they are either a) surgically sterile or b) have had spontaneous amenorrhea for at least the last 2 years and at least 2 years after the onset of amenorrhea while not receiving hormone replacement therapy and had a Follicle-Stimulating Hormone (FSH) level greater than 40 mIU/mL and an estradiol level less than 30 pg/mL
3. All fertile female subjects as described above need to have a negative urine pregnancy test at the screening and baseline visits
4. Subject is capable of providing informed consent and is willing to sign the ICF prior to study Screening and agrees to comply with the study protocol requirements
5. Subject is able to apply topical products on all treatable assigned areas by self and/or caregiver (if applicable), per the Investigator
6. Subject is in general good physical/mental health per the Investigator
7. Subject's Total Body Surface Area (BSA) is between 1.5 and 2.1 m^2 per the Mosteller formula
8. The subject has physician confirmed mild to moderate Atopic Dermatitis (AD) defined by the Eichenfield revised criteria of Hannifin and Rajka, for at least 6 months prior to study enrollment
9. Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™) score of 2 or 3 (mild to moderate) at the screening and baseline visits
10. Subject has Atopic Dermatitis (AD) involvement with eligible treatable percent of the BSA appropriate for topical treatment per the assigned cohort at the screening and baseline visits per below:
    a. Cohort 1: 3% BSA ≤ AD Affected Area ≤ 6% BSA

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b. Cohort 2: 6% BSA < AD Affected Area ≤ 12% BSA

c. Cohort 3: 12% BSA < AD Affected Area ≤ 24% BSA

d. Cohort 4: 24% BSA < AD Affected Area ≤ 48% BSA

e. Cohort 5: 48% BSA < AD Affected Area ≤ 70% BSA

[redacted]

Phase I (Part 1) Subject Eligibility

Exclusion Criteria:

Subjects are required to meet NONE of the following criteria for enrollment into the Phase I (Part 1) of the study:

1. Pregnant or lactating females or women who are planning for pregnancy in the next 6 months
2. Women at postpartum for 3 months or less prior to screening
3. Serious medical illnesses such as end-stage renal disease, liver failure or heart failure that, in the opinion of the Investigator may interfere with the conduct of the study
4. Subjects with abnormal vital signs, physical and dermatological exams or clinical laboratory evaluations considered clinically significant by the Principal Investigator, which in the opinion of the PI would significantly interfere with the study conduct
5. Subjects with any concurrent skin condition that could interfere with the evaluation of the treatment areas, as determined by the investigator
6. The subject has a planned major surgical intervention for a pre-existing condition within the duration of the study
7. The subject has a history of drug or alcohol abuse that would impair or risk the subject's full participation in the study, in the opinion of the investigator.
8. Participation in a clinical trial within 3 months, or more than two clinical trials within 12 months prior to screening
9. Concurrent or recent use of topical steroids, topical immunosuppressive/immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar (except when used as shampoo) or salicylic acid within 14 days of the baseline visit
10. The subject has severe AD as determined by vIGA-AD™ score higher than 3
11. The subject cannot avoid systemic treatments (including systemic corticosteroids, immunotherapy, biologics or phototherapy) for AD during the study per the Investigator

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12. The subject has previously received any systemic treatments, immunotherapy, biologics or phototherapy for AD within 12 months prior to study enrollment
13. Current or expected use of prohibited medications as described in Section 7, unless approved by the study Medical Monitor
14. The subject has concurrent contact dermatitis or history of anaphylactic reaction

Phase II (Part 2) Subject Eligibility

Inclusion Criteria:

Subjects are required to meet ALL of the following criteria for randomization into the Phase II (Part 2) of the study:

1. Male or female subjects who are 18 years or older.
2. If female and not infertile (defined below), the subject must agree for the duration of the study to use one of the following forms of contraception 1) systemic hormonal treatment 2) an intrauterine device (IUD) which was implanted at least 2 months prior to screening or 3) "double-barrier" contraception (condom, diaphragm and spermicide are each considered a barrier). Females are considered to be infertile if they are either a) surgically sterile or b) have had spontaneous amenorrhea for at least the last 2 years and at least 2 years after the onset of amenorrhea while not receiving hormone replacement therapy.
3. All fertile female subjects as described above need to have a negative urine pregnancy test at the screening and baseline visits.
4. Subject is capable of providing informed consent and is willing to sign the ICF prior to study Screening and agrees to comply with the study protocol requirements.
5. Subject is able to apply topical products on all the treatable areas by self and/or caregiver (if applicable), per the Investigator.
6. Subject is willing and able to comply with all clinic visits and study-related procedures.
7. Subject is able to understand and complete study-related questionnaires.
8. The subject has physician confirmed mild to moderate Atopic Dermatitis (AD) defined by the Eichenfield revised criteria of Hannifin and Rajka, for at least 6 months prior to study enrollment.
9. Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™) score of 2 or 3 (mild to moderate) at the screening and baseline visits.
10. Eczema Area and Severity Index (EASI) score lower than 23 at the screening and baseline visits

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11. Subject has Atopic Dermatitis (AD) involvement of between 5% and 30% of the treatable BSA (excluding the scalp, face, eyes, eyelids, hands, palms, feet, groin, genitals or the axillae) appropriate for topical treatment at the screening and baseline visits.

    Note: *Calculation of Treatable BSA percentage (% of the total BSA that is AD-involved, excluding the scalp, face, eyes, eyelids, hands, palms, feet, groin, genitals or the axillae) will be completed by the "Rule of Nines" method:*

    - *Where values of 9% or 18% of BSA are assigned to specific regions in the adult subject (head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%])*

12. Subjects must be applying an additive-free, basic bland emollient twice-daily for at least 1 week immediately before the baseline visit (Visit 2, Day 0), and to be continued throughout the study.

    Note: *The additive-free, basic bland emollients should be applied no earlier than 1 hour before or after the administration of the study treatment.*

Phase II (Part 2) Subject Eligibility

Exclusion Criteria:

Subjects are required to meet NONE of the following criteria for randomization into the Phase II (Part 2) of the study:

1. Pregnant or lactating females or women who are planning for pregnancy in the next 6 months
2. Women at postpartum for 3 months or less prior to screening
3. Serious medical illnesses such as end-stage renal disease, liver failure or heart failure that, in the opinion of the Investigator may interfere with the conduct of the study
4. Subjects with abnormal vital signs, physical and dermatological exams or clinical laboratory evaluations considered clinically significant by the Principal Investigator, which in the opinion of the PI would significantly interfere with the study conduct
5. Subjects with any concurrent skin condition that could interfere with the evaluation of the treatment areas, as determined by the investigator
6. The subject has a planned major surgical intervention for a pre-existing condition within the duration of the study
7. The subject has a history of drug or alcohol abuse that would impair or risk the subject's full participation in the study, in the opinion of the investigator.
8. Participation in a clinical trial within 3 months, or more than two clinical trials within 12 months prior to screening
9. Concurrent or recent use of prescription moisturizers, topical steroids, topical immunosuppressive/immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar (except when used as shampoo) or salicylic acid within 14 days of the baseline visit

Name of Sponsor/Company: Amytrx Therapeutics, Inc.	
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10. The subject has severe AD as determined by vIGA-AD™ score higher than 3
11. The subject cannot avoid systemic treatments (including systemic corticosteroids, immunotherapy, biologics or phototherapy) for AD during the study per the Investigator
12. The subject has previously received any systemic treatments, immunotherapy, biologics or phototherapy for AD within 12 months prior to study enrollment
13. Current or expected use of prohibited medications and procedures during study treatment, as described in Section 7, unless approved by the study Medical Monitor
14. Subject has unstable AD or any consistent requirement for high-potency topical corticosteroids to manage AD signs and symptoms
15. Subject has a significant active systemic or localized infection, including known actively infected AD
16. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit
17. The subject has previously received AMTX-100 *CF*
18. Subject has any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments
19. The subject has concurrent contact dermatitis; or history of anaphylactic reaction

Sample size:

Sample size for Phase I (Part 1): The sample size of 25 subjects (5 subjects per cohort) for Phase I of this study is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

Sample size for Phase II (Part 2): The sample size of 60 subjects for Phase II of this study is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful results consistent with study objectives.

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Name of Sponsor/Company:

Amytrx Therapeutics, Inc.

Name of Study Product: AMTX-100 *CF3* Topical Cream

Comparator Product: Placebo (Vehicle)

Protocol Number:	**Indication:**
AMTX100-AD-01	Mild to Moderate Atopic Dermatitis in Adults

[redacted]

Statistical Considerations:

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical variables.

Randomization and Blinding:

There is no randomization or blinding for the Phase I (Part 1) of the study.

In Phase II (Part 2) of the study, subjects will be randomized using a web-based randomization system at Visit 2 and site personnel will be trained on this system. Only those subjects who successfully complete the screening phase and meet the study eligibility criteria will proceed to randomization. The randomized subjects will receive study treatment for 28 consecutive days (56 applications in total) and followed up for 2 weeks to assess post-treatment safety.

All subjects, Investigators and their staff, and all Sponsor/CRO personnel involved in the management of the study will be blinded to treatment assignments for the Phase II (Part 2) of the study.

[redacted]

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1 INTRODUCTION

1.1 STATEMENT OF INTENT

The design, conduct and reporting of this trial shall be conducted in compliance with the protocol, International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and all appropriate regulatory requirements. The protocol will follow 21 Code of Federal Regulations (CFR) 50, subpart D and will provide all the necessary safeguards for study subjects. All of the Investigators will have documented training in GCP. Independent monitoring of the trial will be accomplished by utilizing a Contract Research Organization (CRO).

1.2 STUDY BACKGROUND

Atopic Dermatitis (AD) is a chronic, pruritic inflammatory skin disease of unknown origin that usually starts in early infancy, but also affects a substantial number of adults. AD affects 15-30% of children and 2-10% of adults globally, and its prevalence rate is rising (Alhazmi, 2017). AD onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by 5 years of age (Kay, 1994; Perkin, 2004). While the majority of affected individuals have resolution of disease by adulthood, 10% to 30% do not, and a smaller percentage of individuals first develop symptoms as adults (Ellis, 2012).

AD is often associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and asthma (Eichenfield, 2014). AD typically presents with pruritus, xerosis, lichenification, and eczematous lesions. Excoriations and crusting are common and some patients exhibit prurigo nodularis–like lesions. The eczematous changes and its morphology are seen in different locations depending on the age of the patient. In adults, lesions are more diffuse with an underlying background of erythema. The face is commonly involved and is dry and scaly. The mainstays of treatment are moisturization (frequent lukewarm baths, and using petrolatum or Aquaphor, etc.), along with topical steroids (Eichenfield, 2014). For more severe cases, other treatment options such as immunomodulators (ex. tacrolimus and pimecrolimus), biologicals (ex. dupilumab and omalizumab), topical phosphodiesterase-4 (PDE-4) inhibitors (ex. crisaborole), probiotics and phototherapy are also used (Sidbury, 2014). All of these options for AD management, and many of these treatment regimens are considered expensive and with various side effects in chronic use. Thus, patients with AD are in need of new treatment options that are efficacious and safe in the long term use.

AMTX-100 *CF3* drug product is formulated as a water-based, topical cream incorporating a 28-amino acid synthetic polypeptide (AMTX-100) as the active pharmaceutical ingredient (API). AMTX-100 is a chimeric, cell-penetrating, bifunctional nuclear transport modifier (NTM), that is engineered to modulate nuclear transport of transcription factors (NF-κB, NFAT, AP-1 and STAT1) involved in activation of gene expression of key mediators of inflammation (TNFα, IL-1β, IL-6, IL-17, MCP-1, etc.) and metabolic syndrome (ChREBP and SREBP) by importin α/β complex and importin β,

respectively. This further leads to a reduction in pro-inflammatory cytokine/chemokine production and carbohydrate and lipid metabolic products.

Several nonclinical safety studies have been conducted with AMTX-100 and AMTX-100 *CF* to evaluate its toxicological profile and additional studies are currently ongoing. Substantial scientific literature is also available on the anti-inflammatory mechanisms of AMTX-100.

The current study is designed to evaluate the safety and tolerability of open-label topically applied AMTX-100 *CF3* (in 1.1% concentration) and to evaluate the safety and efficacy of topically applied AMTX-100 *CF3* (1.1% w/w) in adult patients with mild to moderate AD.

