STATISTICAL ANALYSIS PLAN - TEXT

Title: A PHASE 2A SAFETY STUDY OF ATI-502 TOPICAL SOLUTION IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS
Protocol: ATI-502-AD-201
Study Drug: ATI-502
Sponsors: Aclaris Therapeutics, Inc.
Version (Date): Text 1.0 (14 May 2019)
Status: ***Final***

Prepared by:

John Ilgenfritz: Statistical Consultant Date: 14 May 2019

Approved by:

Aclaris:

David Burt: Sr. Director, Biostatistics Date: 14 May 2019

TABLE OF CONTENTS

INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a description of the statistical analyses performed for the Phase 2a protocol, ATI-502-AD-201, V1.0 (23Apr2018).

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective for this study is to assess the safety and tolerability of ATI-502 Topical Solution, 0.46% in subjects with moderate to severe atopic dermatitis.

1.2 Secondary Objectives

The secondary outcome measures for this study are to assess the following:

- Change from baseline in Physician Global Assessment (PGA) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%
- Change from baseline in body surface area affected by atopic dermatitis following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
- Change from baseline in Eczema Area and Severity Index (EASI) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
- Change from baseline in the subjects Signs of Atopic Dermatitis (SAD) assessment following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
- Change from baseline in Subjects Pruritus Assessment (SPA) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%...

2. STUDY DESIGN

This is an open label, multicenter, phase 2a study designed to evaluate the safety and tolerability of ATI-502 Topical Solution, 0.46% in male and female subjects with a diagnosis of AD as defined by the Hanifin and Rajka criteria. Based on the 5-point Physician's Global Assessment (PGA) scale, subjects must have a score of 3 (moderate) or 4 (severe). Subjects will be required to apply ATI-502 study medication to their identified AD treatment areas twice a day (BID) for a total of 4 weeks. Subjects will be allowed to treat new disease areas with ATI-502 Topical Solution, 0.46% if they appear after Visit 2. All subjects will be required to complete a safety follow up visit 4 weeks post last study medication application.

A total of 30 evaluable subjects who are ≥ 18 years of age with a clinical diagnosis of moderate or severe AD will be enrolled to the study.

Safety and tolerability will be evaluated by assessment of adverse events, physical examinations, vital signs, ECGs and clinical laboratory tests.

3. SCHEDULE OF ASSESSMENTS

The study schedule of assessments can be found in Table 1.

Table 1 Schedule of Assessments

	Screening	Baseline	Treatment			Post Treatment Safety Follow up Visit[13]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Week		0	1	2	4	8
Treatment Day	-14 to 0	1	8	15	29	56
Treatment Window(days)	N/A	N/A	± 3	± 3	± 3	+7
Informed consent[1]	▲					
Inclusion/exclusion criteria	▲	▲				
Physical exam[2]	▲					▲
Demographics & Medical History	▲					
Vital Signs[3]	▲	▲	▲	▲	▲	▲
Fitzpatrick Skin Type	▲					
Atopic Dermatitis History [4]	▲					
Clinical Chemistry and CBC[5]	▲	▲	▲	▲	▲	▲
QuantiFERON Gold[6]	▲					
Virology [HepB (HBsAg), HCV (antibody), HIV (antibody)]	▲[7]					
Serum Pregnancy	▲					
Urine Pregnancy		▲				▲
ECG	▲		▲	▲	▲	▲
Physician's Global Assessment (PGA)	▲	▲	▲	▲	▲	▲
Body Surface Areas Assessment	▲	▲	▲	▲	▲	▲
Identification of AD Treatment Area	▲	▲				
Eczema Area and Severity Index (EASI)	▲	▲	▲	▲	▲	▲
Subjects Pruritus Assessment (SPA)		▲	▲	▲	▲	▲
Signs of Atopic Dermatitis (SAD)		▲	▲	▲	▲	▲
Standardized Photography[8]	▲	▲	▲	▲	▲	▲
Dispensing of study medication[9]		▲	▲	▲		
Treatment with ATI-502		▲[10]	▲	▲	▲	
Subject Instructions[11]	▲	▲	▲	▲	▲	
Concomitant medications/therapies	▲	▲	▲	▲	▲	▲
Adverse Events[12]	▲	▲	▲	▲	▲	▲

[1] A written, signed ICF must be obtained from each subject prior to performing any study related procedure.

