STATISTICAL ANALYSIS PLAN
FOR PART 1 USING 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 2.0/ 20 Jan 2020

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Plan Version:	Part 1 Version 1.0		
Plan Date:	16Sep2021		

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Prepared by:	Amarex Clinical Research 20201 Century Boulevard Germantown, Maryland 20874
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I have read and approve the Statistical Analysis Plan specified above and agree on its content:

Statistician, Amarex Clinical Research	Date
SPONSOR Representative	Date

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ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation/Acronym	**Definition**
AD	Atopic Dermatitis
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASA	American Statistical Association
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CI	Confidence Interval
CM	Concomitant Medications
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DLT	Dose-Limiting Toxicity
DSMC	Data Safety Monitoring Committee
EASI	Eczema Area and Severity Index
eCRF	Electronic Case Report Form
FDA	U.S. Food and Drug Administration
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Council on Harmonization
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
IWRS	Interactive Web Randomization System
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerable Dose
NRS	Pruritus Numerical Rating Scale
PI	Principal Investigator
PT	Preferred Term level of MedDRA
QOL	On Quality of Life

Abbreviation/Acronym	**Definition**
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SOC	System Organ Class
SOP	Standard Operating Procedure
TCS	Topical corticosterioids
TEAE	Treatment-emergent Adverse Event
USA	United States of America
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the Phase I (Part 1) 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 2.0/ 20 Jan 2020
- 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 study: Part 1 (Maximum Tolerable Dose (MTD) Finding by maximum percentage of BSA treated).

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 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.

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Assuming no DLTs occur at any cohorts, in Part 2 (Phase II) of the study, three dose concentrations (low doset-treatment safety. concentration (0.11% w/w), medium dose concentration (0.33% w/w) and high dose concentration (1.1% w/w)) of AMTX-100 CF will be further evaluated for safety and efficacy, compared to placebo (vehicle), in adult patients with mild to moderate AD, with up to 70% treatable BSA involvement.

[redacted]

2.2 Cohorts

The cohorts to be evaluated in this study described as Table 2-1.

[redacted]

2.3 Randomization and Stratification

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

2.4 Blinding

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

2.5 Protocol Objective(s)

Primary Objective

- 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.

Secondary Objective

- 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.

2.6 Efficacy Assessments/ Outcome Measures

2.6.1.1 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

2.6.1.2 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

[redacted]

3. Sample Size Determination, Statistical Power, And Significance Level

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.

4. INTERIM ANALYSIS

[redacted]

5. PRIMARY HYPOTHESIS TO BE TESTED

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

6. ANALYSIS POPULATIONS

[redacted]

7. DATA CONVENTION AND RELATED DEFINITIONS

[redacted]

7.4 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

7.5 Multicenter Clinical Trials

This is a multi-center clinical trial.

[redacted]

7.8 Subgroups

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

7.9 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]

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 cohort:

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

[redacted]

8.1.2 Protocol Deviations

Protocol deviations for all randomized subjects will be listed as by-subject listing and deviations will be summarized descriptively according to the following categories:

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

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, race, gender, Ethnicity, Height, Weight, BMI and BSA etc.) will be presented as by-subject listing and summarized by cohort.

Atopic dermatitis history and medical history will be provided as by-subject listings.

8.1.4 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 the drug substance level (i.e., generic term) using the most recent version of WHO Drug dictionary, and summarized by cohort and by the number and percentage of subjects taking each medication for the Safety population.

8.1.5 Extent of Exposure

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

The extent of exposure will be summarized descriptively.

[redacted]

8.1.6 Study Treatment Compliance

[redacted]

8.2 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.

8.2.1 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 cohort, System Organ Class, and preferred term. The following TEAE summaries will be provided:

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

8.2.2 Application Site Reaction

Local skin reactions will be assessed in all areas treated with study drug and graded by the investigator on a scale of 0 to 4 based on the area with the most severe skin reaction among all treated areas. A grade of 0 represents no reaction, and a grade of 4 indicates a marked and severe skin reaction that extended beyond the treated areas.

8.2.3 Clinical Laboratory Evaluations

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

[redacted]

8.2.4 Vital Signs

Vital sign assessments are performed in order to characterize basic body function. The parameters collected in this study are: systolic BP (mmHg), diastolic BP (mmHg), temperature (^{0}C), heart rate (bpm), respiratory rate (bpm).

[redacted]

[redacted]

8.2.5 Physical Examination

[redacted]

[redacted]

8.2.6 Urine Pregnancy Test

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

[redacted]

9. APPENDIX 1

FIGURE 9-1: PHASE I (PART 1) - SCHEDULE OF ASSESSMENTS

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[1]	X	X

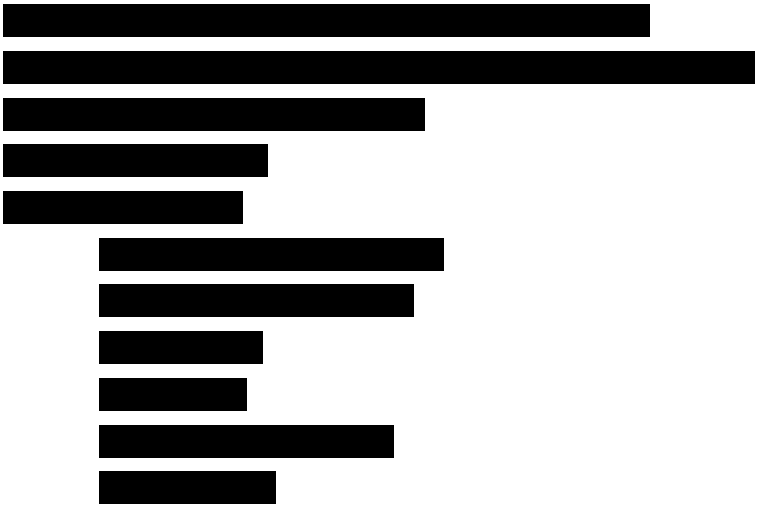
[redacted]	X		X[1]	X	X
		X			
			X		
			X		
			2nd dose (PM) on Day 0, then BID through Day 6		
			X[2]	X	
				X	
			X[1][2]	X	X
			X[2]	X	X

[redacted]

10. APPENDIX 2

[redacted]

10.2 Planned Summary Tables



11. REFERENCES

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12. VERSION HISTORY

Version 1

This is the first version of this document.