[redacted]

1.3.1 AMTX-100 PRE-CLINICAL STUDIES

Several nonclinical safety studies have been conducted with AMTX-100 and AMTX-100 *CF* to evaluate its toxicological profile; additional studies are currently ongoing. Substantial scientific literature is also available on the anti-inflammatory mechanisms of AMTX-100.

1.4 STUDY DESIGN RATIONALE

Following substantial prior pre-clinical studies, to further evaluate the safety and efficacy of different doses of AMTX-100 drug product in improving symptoms associated with mild to moderate atopic dermatitis, Amytrx Therapeutics, Inc (Sponsor) plans to conduct this Two-part, Phase I/II, Multi-center, Double-Blind, Randomized, Vehicle-controlled Study of the Safety and Efficacy of topically applied AMTX-100 *CF* in adult patients with Mild to Moderate Atopic Dermatitis.

1.5 RISKS AND BENEFITS, AND PRECAUTIONS TO MINIMIZE RISK

To ensure that AMTX-100 (active pharmaceutical ingredient) and AMTX-100 *CF* (topical formulation) are safe as a human therapeutic agent, below safety studies were conducted. All toxicology studies of AMTX-100 *CF* and AMTX-100 are listed in Table 1-1, including information on the Good Lab Practices (GLP) status and testing facility.

[redacted]

All these study results indicate that AMTX-100 *CF* topical formulation is safe for clinical application. Based on the current data, AMTX-100 may show anti-inflammatory mechanism of action and improve symptoms associated with atopic dermatitis.

1.5.1 Allergic Reaction

Pre-clinical studies have not shown that AMTX-100 or AMTX-100 *CF* topical administration might be associated with allergic reactions, however in this first in human study sufficient surveillance of any adverse events and administration reactions will be conducted.

1.5.2 Pregnancy

Risks to unborn babies are unknown at this time, thus pregnant females will be excluded from this study. Females of childbearing potential must have a negative pregnancy test prior to enrollment and must agree to use appropriate birth control methods throughout the study duration (excluding women who are not of childbearing potential).

1.5.3 Venipuncture for Blood Sampling

Venipuncture for blood sample collection carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

1.5.4 Unknown Risks

As with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

[redacted]

2 STUDY OBJECTIVES

This is an adaptive, Phase I/II study in 2 parts: Part 1 (Maximum Tolerable Dose (MTD) Finding by maximum BSA percentage treated) and Part 2 (evaluating efficacy of AMTX-100 *CF3* versus placebo (vehicle)).

Phase I (Part 1) Objectives:

- The primary objective of Part 1 of this study is to determine the MTD of topically applied AMTX-100 *CF* (in 1.1% w/w concentration) in adult patients with mild to moderate Atopic Dermatitis (AD) while escalating the treatable BSA involved in sequential cohorts.
- The secondary objective of Part 1 of this study is to evaluate the safety, tolerability and efficacy of topically applied AMTX-100 *CF* (in 1.1% w/w concentration) in improving symptoms associated with mild to moderate Atopic Dermatitis in adults.

Phase II (Part 2) Objectives:

- The primary objective of Part 2 of this study is to evaluate efficacy of AMTX-100 *CF3* 1.1% w/w versus placebo (0 % w/w)(Vehicle).
- The secondary objective of Part 2 of this study is to evaluate the safety and tolerability of AMTX-100 *CF3* 1.1% w/w compared to placebo (0 % w/w).

[redacted]

3 STUDY DESIGN

This is an adaptive, Phase I/II study in 2 parts: Part 1 (Maximum Tolerable Dose (MTD) Finding by maximum BSA percentage treated) and Part 2 (evaluating efficacy of AMTX-100 *CF3* 1.1% w/w concentration versus placebo (vehicle)).

3.1 PHASE I (PART 1) STUDY DESIGN

Part 1 of this study is an open-label, dose escalation study of the safety and tolerability of topically applied AMTX-100 *CF* in adult patients with mild to moderate AD. Part I of this study is designed to determine the MTD of AMTX-100 *CF* (1.1% w/w concentration) for the highest treated percentage of the BSA affected with AD. The MTD is defined as 1 cohort dose level below the dose, in which dose limiting toxicities (DLTs) as defined below were observed.

In total, five (5) cohort dose levels will be tested sequentially by escalating AMTX-100 *CF* 1.1% to higher percentage of BSA affected with AD at each cohort. Each enrolled subject will receive the assigned dose of Open-label AMTX-100 *CF* 1.1% w/w to be applied twice daily to all treatable lesions of AD (excluding the scalp, face, eyes, eyelids, neck, hands, palms, feet, groin, genitals or in the axillae) for 7 consecutive days (14 applications in total), regardless of whether the lesions become clinically clear during the 7 days treatment period.

[redacted]

For schematics of the cohort escalation and design of Phase I (Part 1) of the study, see text Figure 3-1 and Figure 3-2.

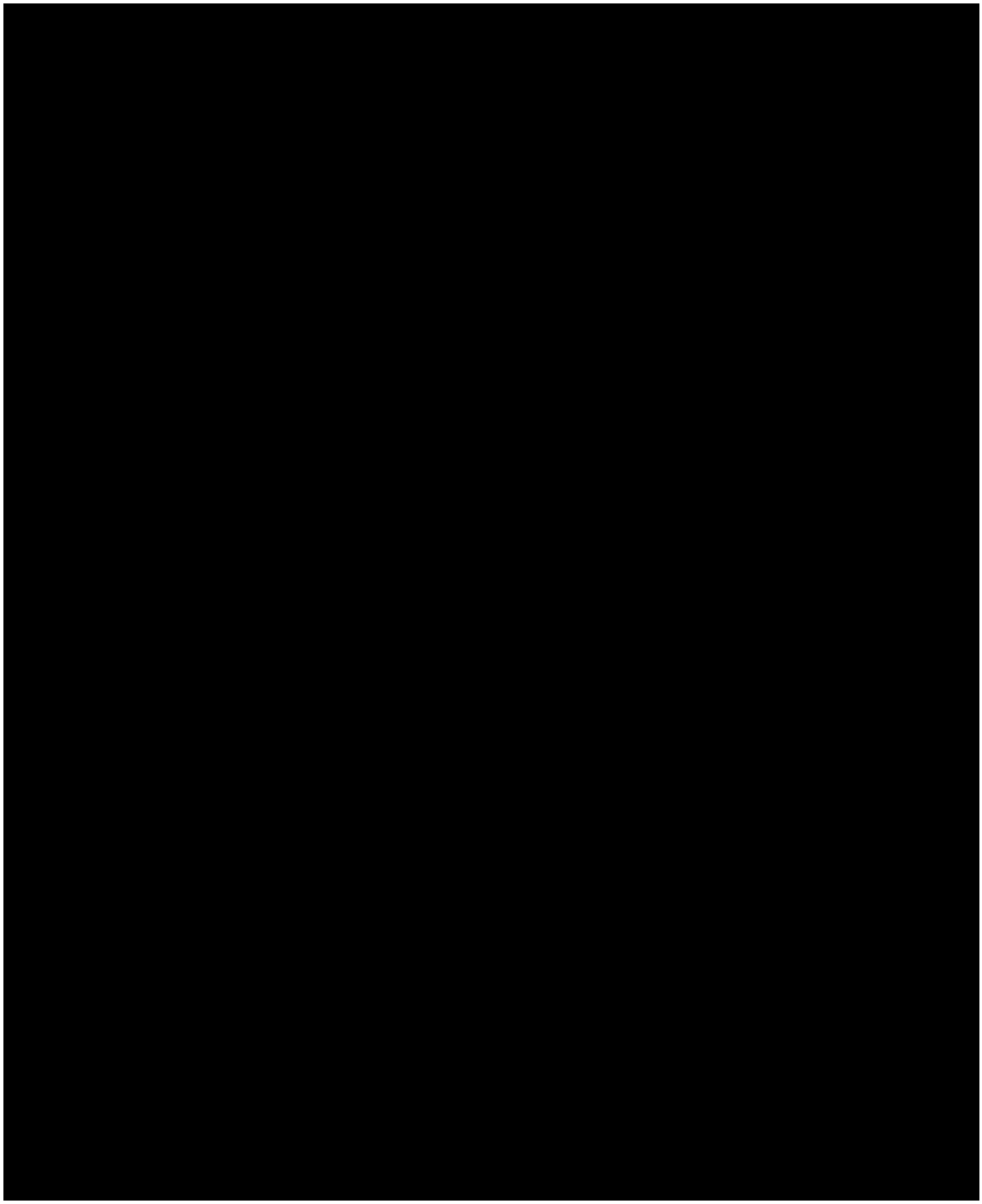
[redacted]

3.2 PHASE I (PART 1) STUDY VISITS

[redacted]

[redacted]

Assuming no DLTs occur at any cohorts, in Part 2 (Phase II) of the study, 1.1% w/w dose concentration of AMTX-100 *CF3* will be further evaluated for the safety and efficacy, compared to placebo (vehicle), in adult patients with mild to moderate AD, with up to 30% treatable BSA involvement.



3.3 PHASE II (PART 2) STUDY DESIGN

Phase II (Part 2) of this study is a multi-center, double-blind, randomized, vehicle-controlled study of the safety and efficacy of topically applied AMTX-100 *CF3* in adult patients with Mild to Moderate AD. Sixty (60) subjects will be enrolled in 2 groups of AMTX-100 *CF3* and placebo (vehicle). The subjects will be randomized in a 1:1 ratio, thus thirty (30) subjects will be randomized in each group (Group A: Treatment 1.1% w/w of AMTX-100 *CF3*) and Group B: placebo (vehicle 0% w/w)). Each enrolled subject, after screening and randomization, will receiveAMTX-100 *CF3* 1.1% w/w or placebo (vehicle) to be applied twice daily to all treatable AD lesions (excluding the scalp, face, eyes, eyelids, hands, palms, feet, groin, genitals or in the axillae) for 28 consecutive days.

The study groups are as follows:

- **Group A**: AMTX-100 *CF3* dose concentration (1.1% w/w), topically applied twice a day for 28 consecutive days to all treatable AD affected areas
- **Group B**: Placebo (Vehicle) (0% w/w), topically applied twice a day for 28 consecutive days to all treatable AD affected areas

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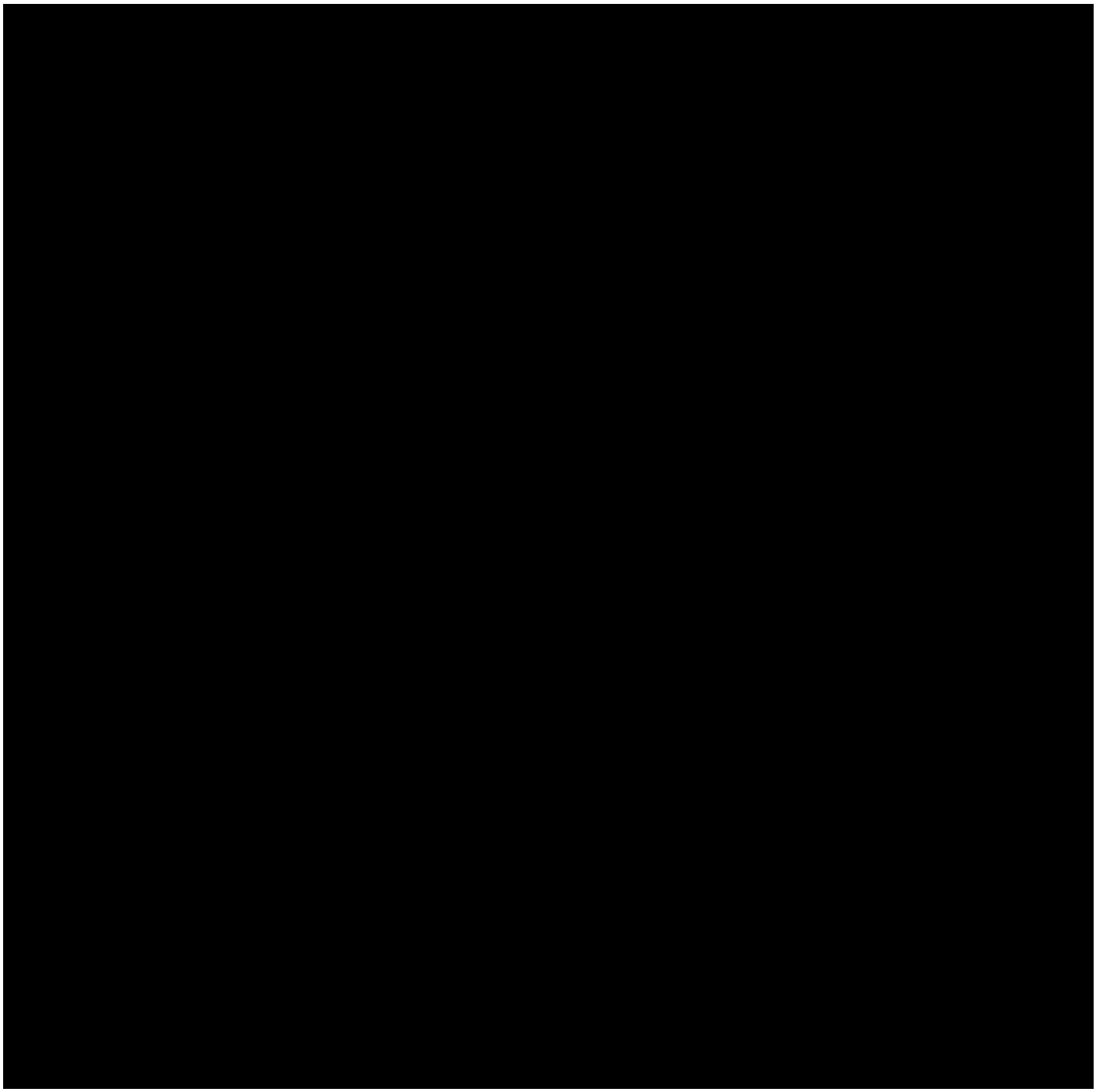
[redacted]