[2] A physical exam includes: general appearance, examination of head, eyes, ears, nose and throat, extremities, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, lymphatic and skin assessment.

[3] Vital signs include: oral or ear temperature, blood pressure, heart rate, respiration rate (height and weight at baseline only).

[4] Prior therapies or treatments a subject received to treat AD must be documented for each subject.

[5] Serum chemistry panel to include: albumin, alkaline phosphatase, ALT, AST, BUN, bicarbonate, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, total protein, uric acid, total cholesterol, LDL, HDL triglycerides, and complete blood count including differential.

[6] All subjects must have a blood sample drawn to test for the tuberculosis virus (QuantiFERON Gold). The blood sample will be sent to a central laboratory for analysis and results must be received prior to enrolling the subject.

[7] All subjects will be required to have virology testing for HepB (HBsAG), HCV(antibody), and HIV (antibody). If a subject demonstrates to have serological evidence HepB (HBsAG), HCV (antibody) or HIV (antibody), the subject will not be allowed to enroll to the study.

[8] Canfield staff will review all photographs within 2 days of the photographs being submitted. If a re-take is required, Canfield will notify the site and the re-take photographs will need to be performed within 7 days of the visit. Prior to enrollment to the study, each subject's Visit 1 photos will be reviewed by a panel of board certified dermatologists to ensure that the subject's target areas for treatment meet the study entry criteria.

[9] At visit 2, following confirmation that the subject is approved for enrollment to the study, the site will weigh and dispense supplies of ATI-502 study medication and disposable droppers to the subject for at home application of the study medication.

[10] All subjects will have their first application of study medication applied in the clinic during Visit 2. Subjects will continue to apply ATI-502 Topical Solution, 0.46% to all target areas twice a day for 4 weeks (Day 28) unless the subject meets the criteria for treatment interruption. If new areas of AD develop, subjects will be allowed to treat these areas with the ATI-502 study medication.

[11] Sites will be required to review with each subject the proper application of the study medication and remind that they must refrain from exercise that may cause excessive sweating, bathing or swimming for a period of 6 hours after the application of study medication. Subjects are also to be reminded that they may not apply moisturizers, emollients, or sunscreen to target AD areas during protocol treatment.

[12] All non-serious AEs will be collected from the time of first study medication application until the final study visit. Serious AEs will be collected from the time of consent through the final study visit.

[13]A final safety follow up visit will be conducted at week 8 (Visit 6). For those subjects that discontinue the study early, they must return to the clinic 4 weeks following the last study medication application for a final safety visit.

4. STATISTICAL METHODS

Summaries will be presented for all subjects combined.

All Data listings will be sorted by subject ID, and where applicable date/study day.

4.1 Study Population, Disposition, Baseline Characteristics, Medical History Concomitant Medications, Exposure and Protocol Violations

4.1.1 Analysis Populations

Safety Population: Includes all subjects with at least one application of study medication. The Safety Population will be used for all safety analyses.

Efficacy Population: Includes all subjects with at least one application of study medication. The Efficacy Population will be used for all efficacy analyses.

Per-Protocol (PP) Population: Includes all subjects who completed Visit 6 (Week 8). The PP Population will be used for sensitivity assessments of key efficacy analyses.

4.1.2 Subject Disposition

The number of subjects in the Safety population will be presented with the study completion status and the reasons for discontinuation.

4.1.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be presented in the data listings. Descriptive summary statistics (n, mean, standard deviation, median, minimum, and maximum) and/or frequency distributions, as appropriate, will be generated for the Safety population.

4.1.4 Diagnosis and Prior Therapies and Treatments for Atopic Dermatitis

Prior therapies and treatment for atopic dermatitis will be summarized by frequency distributions. The time since diagnosis of atopic dermatitis will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Summaries will be generated for the Safety Population.

4.1.5 History of Allergies

Allergy history will be listed.

4.1.6 Prior and Concomitant Medications, Therapies and Procedures

Medications will be coded using the WHO Drug Reference (B3 Format Sept 2018). Prior and concomitant medications will be listed only. The period(s) in which the medications were administered will be flagged.

4.1.7 Exposure to Study Medication and Study Medication Administration

Exposure will be summarized and listed for the Safety population. The duration of treatment, total weight, total volume, and average volume per application will be summarized using descriptive statistics (n, mean, SD, median, minimum and maximum).

