STATISTICAL ANALYSIS PLAN
FOR PROTOCOL AMTX100-AD-01

Sponsor:	**Amytrx Therapeutics, Inc.**
Protocol Number:	AMTX100-AD-01 (NCT04313400)
Protocol Title:	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 Version / Date:	Final Version 4.0/ 12 Jul 2023

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Study Part	Part 2
Plan Version:	Final Version 1.0
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Sponsor:	Amytrx Therapeutics, Inc.
Prepared by:	Amarex Clinical Research 20201 Century Boulevard Germantown, Maryland 20874
Study Part:	Part 2
SAP Version:	Final Version 1.0
SAP Date:	29 Aug 2023

I have read and approve the Statistical Analysis Plan specified above and agree on its content:

Statistician, Amarex Clinical Research	Date
Amytrx Therapeutics, Inc. Representative	Date

TABLE OF CONTENTS

ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation/Acronym	**Definition**
ADSL	Subject-Level Analysis Dataset
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Amarex	Amarex Clinical Research, LLC.
ASA	The American Statistical Association
AST	Aspartate Aminotransferase
BID	Twice a Day
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CRO	Contract Research Organization
CTCAE	Common Terminology criteria for Adverse events
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
DSMC	Data Safety and Monitoring Committee
EASI	Eczema Area Severity Index
ECG	Electrocardiogram
EDC	Electronic Data Capture
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Council on Harmonization
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MTD	Maximum Tolerable Dose
Pruritus NRS	Pruritus Numeric Rating Scale
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SOC	System Organ Class
SOP	Standard Operating Procedures
TCS	Topical Corticosteroids
TSLP	Thymic Stromal Lymphopoietin
TEAE	Treatment Emergent Adverse Event
TARC	Thymus and Activation-Regulated Chemokine
USA	United States of America
vIGA-AD™	Validated Investigator Global Assessment scale for Atopic Dermatitis
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for part 2 of the clinical trial protocol AMTX100-AD-01, conducted by Amytrx Therapeutics, Inc.. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objectives of this plan are to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this SAP are structured to provide sufficient detail to meet the requirements specified by the International Council on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this Statistical Analysis Plan will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents were reviewed in preparation of this Statistical Analysis Plan:

- Final protocol Version 4.0/ 12 Jul 2023
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

2. PROTOCOL DESIGN

2.1 Design Overview

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)). The Part 1 of the study has been completed.

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 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.