3.4 PHASE II (PART 2) STUDY VISITS

[redacted]



3.5 STUDY POPULATION

3.5.1 NUMBER OF SUBJECTS

Phase I (Part 1): Twenty-five (25) subjects will be enrolled in Phase I of the study at up to 5 centers within the USA, including hospitals and freestanding/outpatient dermatology or allergy/immunology clinics. The sample size of 25 subjects (5 subjects per cohort) for phase I of this study is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

Phase II (Part 2): Sixty (60) subjects will be enrolled in Phase II of the study at up to 20 centers within the USA, including hospitals and freestanding/outpatient dermatology or allergy/immunology clinics. The sample size of 60 subjects for Phase II of this study is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful results consistent with study objectives.

3.5.2 SUBJECT SOURCES

Patients referred to and those who are current patients of hospitals and freestanding/outpatient dermatology or allergy/immunology clinics for treatment of atopic dermatitis will be eligible for the study.

3.5.3 PHASE I (PART 1) INCLUSION CRITERIA

Subjects are required to meet ALL of the following criteria for enrollment into the Phase I (Part 1) of the study:

1. Male or female subjects who are 18 years or older
2. If female and not infertile (defined below), the subject must agree for the duration of the study to use one of the following forms of contraception 1) systemic hormonal treatment 2) an intrauterine device (IUD) which was implanted at least 2 months prior to screening or 3) "double-barrier" contraception (condom, diaphragm and spermicide are each considered a barrier). Females are considered to be infertile if they are either a) surgically sterile or b) have had spontaneous amenorrhea for at least the last 2 years and at least 2 years after the onset of amenorrhea while not receiving hormone replacement therapy and had a Follicle-Stimulating Hormone (FSH) level greater than 40 mIU/mL and an estradiol level less than 30 pg/mL
3. All fertile female subjects as described above need to have a negative urine pregnancy test at the screening and baseline visits
4. Subject is capable of providing informed consent and is willing to sign the ICF prior to study Screening and agrees to comply with the study protocol requirements
5. Subject is able to apply topical products on all treatable assigned areas by self and/or caregiver (if applicable), per the Investigator

6. Subject is in general good physical/mental health per the Investigator
7. Subject's Total Body Surface Area (BSA) is between 1.5 and 2.1 m^2 per the Mosteller formula
8. The subject has physician confirmed mild to moderate Atopic Dermatitis (AD) defined by the Eichenfield revised criteria of Hannifin and Rajka, for at least 6 months prior to study enrollment
9. Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™) score of 2 or 3 (mild to moderate) at the screening and baseline visits
10. Subject has Atopic Dermatitis (AD) involvement with eligible treatable percent of the BSA appropriate for topical treatment per the assigned cohort at the screening and baseline visits per below:
    f. Cohort 1: 3% BSA ≤ AD Affected Area ≤ 6% BSA
    g. Cohort 2: 6% BSA < AD Affected Area ≤ 12% BSA
    h. Cohort 3: 12% BSA < AD Affected Area ≤ 24% BSA
    i. Cohort 4: 24% BSA < AD Affected Area ≤ 48% BSA
    j. Cohort 5: 48% BSA < AD Affected Area ≤ 70% BSA

[redacted]

3.5.4 PHASE I (PART 1) EXCLUSION CRITERIA

Subjects are required to meet NONE of the following criteria for enrollment into the Phase I (Part 1) of the study:

1. Pregnant or lactating females or women who are planning for pregnancy in the next 6 months
2. Women at postpartum for 3 months or less prior to screening
3. Serious medical illnesses such as end-stage renal disease, liver failure or heart failure that, in the opinion of the Investigator may interfere with the conduct of the study
4. Subjects with abnormal vital signs, physical and dermatological exams or clinical laboratory evaluations considered clinically significant by the Principal Investigator, which in the opinion of the PI would significantly interfere with the study conduct
5. Subjects with any concurrent skin condition that could interfere with the evaluation of the treatment areas, as determined by the investigator
6. The subject has a planned major surgical intervention for a pre-existing condition within the duration of the study

7. The subject has a history of drug or alcohol abuse that would impair or risk the subject's full participation in the study, in the opinion of the investigator.
8. Participation in a clinical trial within 3 months, or more than two clinical trials within 12 months prior to screening
9. Concurrent or recent use of topical steroids, topical immunosuppressive/immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar (except when used as shampoo) or salicylic acid within 14 days of the baseline visit
10. The subject has severe AD as determined by vIGA-AD™ score higher than 3
11. The subject cannot avoid systemic treatments (including systemic corticosteroids, immunotherapy, biologics or phototherapy) for AD during the study per the Investigator
12. The subject has previously received any systemic treatments, immunotherapy, biologics or phototherapy for AD within 12 months prior to study enrollment
13. Current or expected use of prohibited medications as described in Section 7, unless approved by the study Medical Monitor
14. The subject has concurrent contact dermatitis; or history of anaphylactic reaction

3.5.5 PHASE II (PART 2) INCLUSION CRITERIA

Subjects are required to meet ALL of the following criteria for randomization into the Phase II (Part 2) of the study:

1. Male or female subjects who are 18 years or older.
2. If female and not infertile (defined below), the subject must agree for the duration of the study to use one of the following forms of contraception 1) systemic hormonal treatment 2) an intrauterine device (IUD) which was implanted at least 2 months prior to screening or 3) "double-barrier" contraception (condom, diaphragm and spermicide are each considered a barrier). Females are considered to be infertile if they are either a) surgically sterile or b) have had spontaneous amenorrhea for at least the last 2 years and at least 2 years after the onset of amenorrhea while not receiving hormone replacement therapy.
3. All fertile female subjects as described above need to have a negative urine pregnancy test at the screening and baseline visits.
4. Subject is capable of providing informed consent and is willing to sign the ICF prior to study Screening and agrees to comply with the study protocol requirements.
5. Subject is able to apply topical products on all the treatable areas by self and/or caregiver (if applicable), per the Investigator.
6. Subject is willing and able to comply with all clinic visits and study-related procedures.
7. Subject is able to understand and complete study-related questionnaires.

8. The subject has physician confirmed mild to moderate Atopic Dermatitis (AD) defined by the Eichenfield revised criteria of Hannifin and Rajka, for at least 6 months prior to study enrollment.
9. Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™) score of 2 or 3 (mild to moderate) at the screening and baseline visits.
10. Eczema Area and Severity Index (EASI) score lower than 23 at the screening and baseline visits
11. Subject has Atopic Dermatitis (AD) involvement between 5% and 30% treatable BSA (excluding the scalp, face, eyes, eyelids, hands, palms, feet, groin, genitals or in the axillae) appropriate for topical treatment at the screening and baseline visits.

    Note: *Calculation of Treatable BSA percentage (% of the total BSA that is AD-involved, excluding the scalp, face, eyes, eyelids, hands, palms, feet, groin, genitals or in the axillae) will be completed by Rule of Nines method:*

    - *Where values of 9% or 18% of BSA are assigned to specific regions in the adult subject (head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%])*

12. Subjects must be applying an additive-free, basic, bland emollient twice-daily for at least 1 week immediately before the baseline visit (Visit 2, Day 0), and to be continued throughout the study.

    Note: *The additive-free, basic, bland emollients should be applied no earlier than 1 hour before or 1 hour after the administration of the study treatment.*

3.5.6 PHASE II (PART 2) EXCLUSION CRITERIA

Subjects are required to meet NONE of the following criteria for randomization into the Phase II (Part 2) of the study:

1. Pregnant or lactating females or women who are planning for pregnancy in the next 6 months
2. Women at postpartum for 3 months or less prior to screening
3. Serious medical illnesses such as end-stage renal disease, liver failure or heart failure that, in the opinion of the Investigator may interfere with the conduct of the study
4. Subjects with abnormal vital signs, physical and dermatological exams or clinical laboratory evaluations considered clinically significant by the Principal Investigator, which in the opinion of the PI would significantly interfere with the study conduct
5. Subjects with any concurrent skin condition that could interfere with the evaluation of the treatment areas, as determined by the investigator
6. The subject has a planned major surgical intervention for a pre-existing condition within the duration of the study
7. The subject has a history of drug or alcohol abuse that would impair or risk the subject's full participation in the study, in the opinion of the investigator.

8. Participation in a clinical trial within 3 months, or more than two clinical trials within 12 months prior to screening
9. Concurrent or recent use of prescription moisturizers, topical steroids, topical immunosuppressive/immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar (except when used as shampoo) or salicylic acid within 14 days of the baseline visit
10. The subject has severe AD as determined by vIGA-AD™ score higher than 3
11. The subject cannot avoid systemic treatments (including systemic corticosteroids, immunotherapy, biologics or phototherapy) for AD during the study per the Investigator
12. The subject has previously received any systemic treatments, immunotherapy, biologics or phototherapy for AD within 12 months prior to study enrollment
13. Current or expected use of prohibited medications and procedures during study treatment, as described in Section 7, unless approved by the study Medical Monitor
14. Subject has unstable AD or any consistent requirement for high-potency topical corticosteroids to manage AD signs and symptoms
15. Subject has a significant active systemic or localized infection, including known actively infected AD
16. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit
17. The subject has previously received AMTX-100 *CF*
18. Subject has any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments.
19. The subject has concurrent contact dermatitis; or history of anaphylactic reaction.

4 STUDY SCHEDULE

The schedules for the protocol-specified assessments and procedures for Phase I (Part 1) and Phase II (Part 2) of this study are detailed in this section. Day 0 is used as the day of baseline/randomization and first study treatment administration in both parts of the study. See Table 4-1: Phase I (Part 1) - Study Schedule of Events and Table 4-2: Phase II (Part 2) - Study Schedule of Events.

Table 4-1: Phase I (Part 1) - Study Schedule of Events

Visit		Visit 1 (Screening)	Visit 2 (Phone call)	Visit 3 (Baseline)	Visit 4 (End of Treatment)	Visit 5 (Follow Up)
Days From Randomization		Up to -21 days	Up to -7 days	Day 0	Day +7	Day +21
Weeks From Randomization		Week -3	Week -1	Week 0	Week 1	Week 3
Window Period			±2 days			±2 days
	Protocol Section					
[redacted]		X				
		X	X			
		X				
		X				
		X		X[1]		
		X		X[1]	X	X
		X				
		X		X[1]	X	X
		X		X[1]	X	X
		X		X[1]	X	X
		X		X[1]	X	X
		X		X[1]	X	X
				X[1]	X	X
		X		X[1]	X	X
			X			
				X		
				X		
				2nd dose (PM) on Day 0, then BID through Day 6		
				X[2]	X	
					X	
				X[1][2]	X	X

Visit		Visit 1 (Screening)	Visit 2 (Phone call)	Visit 3 (Baseline)	Visit 4 (End of Treatment)	Visit 5 (Follow Up)
Days From Randomization		**Up to -21 days**	**Up to -7 days**	**Day 0**	**Day +7**	**Day +21**
Weeks From Randomization		**Week -3**	**Week -1**	**Week 0**	**Week 1**	**Week 3**
Window Period			**±2 days**			**±2 days**
	Protocol Section					
[redacted]				X[2]	X	X

Table 4-2: Phase II (Part 2) - Study Schedule of Events

Visit		Visit 1 (Screening)	Visit 2 (Baseline/ Randomization)	Visit 3	Visit 4	Visit 5	Visit 6 (End of Treatment)	Visit 7 (Follow Up)
Days From Randomization		Up to -28 days	Day 0	Day +7	Day +14	Day +21	Day +28	Day +42
Weeks From Randomization		Week -4	Week 0	Week 1	Week 2	Week 3	Week 4	Week 6
Window Period				±1 days	±1 days	±1 days	±1 days	±3 days
	Protocol Section							
[redacted]		X						
		X	X[1]					
		X						
		X	X[1]					
		X	X[1]	X	X	X	X	X
		X						
		X	X[1]		X		X	X
		X	X[1]	X	X	X	X	X
		X	X[1]		X		X	X
			X[1]		X		X	X
			X[1]		X		X	X
		X	X[1]		X		X	X
			X[1]		X		X	X
			X[1]		X		X	X
		X	X[1]				X	X
			X[1]		X		X	X

Visit		Visit 1 (Screening)	Visit 2 (Baseline/ Randomization)	Visit 3	Visit 4	Visit 5	Visit 6 (End of Treatment)	Visit 7 (Follow Up)
Days From Randomization		**Up to -28 days**	**Day 0**	**Day +7**	**Day +14**	**Day +21**	**Day +28**	**Day +42**
Weeks From Randomization		**Week -4**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**
Window Period				**±1 days**	**±1 days**	**±1 days**	**±1 days**	**±3 days**
	Protocol Section							
[redacted]		X	X[1]	X	X	X	X	X
		X	X[1]	X	X	X	X	X
		X	X	X	X	X	X	X
			X[1]		X		X	
			X					
			X[2]	X	X	X		
			X[2]					
			2nd dose (PM) on Day 0, then BID through Day 27					
		Twice daily (no earlier than 1 hour before or after the study treatment administration), starting at least 1 week immediately before the baseline visit (Visit 2, Day 0) and continued throughout the study						
		X	X[2]	X	X	X	X	
			X	X	X	X	X	X
				X	X	X	X	
			X[1][2]	X	X	X	X	X
			X[2]	X	X	X	X	X

Visit		Visit 1 (Screening)	Visit 2 (Baseline/ Randomization)	Visit 3	Visit 4	Visit 5	Visit 6 (End of Treatment)	Visit 7 (Follow Up)
Days From Randomization		**Up to -28 days**	**Day 0**	**Day +7**	**Day +14**	**Day +21**	**Day +28**	**Day +42**
Weeks From Randomization		**Week -4**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**
Window Period				**±1 days**	**±1 days**	**±1 days**	**±1 days**	**±3 days**
	Protocol Section							

4.1 PHASE I (PART 1) STUDY VISITS

4.1.1 PHASE I (PART 1) - VISIT 1: SCREENING VISIT (UP TO -21 DAYS)

The subject will sign and date the ICF, and Health Insurance Portability and Accountability Act (HIPAA) authorization (according to site practices) prior to any study-related procedures. A subject number will be assigned to each subject in successive order of consent signing at each center, beginning with 001 at each site. Each study site will receive a unique numeric designation, and will precede the subject number (e.g. at study center 01 the first two consented subjects would be 01-001 and 01-002; at study center 02 the first two consented subjects would be 02-001 and 02-002).

Screening Visit procedures of Phase I (Part 1) of the study are per below:

[redacted]

4.1.2 PHASE I (PART 1) - VISIT 2 (UP TO – 7 DAYS±2)

If continued to be eligible for the study at Visit 2, the subject will proceed to be enrolled into Phase I (Part 1) of the study. All entrance criteria must be met; and continued study participation should be confirmed via telephone call with the subject by study coordinator or designee, prior to study treatment shipment request. The following assessment will be performed:

[redacted]

4.1.3 PHASE I (PART 1) - VISIT 3: BASELINE VISIT (DAY 0)

The following assessments will be performed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4.1.4 PHASE I (PART 1) - VISIT 4: END OF TREATMENT (WEEK 1: DAY 7)

The following assessments will be performed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

4.1.5 PHASE I (PART 1) - VISIT 5: FOLLOW UP (WEEK 3: DAY 21±2)

After completion of Visit 4 procedures, subject will be followed up 14 days to assess safety and tolerability of topically applied AMTX-100 *CF*. The following assessments will be performed:

[redacted]

4.2 PHASE II (PART 2) STUDY VISITS

4.2.1 PHASE II (PART 2) - VISIT 1: SCREENING VISIT (UP TO -28 DAYS)

The subject will sign and date the ICF, and Health Insurance Portability and Accountability Act (HIPAA) authorization (according to site practices) prior to any study-related procedures. A subject number will be assigned to each subject in successive order of consent signing at each center, beginning with 01 at each site. Each study site will receive a unique numeric designation, and will precede the subject number (e.g. at study center 01 the first two consented subjects would be 01-001 and 01-002; at study center 02 the first two consented subjects would be 02-001 and 02-002).

Screening Visit procedures of Phase II (Part 2) of the study are per below:

[redacted]

[redacted]

4.2.2 PHASE II (PART 2) - VISIT 2: RANDOMIZATION/BASELINE VISIT (DAY 0)

If continued to be eligible for the study at Visit 2, the subject will proceed to be randomized into Phase II (Part 2) of the study. All entrance criteria must be met prior to randomization of a subject into the protocol. The following assessments will be performed:

[redacted]

[redacted]

4.2.3 PHASE II (PART 2) - VISIT 3 (WEEK 1: DAY 7±1)

The following assessments will be performed:

[redacted]

[redacted]

4.2.4 PHASE II (PART 2) - VISIT 4 (WEEK 2: DAY 14±1)

The following assessments will be performed:

[redacted]

4.2.5 PHASE II (PART 2) - VISIT 5 (WEEK 3: DAY 21±1)

The following assessments will be performed:

[redacted]

4.2.6 PHASE II (PART 2) - VISIT 6: END OF TREATMENT (WEEK 4: DAY 28±1)

The following assessments will be performed:

[redacted]

[redacted]

4.2.7 PHASE II (PART 2) - VISIT 7: FOLLOW UP (WEEK 6: DAY 42±3)

After completion of Visit 6 procedures, subject will be followed up 14 days to assess safety and tolerability of topically applied AMTX-100 *CF3*. The following assessments will be performed:

[redacted]

[redacted]

4.3 UNSCHEDULED VISITS

Unscheduled visits may be required in addition to the scheduled visits per the Investigator's discretion. The details of these unscheduled visits with subjects will be recorded in the medical records and on the electronic Case Report Form (eCRF).

4.4 MISSED VISITS

If a subject misses a visit, the site is to make every effort to have the subject return as soon as possible to make up the visit. Once the subject is seen, he/she is to return to his/her original visit schedule.

5 SUBJECT COMPLETION AND WITHDRAWAL, STUDY EARLY DISCONTINUATION

5.1 SUBJECT COMPLETION

[redacted]

5.2 SUBJECT PREMATURE WITHDRAWAL FROM THE STUDY

[redacted]

Reasons for subject withdrawal/discontinuation may constitute one of the following:

- Subject chooses to withdraw
- Subject is withdrawn due to an AE
- Pregnancy or positive pregnancy test
- Lost to follow-up
- The Investigator determines that it is in the subject's best interest
- Excessive protocol deviations, as determined by the Investigator or the Sponsor

- Discontinuation of the study by the Sponsor

[redacted]

Important Notes:

1. Subjects may drop out or be withdrawn at their own request. Although subjects do not need to give a reason for requesting withdrawal from the trial, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.
2. Any subjects reporting Serious Adverse Events (SAEs) that have not been resolved by their last study visit will be followed to resolution or until 30 days after the subject completes the study.
3. Every attempt should be made to collect follow-up information. The reason for withdrawal from the study (if known) will be recorded in the source documents and on the appropriate page of the eCRF.
4. Before a subject is identified as lost-to-follow-up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one follow-up letter.

5.3 SCREEN FAILURES

A subject who has signed the consent form but is not randomized is classified as a screen failure. The screen failure must be entered into the study eCRFs. Subject number, demographic information, and reason for screen failure will be collected. If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject can be re-consented only once more, at least 30 days after the initial screening. The subject will need to be re-consented in such a case and will be assigned a new screening number at the time of re-screening.

5.4 EARLY DISCONTINUATION OF THE CLINICAL TRIAL

[redacted]

[redacted]

6 STUDY TREATMENTS

6.1 METHOD FOR ASSIGNING ELIGIBLE SUBJECTS TO TREATMENT

In Part 1 of the study, study eligible subjects will be assigned to open-label AMTX-100 CF (in 1.1% concentration), based on a cohort assignment schedule prepared by the contracted CRO. Details of the cohort assignment and assignment of the subject number are provided in Section 8.11 and Section 4.1.1.

Subjects in Part 1 of the study will be assigned sequentially to one of the following treatment groups:

[redacted]

After a subject has been determined to be eligible for the treatment in Part 1 of the study, a cohort assignment number will be assigned. Once the cohort assignment number is assigned, it cannot be re-assigned even if the subject is subsequently deemed ineligible or withdraws consent.

[redacted]

In Part 2 of the study, study eligible subjects will be randomized based on a randomization schedule prepared by the contracted CRO. Details of the randomization and assignment of the subject number are provided in Section 8.12 and Section 4.2.1.

Subjects will be randomized in a 1:1 ratio to one of the following treatment groups in Part 2 of the study:

- Active Treatment (Group A): **AMTX-100 *CF3* (1.1% w/w);**
- Placebo (Group B): **Vehicle (0% w/w)**

After a subject has been determined to be eligible for the treatment in the study, a randomization number will be assigned. Once the randomization number is assigned, it cannot be re-assigned even if the subject is subsequently deemed ineligible or withdraws consent.

[redacted]

6.2 STUDY TREATMENT DESCRIPTION

Test treatment for this trial is AMTX-100 *CF3*. AMTX-100 *CF3* is a water-based, white topical cream that will be administered to the AD-affected area twice daily for 7 days (total 14 applications) during Part 1 of this study and for 28 days (total 56 applications) during Part 2 of this study.

AMTX-100 *CF*3 formulation dose per area of skin is 0.002575 g/cm^2 in humans.

AMTX-100 *CF3* formulation will be provided in 1.1% w/w concentration.

The ingredients in each are included in Table 6-1 below. Inactive ingredients used in the manufacturing of the drug product are of pharmacopeial quality.

[redacted]

[redacted]

6.3 STUDY TREATMENT LABELING AND PACKAGING

Study treatment tubes and cartons will be provided under appropriate investigational product labeling.

[redacted]

[redacted]

6.4 STUDY TREATMENT STORAGE

[redacted]

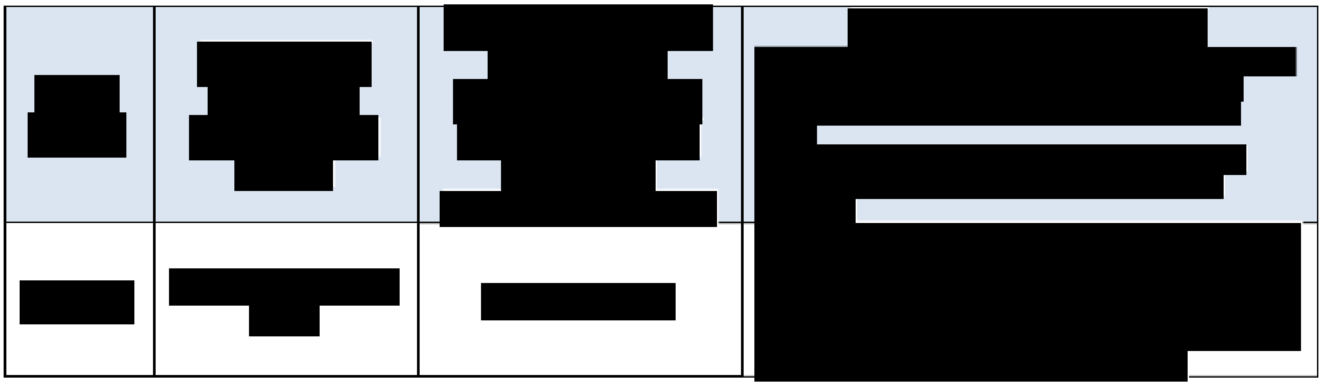
6.5 STUDY TREATMENT ADMINISTRATION

Detailed guidelines for dose of formulation, administration technique and administration direction can be found in the study pharmacy manual.