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

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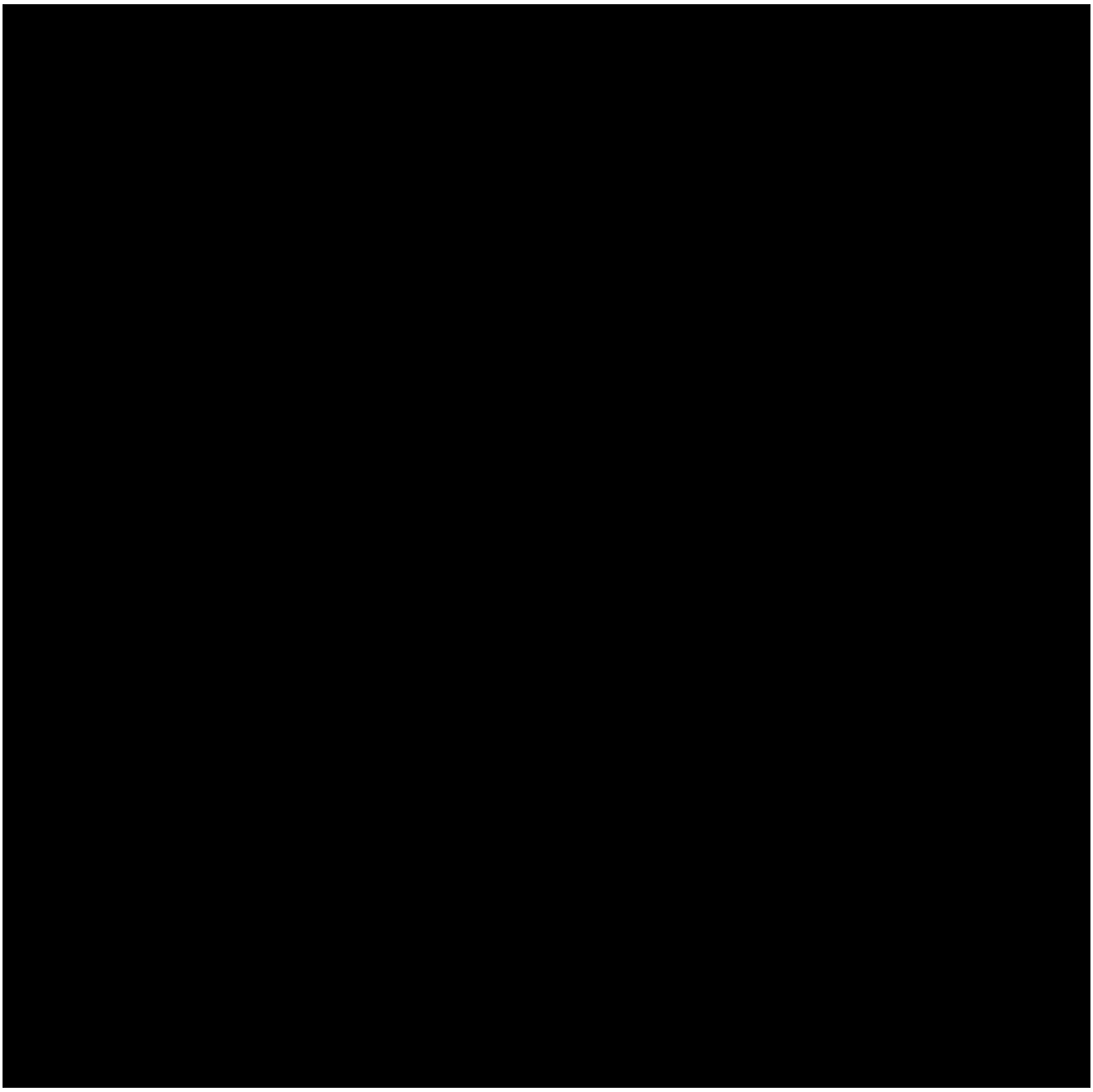
[redacted]

[redacted]

[redacted]



2.2 Treatment Groups

The treatment groups to be evaluated in part 2 of this study are described below.

Table 2-1 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

2.3 Randomization and Stratification

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.

2.4 Blinding

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

[redacted]

[redacted]

2.5.2 Emergency Un-Blinding

The process for emergency unblinding will be outlined in the Randomization Plan for the study. In addition, any subject that is unblinded for any reason will be identified and discussed in the final clinical study report.

2.5.3 Final Analysis

Treatment assignment unblinding and release of the randomization codes for the investigational product assignments for the study will occur following database lock. Database lock shall not occur until all randomized subjects have completed the study or discontinued from the study, all clinical data have been received and data inconsistencies resolved, and subject assignments to analysis populations have been completed.

2.6 Protocol Objective(s)

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).

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]

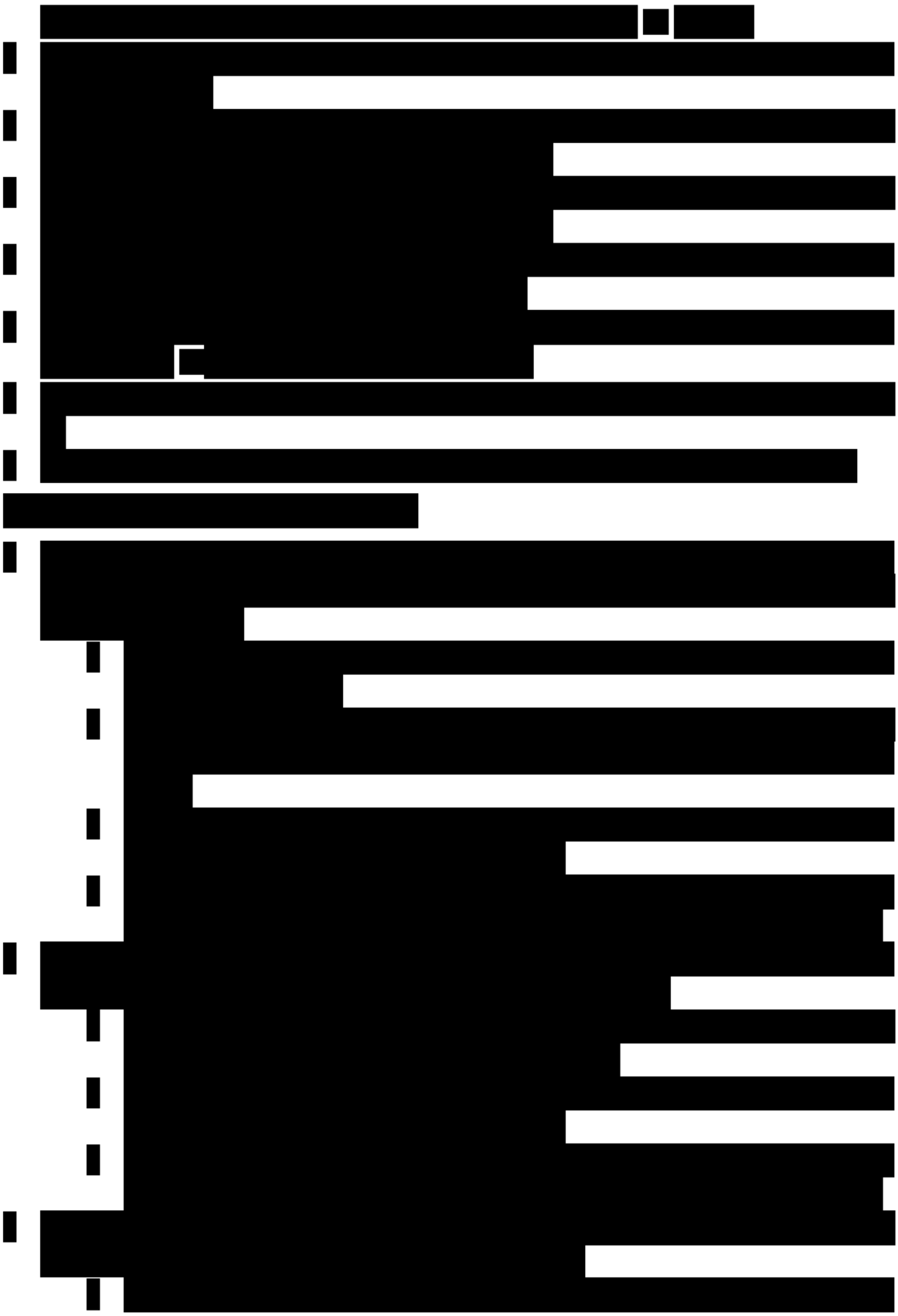
2.7 Efficacy Assessments/ Outcome Measures

2.7.1 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 have received rescue treatments will be considered non-responders

[redacted]



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2.7.4 Safety Assessments

- 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

3. SAMPLE SIZE DETERMINATION, STATISTICAL POWER, AND SIGNIFICANCE LEVEL

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.

[redacted]

[redacted]

5. PRIMARY HYPOTHESIS TO BE TESTED

There is no formal hypothesis testing for this study as the study is a Phase II evaluation and is not intended to be hypothesis generating. The study is not powered to reliably yield statistically significant conclusions.