In Phase I (Part 1) of study, application areas will be all treatable areas, excluding the scalp, face, eyes, eyelids, neck, hands, palms, feet, groin, genitals or in the axillae. The applied amount of AMTX-100 *CF* formulation to the affected assigned areas will depend on the percentage of the BSA affected with AD, as assessed by the investigator, and per the formulation dosing tables in the protocol (refer to Table 6-3).

[redacted]

[redacted]



In Phase II (Part 2) of the study, application areas will be all treatable lesions of AD, excluding the scalp, face, eyes, eyelids, hands, palms, feet, groin, genitals or the axillae. The applied amount of AMTX-100 *CF3* formulation to the affected assigned areas will depend on involvement percentage of treatable BSA, as assessed by the investigator, and per the formulation dosing tables in the protocol and formula of study treatment administration (refer to Table 6-4).

6.6 STUDY TREATMENT DISPENSATION

In Part 1 of the study, subjects will be assigned in the designated cohort (dose level) at the time of screening, using an Interactive Web Response System (IWRS) and each subject enrolled into the study will receive assigned number of study treatment tubes with specific tube serial number via IWRS, per the study cohort assignment scheme and Part 1 study treatment assignment chart (Refer to Table 6-2 and Table 6-3). Site study coordinator or designated site personnel will dispense assigned study treatment tubes to subject in a carton. The subject will receive sufficient instructions on study drug administration compliance and accountability per the above sections.

In Part 2 of the study, subjects will be randomized using a web-based randomization system (IWRS) and each subject enrolled into the study will receive assigned number of study treatment tubes with specific tube serial number via IWRS per the study randomization scheme and Part 2 Dosing Chart (refer

to Table 6-4). The subject will receive sufficient instructions on study drug administration compliance and accountability per the above sections.

6.7 STUDY TREATMENT ACCOUNTABILITY

Study treatments must be used in accordance with this protocol and only under the direction of the responsible investigator. The investigational site must maintain complete and accurate records showing receipt and disposition of all study treatments, including master records listing the date of receipt, the number of the kits received, and a dispensing record which includes each quantity dispensed, identification of the staff member to whom dispensed, the date of dispensing, the intended study participant subject number, and the identification of the preparer. All used and unused study kits will be retained by the investigational site until study treatment accountability can be confirmed by study CRA during the monitoring visits. Instructions will be provided by Sponsor regarding final disposition of all study drug in compliance with applicable regulations.

A study treatment accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the receipt, dispensing and the return/destruction of all the study treatments.

At the conclusion of the study, the Investigator must agree to return or destroy all study materials as instructed by the Sponsor.

6.8 STUDY TREATMENT COMPLIANCE

[redacted]

7 CONCOMITANT AND PROHIBITED MEDICATIONS AND FOODS

Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

All medications and therapies administered or taken by the subject will be recorded in the source documents and on the appropriate page of the eCRF per below:

[redacted]

[redacted]

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose). Note: Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing)

During the study, the subjects will not have any food restrictions, unless food items known to the subject/Investigator to trigger AD symptoms.

8 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

8.1 INFORMED CONSENT

Written informed consent will be obtained for this study by the Investigator or suitably qualified designee from all subjects before the performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to GCP. The Investigator, or designee, must fully inform subjects of all pertinent aspects of the study. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the trial. All questions about the trial must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

8.2 ELIGIBILITY ASSESSMENT

The eligibility assessment will be done as per inclusion and exclusion criteria of this Protocol as described in Sections 3.5.3 and 3.5.4 for Phase I (Part 1) of the study and in Sections 3.5.5 and 3.5.6 for Phase II (Part 2) of the study. Diagnosis of atopic dermatitis (AD) will be based on subjects' medical history and records, and confirmed by the Investigator through physical exam, per the Eichenfield revised criteria of Hannifin and Rajka (Eichenfield, 2014) (refer to text Table 8-1), and through Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™).

8.3 SUBJECT DEMOGRAPHICS

For the purposes of this study, demographic information will include:

- Date of birth
- Gender
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

8.4 MEDICAL HISTORY

All ongoing and any prior medical conditions that have resolved in the past year will be recorded at the Screening Visit (Visit 1).

Events that are reported prior to the first study treatment administration will be recorded as part of the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to receiving study treatment.

Medical histories will be recorded using the body system categories outlined below:

- Cardiovascular
- Lymphatic
- Respiratory
- Hematologic
- Gastrointestinal
- Immunologic
- Renal
- Dermatologic
- Hepatic
- Psychiatric
- Neurological
- Genitourinary
- Endocrine
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of onset/diagnosis
- History status (resolved or ongoing)
- Date of resolution, if applicable

Subject's history of AD will be recorded in the Screening eCRF in more details per below:

- Age of onset
- Age of diagnosis
- Treatable % Total Body Surface Area (BSA) with active AD (Refer to Section 8.13)
- Treatments or procedures received for AD:
    - Within 90 days prior to Screening for topical steroids, topical immunosuppressive/immunomodulative drugs, topical vitamin D3 derivative, topical retinoids, anthralin, coal tar (except when used as shampoo) or salicylic acid
    - Within 12 months prior to Screening for systemic treatments, immunotherapy, biologics or phototherapy

8.5 VITAL SIGNS

The following vital signs will be collected in the CRF and should be in the subject's medical records:

- Blood Pressure (systolic and diastolic)*
- Heart Rate (HR)
- Respiration Rate (RR)
- Temperature

**Note: Blood Pressure will be assessed in "Sitting Position" after 5 minutes' rest.*

8.6 HEIGHT, WEIGHT, BMI AND BSA

Measurements will be taken in street clothing with jacket/coat and shoes removed. Body Mass Index (BMI) will be calculated from the height and weight measurements using the following formulas:

- Metric: BMI = Weight (kg) / [Height (m)]^2
  Or,
- Imperial: BMI= Weight (lb) / [Height (in)]^2 x 703

Total Body Surface Area (BSA) will be calculated from the height and weight measurements using the following Mosteller formula (part 1 only):

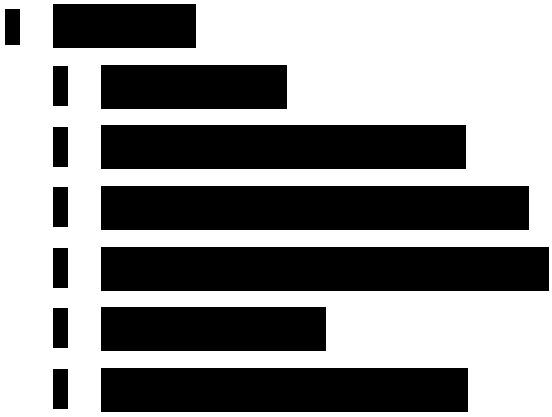
- $BSA(m^2) = \sqrt{\frac{\text{Height (cm) x Weight (kg)}}{3600}}$

8.7 PHYSICAL EXAM

The physical examination will include routine examinations, including dermatologic examination, but not including rectal or genitourinary examinations. All clinically significant abnormalities will be recorded in subject's medical record and on the physical exam CRF page. Any abnormality that, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject will be considered as "clinically significant". After administration of the first dose of study treatment, each physical exam abnormality that is clinically significant will be recorded as an AE.

8.8 LABORATORY ASSESSMENTS

The following lab measurements will be obtained (as part of the subject's medical record) and recorded per the study schedule of events:



8.9 URINE PREGNANCY TEST

Urine pregnancy test will be performed for females of child-bearing potential. The result must be documented on the source documents and in the eCRF. Subjects who are found to be pregnant during the screening period will be considered a screen failure. If pregnancy occurs during the course of the study, the subject will be withdrawn from the study and the pregnancy will be followed up to term for safety purposes. Relevant safety information collected after the study has completed will be reported as supplemental information.

8.10 ELECTROCARDIOGRAM (ECG)

A standard 12-lead ECG will be performed per the site standard procedures. The following parameters will be recorded (as part of the subject's medical record) and recorded on the appropriate page of the CRF: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the ECG reading as either normal or abnormal, and if abnormal, as either "not clinically significant" or "clinically significant." If abnormalities are observed, each will be recorded. Each treatment-emergent abnormality that is clinically significant will be recorded as an AE. Each ECG should be signed by a physician.

8.11 COHORT ASSIGNMENT (PART 1 ONLY, SEQUENTIAL)

In Phase I (Part 1) of the study, five (5) cohort dose levels will be tested sequentially by escalating AMTX-100 *CF* 1.1% application of treatable % BSA involvement at each cohort. Five (5) cohorts will be sequentially enrolled in the Part 1 of the study.

Site personnel will be notified about the cohort (dose level) escalation to the higher dose level cohort. Subjects will be assigned in the designated cohort (dose level) at the time of screening, using an Interactive Web Response System (IWRS) and site personnel will be trained on this system.

8.12 RANDOMIZATION (PART 2 ONLY)

In Phase II (Part 2) of the study, subjects will be randomized using a web-based randomization system at Visit 2 and site personnel will be trained on this system.

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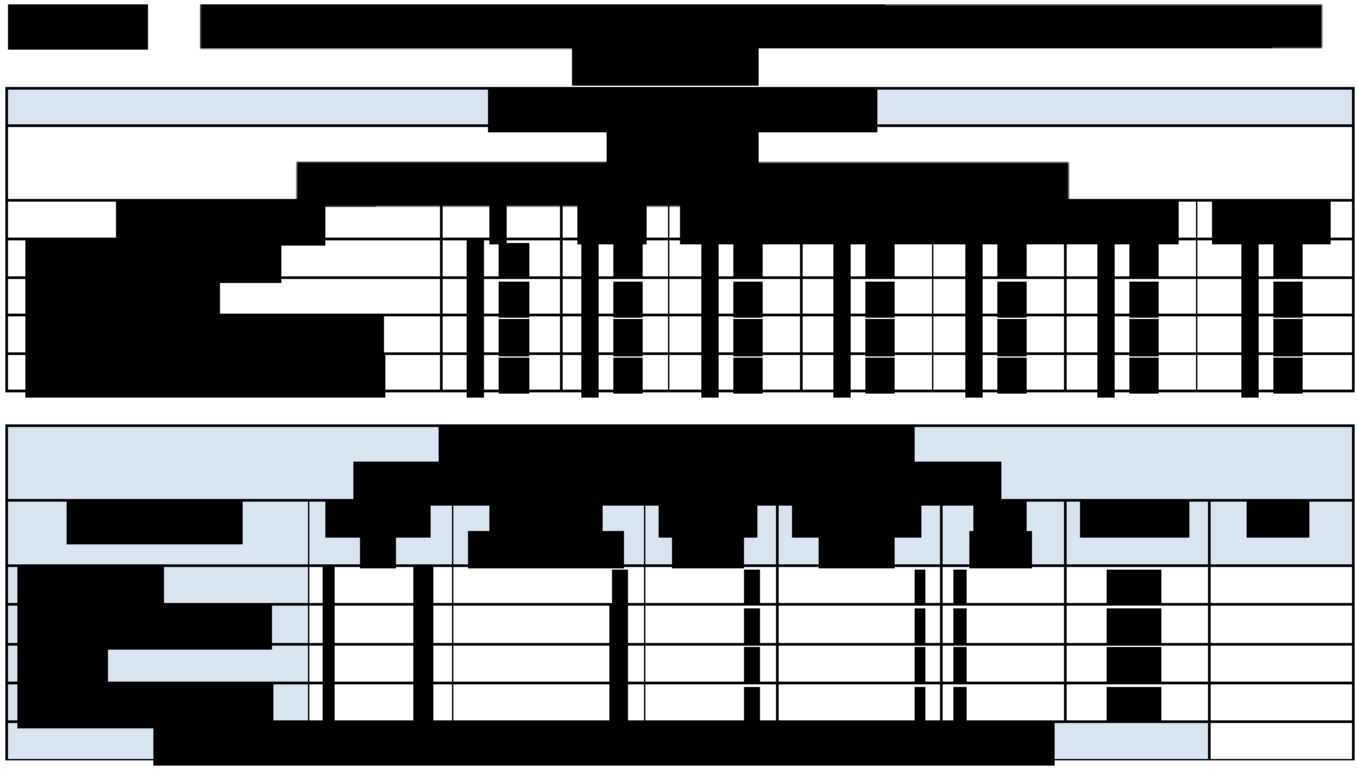