6. ANALYSIS POPULATIONS

[redacted]

[redacted]

7. DATA CONVENTION AND RELATED DEFINITIONS

[redacted]

7.3 Handling of Missing Data

7.3.1 Handling of Missing Data for Efficacy Evaluations

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]

[redacted]

7.4 Multicenter Clinical Trials

This is a multi-center clinical trial.

[redacted]

7.7 Subgroups

There is no prespecified subgroup analysis for this study. Subgroup analysis may be conducted as needed.

7.8 Standard Calculations

[redacted]

8. STATISTICAL METHODS

All statistical analyses will be performed using SAS® for Windows, version 9.4 or later. All data collected during this study will be presented in subject data listings.

[redacted]

[redacted]

8.1 Summarizing Disposition and Baseline Data

8.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects who sign an informed consent to participate in this trial. The following will be summarized by treatment group:

8.1.2 Protocol Deviations

Protocol deviations for all randomized subjects will be listed as by-subject listing and summarized descriptively.

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, race, gender, weight, height, BMI, BSA, disease characteristics etc.) will be presented as by-subject listing and summarized by treatment group for the Safety population. See Section 7.1 for baseline definition.

8.1.4 Medical History

Medical history results will be provided as by-subject listings.

8.1.5 Prior and Concomitant Medications

Prior medication is defined as any medications with an end date prior to the first treatment date.

All prior and concomitant medications recorded in the case report form will be listed and coded to matching Anatomic Therapeutic Classification codes using the most recent version of WHO Drug dictionary, and summarized by treatment group and by the number and percentage of subjects taking each medication for the Safety population.

8.1.6 Extent of Exposure and Treatment Compliance

All treatment administration data will be listed and summarized for the Safety population.

[redacted]

[redacted]

8.2 Analysis of Efficacy Data

[redacted]

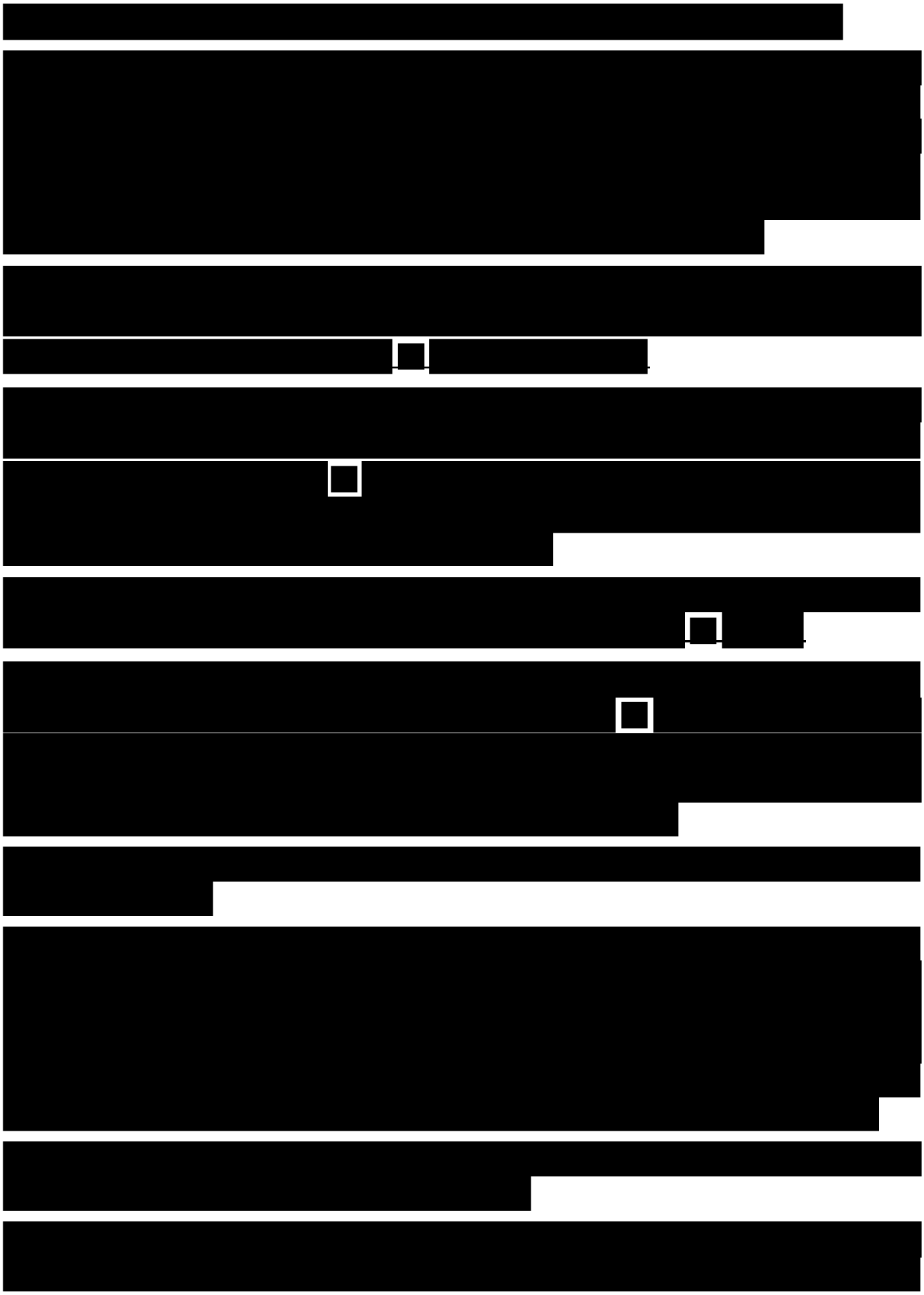
8.2.1 Primary Outcome Measure

The primary efficacy outcome measure for this study is to summarize the 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 $\geqslant$ 2 points from baseline (Note: Subjects who receive rescue treatments will be considered non-responders).

[redacted]

All data from this endpoint will also be presented as by-subject listing.

8.2.2 Secondary Outcome Measures



[redacted]

[redacted]

8.2.3 Exploratory Outcome Measures

[redacted]

[redacted]

8.3 Analysis of Safety Data

All safety analyses will be conducted using the Safety population. All data collected will be summarized according to the variable type. No inferential statistics are planned.

[redacted]

8.3.1 Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent version of MedDRA dictionary.
TEAE are defined as adverse events with onset date on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

[redacted]

All adverse events recorded in the eCRF will be presented as by-subject listings.

8.3.2 Clinical Laboratory Evaluations

All results of laboratory evaluations will be presented as by-subject listings.

[redacted]

[redacted]

8.3.3 Vital Signs

Vital sign assessments are performed in order to characterize basic body function. The parameters collected in this study are: total body surface area (BSA), systolic BP (mmHg), diastolic BP (mmHg), temperature (^{0}C), heart rate (bpm), respiratory rate (bpm). All vital sign results will be listed as by-subject listing.

[redacted]

[redacted]

8.3.4 Electrocardiogram (ECGs)

The ECG parameters include ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). All ECG results will be listed as by-subject listing.

[redacted]

[redacted]

8.3.5 Urine Pregnancy Test

All data from Urine Pregnancy test will be presented as a by-subject listing.

8.3.6 Physical Exam

All data from physical exam will be presented as a by-subject listing.

8.3.7 Application Site Reaction Assessments

All data from Application Site Reaction Assessments will be presented as a by-subject listing and/or summarized.