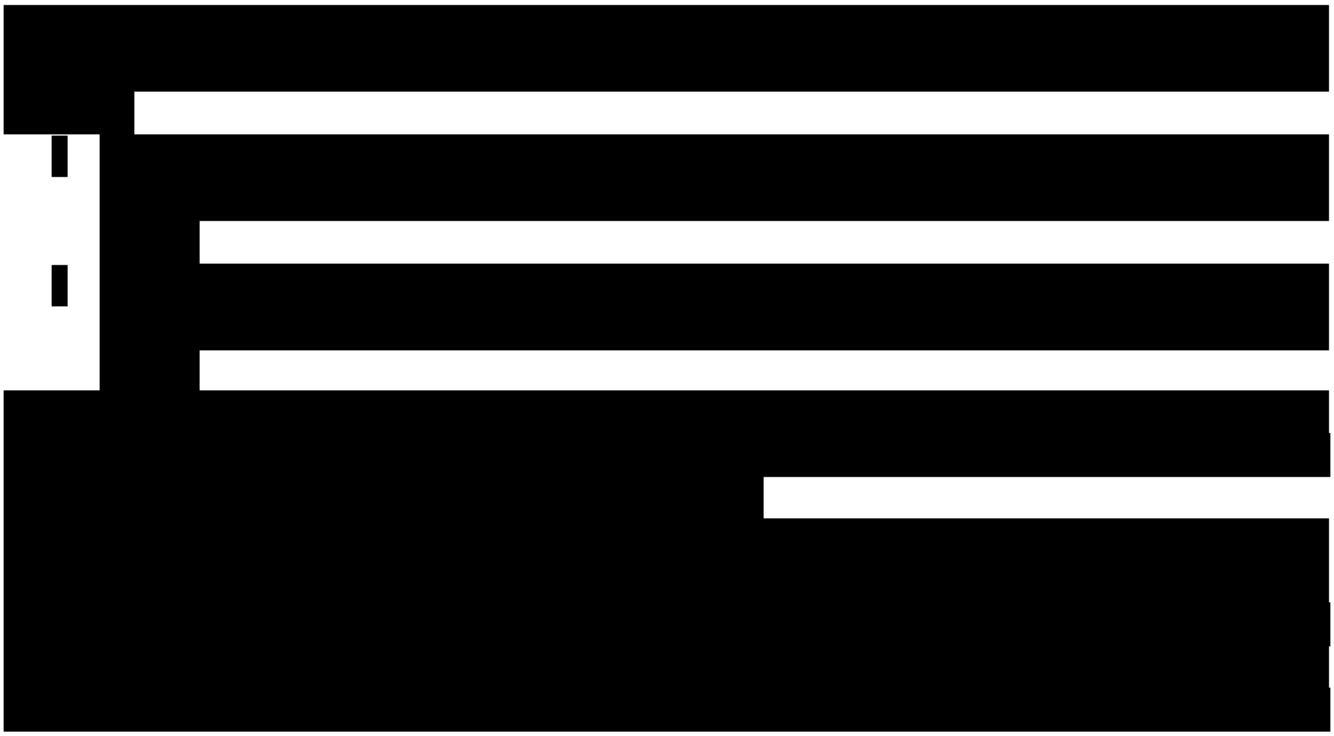

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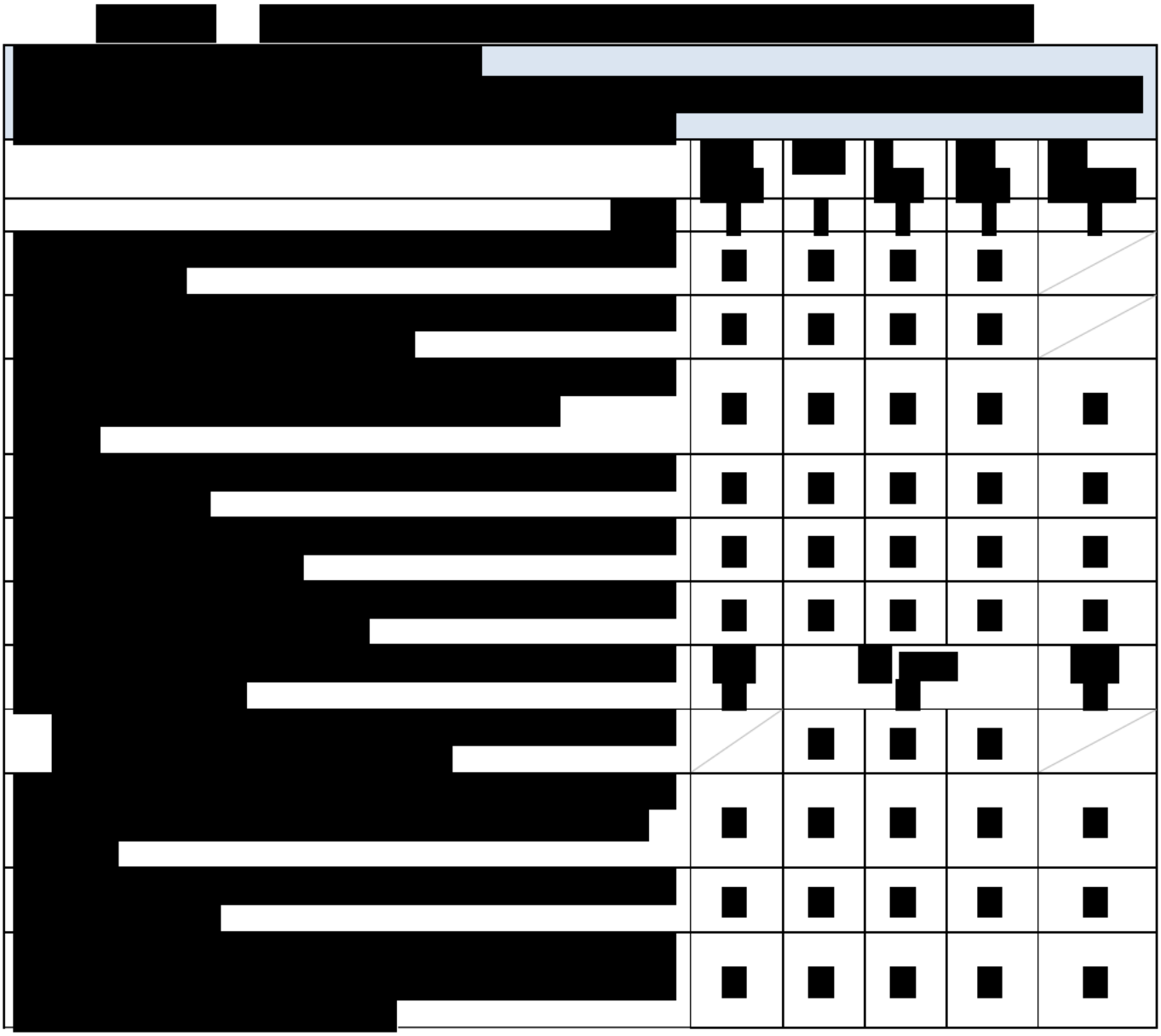

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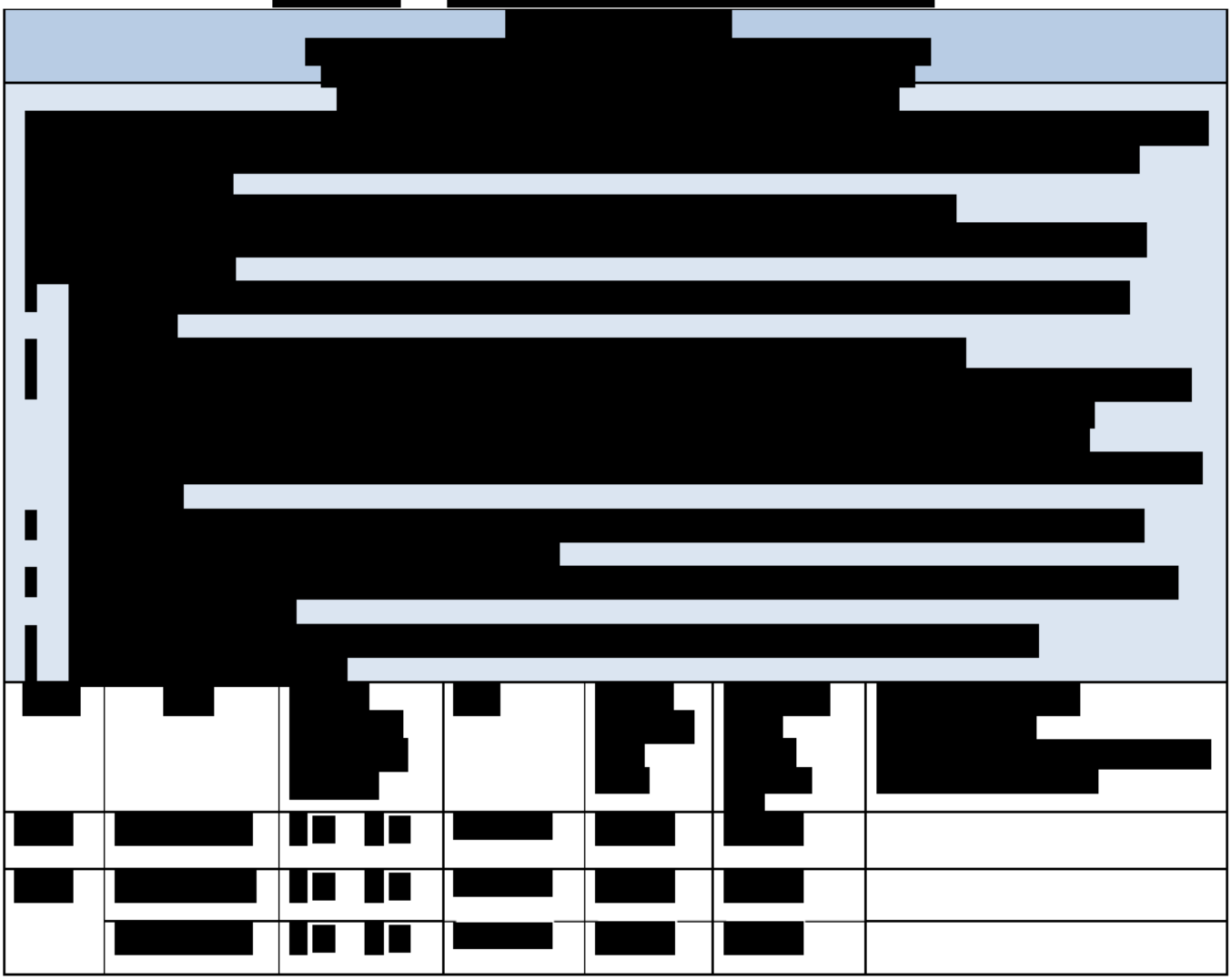

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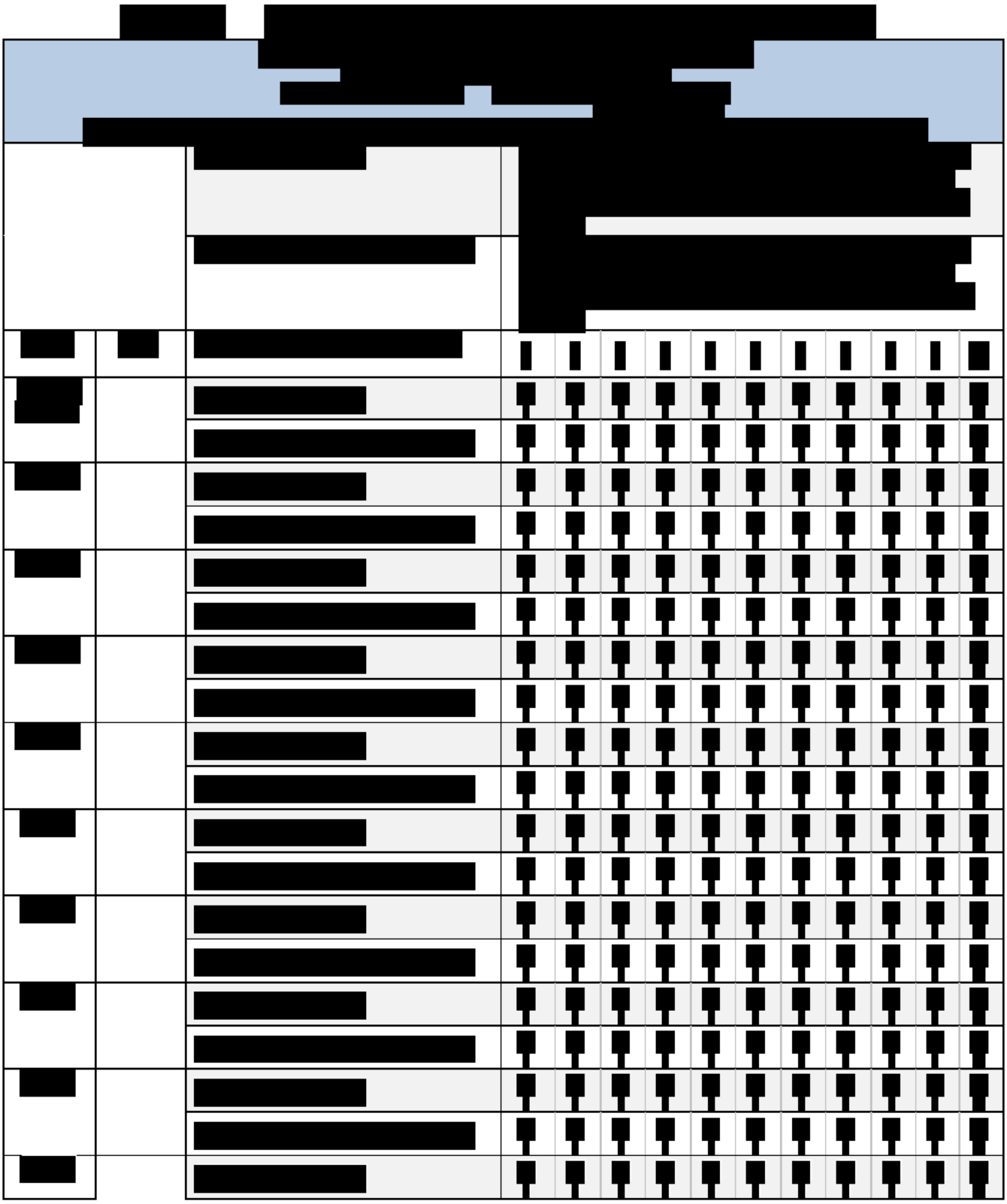

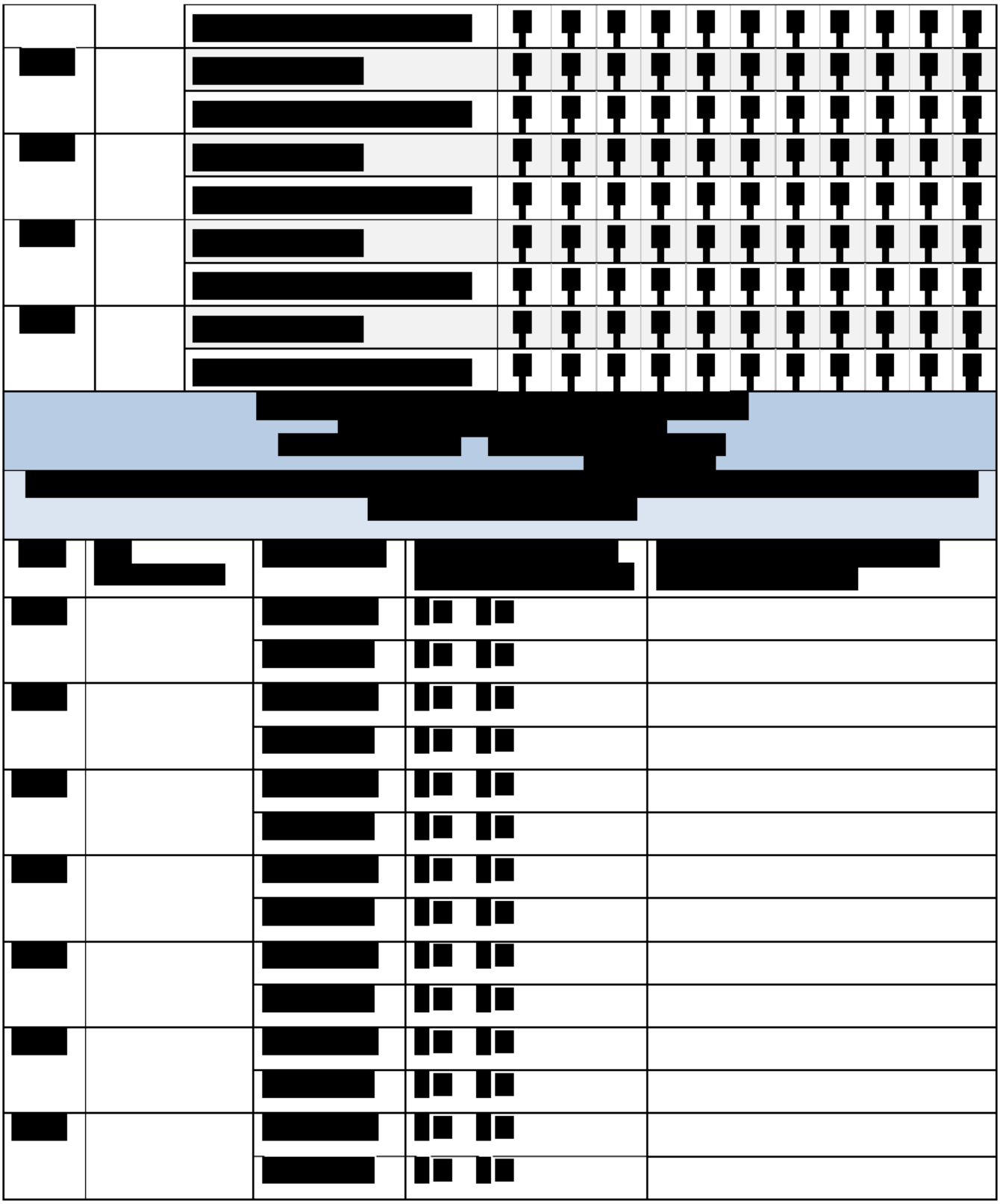

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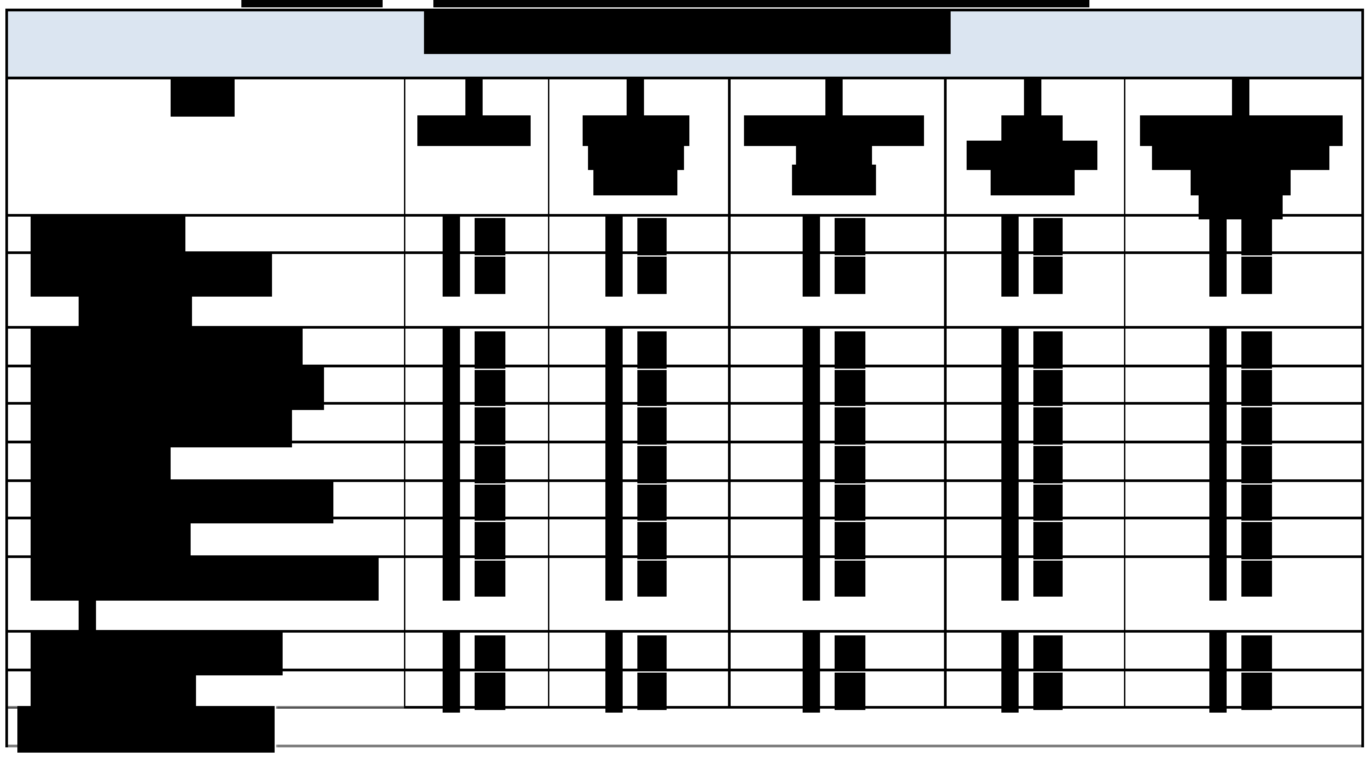

8.21 Study Treatment Shipment Request (Part 1 Only)

In Part 1 of the study, study coordinator or designated site staff will request study treatment shipment via IWRS for eligible subjects per inclusion and exclusion criteria for Phase I (Part 1) of the study, whose continued study participation are confirmed via telephone call at Visit 2. All entrance criteria must be met; and continued study participation should be confirmed via telephone call with the subject by study coordinator or designated site staff, prior to study treatment shipment request (Refer to Section 4.1.2).

[redacted]

[redacted]

9 STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as randomization, covariates, statistical power, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions will be included in a separate document; i.e., the Statistical Analysis Plan (SAP).

9.1 TREATMENT GROUPS

The Part 1 of this study is an open-label, dose escalation study of the safety and tolerability of topically applied AMTX-100 *CF* in adult patients with mild to moderate Atopic Dermatitis (AD). Five (5) cohorts will be sequentially enrolled in this Part 1 of the study. The description of the 5 cohorts is presented below in Table 9-1.

The Part 2 of this study is a multi-center, double-blind, randomized, vehicle-controlled study of the safety and efficacy of topically applied AMTX-100 *CF3* in adult patients with Mild to Moderate Atopic Dermatitis (AD). The description of the treatment groups for this Part of the study is presented below in Table 9-2.

Table 9-2: Treatment Groups in Part 2

Group	Description
Group A	AMTX-100 *CF3* (1.1% w/w), topically applied twice a day for 28 consecutive days to all treatable AD affected areas
Group B	Placebo (Vehicle) (0% w/w), topically applied twice a day for 28 consecutive days to all treatable AD affected areas

9.2 DESCRIPTION OF STUDY OUTCOME MEASURES

9.2.1 PHASE I (PART 1) STUDY OUTCOME MEASURES

9.2.1.1 Primary Outcome Measure:

- Maximum Tolerable Dose (MTD) by maximum percentage of BSA treated, by evaluation of dose-limiting toxicity (DLT) of AMTX-100 *CF* (1.1% w/w concentration) based on the safety profile

9.2.1.2 Safety Outcome Measures:

- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of withdrawals from the study due to TEAEs
- Changes in study treatment application site reaction assessment
- Changes and shifts in laboratory measurements over time
- Changes in vital signs over time treatment

[redacted]

- [redacted]
- [redacted]

9.2.2 PHASE II (PART 2) STUDY OUTCOME MEASURES

9.2.2.1 Primary Efficacy Outcome Measure:

- Proportion of responder subjects at Day 28, defined as subjects with both Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) score of 0 (clear) or 1 (almost clear) (on a 5-point scale) and a reduction of ≥ 2 points from baseline

  Note: Subjects who receive rescue treatments will be considered non-responders

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

9.2.2.4 Safety Outcome Measures

- Incidence of Treatment-Emergent Adverse Events (TEAE)
- Incidence of withdrawals from the study due to TEAEs
- Changes from baseline in study treatment application site reaction assessment
- Changes and shifts in laboratory measurements over time
- Changes in vital signs over time

9.3 Sample Size Determination and Rationale

Sample size for Phase I (Part 1): The sample size of 25 subjects (5 subjects per cohort) for Phase I of this study is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

Sample size for Phase II (Part 2): The sample size of 60 subjects for Phase II of this study is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful results consistent with study objectives.