[redacted]

9. APPENDIX 1

FIGURE 9-1: PHASE II (PART 2) - STUDY SCHEDULE OF EVENTS

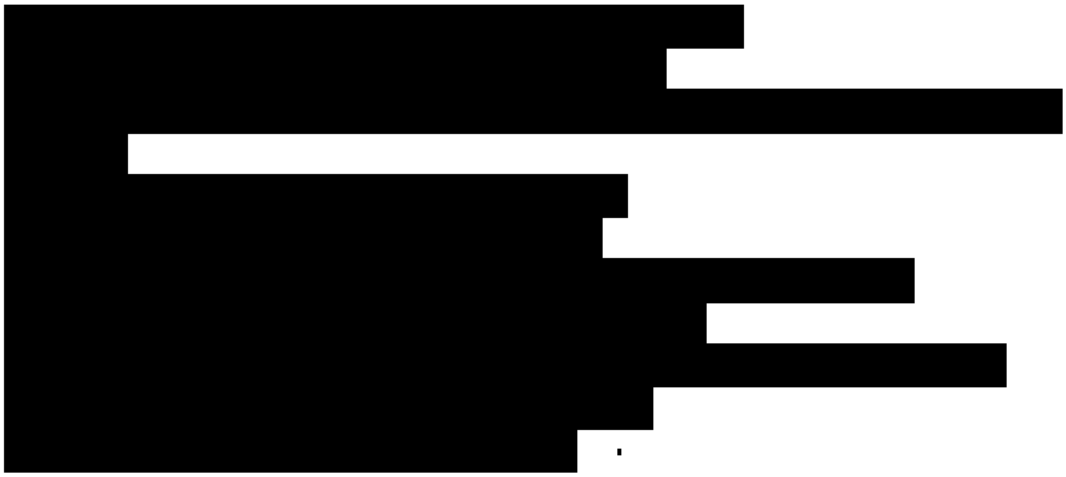
Visit		**Visit 1 (Screening)**	**Visit 2 (Baseline/ Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6 (End of Treatment)**	**Visit 7 (Follow Up)**
Days From Randomization		**Up to -28 days**	**Day 0**	**Day +7**	**Day +14**	**Day +21**	**Day +28**	**Day +42**
Weeks From Randomization		**Week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

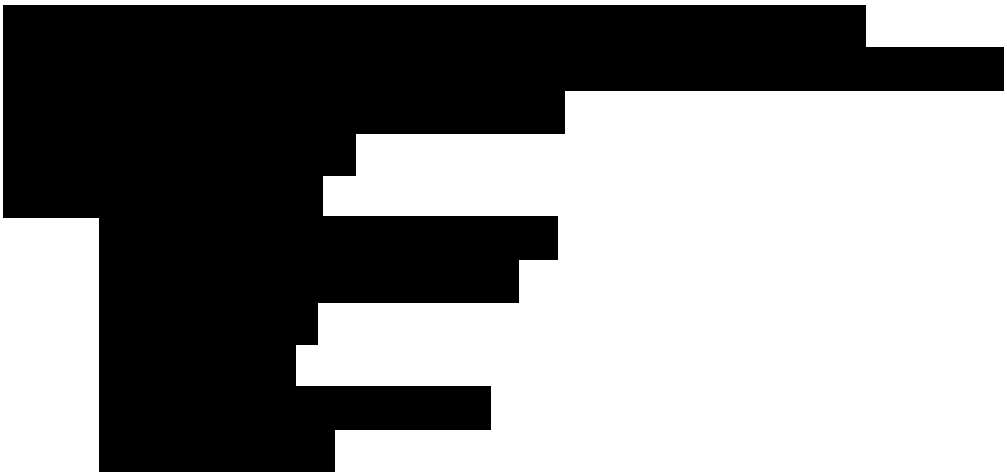
[redacted]

10. APPENDIX 2

10.1 Planned by-subject listings



10.2 Planned Summary Tables



11. REFERENCES

1. ASA Ethical Guidelines for Statistical Practice (2016)
2. The Royal Statistical Society: Code of Conduct (2014)
3. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
4. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
5. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
6. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

12. VERSION HISTORY

This is the first final version of this document.