9.4 Randomization

There is no randomization for the Phase I (Part 1) of the study. In Phase II (Part 2) of the study, subjects will be randomized using a web-based randomization system at Visit 2 and site personnel will be trained on this system. Only those subjects who successfully complete the screening phase and meet the study eligibility criteria will proceed to randomization. The randomized subjects will receive study treatment at the assigned doses for 28 consecutive days (56 applications in total) and followed up for 2 weeks to assess post-treatment safety.

9.5 Blinding and Prevention of Bias

There is no blinding for the Part 1 of the study. However, all subjects, Investigators and their staff, and all Sponsor/CRO personnel involved in the management of the study will be blinded to treatment assignments for the Part 2 of the study. Treatment unblinding for the study will occur after all clinical data have been received, data inconsistencies have been resolved, and the database is locked, except for the interim analysis or for safety reasons on a case-by-case basis (i.e., emergency unblinding).

9.6 INTERIM ANALYSIS (IA)

[redacted]

9.7 GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical variables.

9.8 ANALYSIS POPULATIONS

The details of the analysis populations to be used for the study are described in the below sections.

[redacted]

[redacted]

9.9 HANDLING OF MISSING DATA

All efforts will be made to avoid missing data; however, there will be no imputation of missing data for this early phase study and all summaries will be based on observed data only.

[redacted]

9.11 TYPE I ERROR RATE ADJUSTMENT

This is an early phase study and there is no need for adjustment of Type I error rate.

9.12 STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial. [redacted]

9.12.1 SUBJECT DISPOSITION

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, enrolled/randomized, completed, and discontinued from the study, as well as the reasons for all discontinuations will be summarized for each part of the study. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

9.12.2 Demographics And Baseline Characteristics Analysis

Demographics and baseline characteristics will be summarized for each part of the study using appropriate descriptive statistics.

9.12.3 Concomitant Medications/Therapies

Concomitant medications will be summarized for each part of the study. All prior and concomitant medications recorded in the case report form will be coded to all matching Anatomic Therapeutic Classification codes using the most recent version of the WHO Drug Dictionary. Descriptive summaries will be prepared using the coded term. In addition, all concomitant medications recorded in the case report form will be listed.

9.13 Analyses for the outcomes of the Part 1 study

The primary outcome measure of the Part 1 study is Maximum Tolerable Dose (MTD) by maximum percentage of BSA treated, by evaluation of dose-limiting toxicity (DLT) of AMTX-100 CF (1.1% w/w concentration) based on the safety profile.

AEs will be classified by system organ class (SOC) and preferred term (PT) according to the most recent version of MedDRA dictionary. All AEs that met the dose escalation stopping criteria will be summarized using MedDRA SOC & PT and by relationship to the study treatment for the safety population.

9.14 ANALYSES FOR THE OUTCOMES OF THE PART 2 STUDY

Efficacy Summaries

The efficacy evaluable population will be the primary analysis population for the analysis of the efficacy outcome measures of the Part 2 study. All the primary and secondary outcome measures will be analyzed according to the variable type:

[redacted]

Safety Summaries

Similar to the Part 1 of the study, AEs will be coded using MedDRA. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment groups, system organ class, and preferred term. The following TEAE summaries will be provided:

[redacted]

10 ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this section of the protocol.

10.1 ADVERSE EVENTS

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the subject to have occurred, or a worsening of a pre-existing condition. An AE may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormalities in visit evaluations, physical examination findings or laboratory results that the Investigator believes are clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

10.1.1 REPORTING OF ADVERSE EVENTS

Report initiation for all AEs and SAEs will begin at the time of the first study treatment administration and continue up until the final study visit. All events will be followed to resolution or until they are considered as non-clinically significant event.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be an SAE (see Section 10.2), the impact the event had on study treatment (see Section 10.1.2), the CTCAE grade (intensity) of the event (see Section 10.1.3), the causality of the event (see Section 10.1.4), whether treatment was given as a result of the event (see Section 10.1.5), and the outcome of the event (see Section 10.1.6).

10.1.2 IMPACT ON STUDY TREATMENT

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the subject is no longer in the treatment phase of the protocol, or if the outcome of the event was "death".

10.1.3 SEVERITY (INTENSITY) ASSESSMENT

The guidelines outlined in CTCAE v5.0 will be used for assessing the severity or intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 10-1: CTCAE v5.0 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017

10.1.4 CAUSALITY ASSESSMENT

Adverse events will be assigned a relationship (causality) to the study treatment. The Principal Investigator must review each AE and make the determination of relationship of the event to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) Disappears or is decreased upon discontinuation of the study treatment; (4) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

4. **Unlikely related**: In general this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

10.1.5 Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-medication therapy administered, surgery, or other (with a specification).

10.1.6 Outcome Assessment

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

10.1.7 Expected /Anticipated Adverse Events

[redacted]

10.1.8 Application Site Reactions

For this population, presence of signs/symptoms similar to application site reactions at the eczema lesions at the baseline is expected. Only significant worsening of these signs/symptoms from the baseline per the investigator would be considered adverse events.

[redacted]

[redacted]

10.2 Serious Adverse Events

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the AE)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

10.3 Reporting of Serious Adverse Events (SAE)

The Investigator is required to report all SAEs that occur during the time period specified in Section 10.1.1. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Amarex Safety Department within 24 hours:

CRO Medical Monitor	[redacted] Amarex LLC 20201 Century Boulevard, 4th Floor Germantown, MD 20874 [redacted]

The Amarex Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, discharge summary, hospital notes, etc.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

10.4 SAE FOLLOW-UP

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on CRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The monitors, auditors, personnel authorized by the Sponsor, the local IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research and will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

12 DATA SAFETY MONITORING COMMITTEE (DSMC)

In Phase I (Part 1) of the study, the study will be monitored by an independent Data Safety Monitoring Committee (DSMC) to ensure patient safety. The CRO is responsible for the overall management of the DSMC, including development of its charter and membership selection. The DSMC will be managed in conformance with the FDA guidelines for DSMC independence, management, and oversight.

[redacted]

In Phase II (Part 2) of the study, the DSMC will consider safety data generated during Part 2 of the study and to make recommendations about the IA.

[redacted]

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 MONITORING REQUIREMENTS

In an effort to fulfill the obligations outlined in 21 CFR Part 312 and ICH guidelines which require the Sponsor to maintain current personal knowledge of the progress of a study, the Sponsor's designated monitor will visit the center(s) during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

The Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the CRF. In addition to the original medical records, these data may include but are not limited to, study, laboratory and diagnostic reports, wound images and tracings, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the CRFs, in accordance with federal regulations. A Monitoring Log will be maintained at each study site that the monitor will sign, date, and state the type of visit.

The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA, or other regional regulatory authority.

The final statistical analysis of data will be performed after all clinical monitoring has been completed, all data queries have been resolved, and all data have been verified (Quality Control checked) prior to formal database lock. The Sponsor will authorize the final database lock.

13.2 ACCEPTABILITY OF CASE REPORT FORMS

All CRFs will be completed as soon as possible after the subject's visit. Corrections to data on the CRFs will be made according to standard data correction procedures. The Investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

13.3 MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject’s participation in the trial.

An amendment may also require modification of the ICF. The Investigator will provide an approval letter for the amendment and revised ICF, if applicable, to the Sponsor. An amendment must be in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

13.4 Reporting Protocol Deviations

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

14 ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with the Declaration of Helsinki, GCP, 21 CFR 312, ICH E6, HIPAA regulations in 45 CFR Part 164, and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the change will be reported to the IRB as soon as possible, according to IRB regulations. Additionally, all study products used in this study are manufactured, handled and stored in accordance with applicable Good Manufacturing Practices (GMP) and the products provided for this study will be used only in accordance with this protocol.

14.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The Principal Investigator will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, ICFs, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration.

14.2 INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any study centers participating in this study that cannot comply with these standards will be documented.

14.3 SUBJECT INFORMED CONSENT REQUIREMENTS

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the Principal Investigator and/or designee. Written informed consent will be obtained from each subject accordingly before any procedures or assessments that would not otherwise be

required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The written ICF is to be in compliance with CFR 21 Part 50.27, 45 Part 46 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. Each study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject’s medical record, if allowed by institutional policy.

15 DATA HANDLING AND RECORD KEEPING

15.1 RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical records. If separate research records are maintained by the Investigator(s), the medical records and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to the approved CRFs. The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the Investigator will need to again sign the Investigator signature page. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study. The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and that the subject has provided a signed and dated ICF accordingly as well as the required site HIPAA authorization (if separate from the ICF). The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender; age; eligibility status; reason for ineligibility, if applicable; and study allocated subject number, if applicable.

15.2 CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan. All research data will be entered, either electronically or manually, into a computerized database, designed in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with clinical data manager, including double-data entry. The data will be reviewed, manually and/or electronically, and queries will be prepared for any data discrepancies.

15.3 ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

In accordance with CFR 21 Part 312, study records must be retained by the Investigator for at least two years (or longer per the state/local regulations) after all investigational use of the product is discontinued and the FDA is notified or until two years after the last approval of a marketing application. Study records should not be destroyed without prior written agreement between the Sponsor and the study Investigator. At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Case Report Forms and the source data and the primary records upon which they are based (e.g., subject's progress notes, AE data, test results, and any other diagnostic procedures required to evaluate the progress of the study).
- Signed protocols and protocol amendments
- Laboratory ranges and certifications
- Product accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-Investigator CVs
- Signed informed consent and HIPAA forms
- Subject screening and randomization log
- Serious adverse event reports
- Institutional Review Board approval and re-approval letters
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

16 PUBLICATION PLAN

The Investigator will refer to the Investigator agreement and clinical trial agreement for the publication and disclosure policy.

17 REFERENCES

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18 APPENDICES

18.1 APPENDIX 1: RELATIVE POTENCIES OF TOPICAL CORTICOSTEROIDS

Class (TCS)	Drug	Dosage form(s)
Super high potency	Augmented betamethasone dipropionate 0.05%	Ointment
	Clobetasol propionate 0.05%	Cream, foam, ointment
	Diflorasone diacetate 0.05%	Ointment
	Halobetasol propionate 0.05%	Cream, ointment
High potency	Amcinonide 0.1%	Cream, lotion, ointment
	Augmented betamethasone dipropionate 0.05%	Cream
	Betamethasone dipropionate 0.05%	Cream, foam, ointment, solution
	Desoximetasone 0.25%	Cream, ointment
	Desoximetasone 0.05%	Gel
	Diflorasone diacetate 0.05%	Cream
	Fluocinonide 0.05%	Cream, gel, ointment, solution
	Halcinonide 0.1%	Cream, ointment
	Mometasone furoate 0.1%	Ointment
	Triamcinolone acetonide 0.5%	Cream, ointment
Medium potency	Betamethasone valerate 0.1%	Cream, foam, lotion, ointment
	Clocortolone pivalate 0.1%	Cream
	Desoximetasone 0.05%	Cream
	Fluocinolone acetonide 0.025%	Cream, ointment
	Flurandrenolide 0.05%	Cream, ointment
	Fluticasone propionate 0.05%	Cream
	Fluticasone propionate 0.005%	Ointment
	Mometasone furoate 0.1%	Cream
	Triamcinolone acetonide 0.1%	Cream, ointment
Lower-medium potency	Hydrocortisone butyrate 0.1%	Cream, ointment, solution
	Hydrocortisone probutate 0.1%	Cream
	Hydrocortisone valerate 0.2%	Cream, ointment
	Prednicarbate 0.1%	Cream
Low potency	Alclometasone dipropionate 0.05%	Cream, ointment
	Desonide 0.05%	Cream, gel, foam, ointment

Class (TCS)	Drug	Dosage form(s)
	Fluocinolone acetonide 0.01%	Cream, solution
	Dexamethasone 0.1%	Cream
	Hydrocortisone 0.25%, 0.5%, 1%	Cream, lotion, ointment, solution
	Hydrocortisone acetate 0.5 – 1%	Cream, ointment

[redacted]