4.1.8 Major Protocol Violations

Protocol violations will be identified to measure adherence to key aspects the protocol. Prior to analysis, the sponsor will assess the data and identify all protocol violations. Specific data fields that will be examined to identify protocol violations include entrance inclusion/exclusion criteria and prohibited prior and concomitant medications as well as all violations identified by the investigator. All protocol violations will be listed.

4.2 Efficacy Endpoints

The baseline for all efficacy measures will be the last non-missing value collected on or before the date of the first application of study medication. Analyses of post-baseline data will be performed on observed (non-missing) data based on nominal visits as collected on the CRF.

4.2.1 Eczema Area and Severity Index (EASI)

Descriptive statistics (N, mean, SD, median, minimum and maximum) for the absolute EASI, change, and percent change from baseline will be tabulated by visit. Change will be computed as the timepoint score – baseline score. Percent change as 100*change ÷ baseline. A categorical summary of the number and percentage of subjects achieving a 75% or greater decrease in EASI will be provided by visit as well as those achieving the response at any post-baseline visit. Likewise, a categorical summary of the number and percent of subjects achieving a 50% or greater decrease in EASI will be provided. This categorical summary of the EASI will be conducted on both the Efficacy Population and the PP population, separately.

4.2.1 Subject Pruritus Assessment (SPA)

Descriptive statistics (N, mean, SD, median, minimum and maximum) for the absolute SPA, change, and percent change from baseline will be tabulated by visit. Change will be computed as the timepoint score – baseline score. Percent change as 100*change ÷

baseline.

4.2.2 Signs of Atopic Dermatitis (SAD)

For each symptom (erythema, induration, lichenification, excoriation, exudation), the number and percentage of subjects with a score of 0 (none), ≤ 1 (None or Mild) and improved by at least 1 level from baseline will be tabulated by visit. This categorical summary for the SAD will be conducted on both the Efficacy Population and the PP population, separately

4.2.3 Physician Global Assessment (PGA)

The number and percentage pf patents achieving a PGA score ≤ 1 (Clear or Almost Clear) as well as those with PGA score=0 (Clear) will be tabulated by visit. Scores of 1 or less represent at least a 2-grade improvement from the protocol inclusion criteria of PGA 3 or 4. This categorical summary of the PGA will be conducted on both the Efficacy Population and the PP population, separately.

4.2.4 Body Surface Area of AD

The body surface area of AD will be summarized descriptively (N, mean, SD, median, minimum and maximum) for the absolute BSA, change, and percent change from baseline by visit. Change will be computed as the timepoint score – baseline score. Percent change as 100*change ÷ baseline.

4.3 Safety Analyses

The comprehensive safety analysis is based on all subjects in the Safety population.

The following sections detail the summaries performed on the safety data. Additional data handling rules including those for imputation of partially missing dates will be provided in a separate SAP document pertaining to data handling and programming specifications.

The baseline scores for vital signs, laboratory assessments and ECGs will be the last non-missing value collected on or before the date of the first application of study medication. This baseline will also be used for calculating change from baseline.

4.3.1 Adverse Events

Adverse events will be coded using the MedDRA dictionary V21.1 and will be categorized by system organ class (SOC) and preferred term (PT). Only treatment emergent adverse events will be included in summary tabulation. All adverse events, including those that are not considered treatment emergent, will be included in the data listings.

To differentiate the study period in which an Adverse Event occurred, three categories will be defined based upon onset date. Adverse Events that had onset dates prior to the first application of study medication will be considered "prior". Adverse events with onset dates on or after the first application of study medication and within 30 days following the last application of study medication will be considered "on therapy" or equivalently "treatment emergent". Events with onset dates more than 30 days after the last application of study medication will be considered as "post-therapy".

Frequency tabulations will be presented by MedDRA SOC and preferred term, for all adverse events; study treatment-related, adverse events resulting in discontinuation of study treatment, serious adverse events and adverse events by maximum severity. Adverse events resulting in discontinuation will be those with 'action taken' recorded as 'drug withdrawn'.

4.3.2 Physical Examinations

Physical examination findings will be listed for each subject.

4.3.3 Vital Signs

Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature will be summarized using descriptive statistics for each visit. Both actual values and changes from baseline will be summarized.

4.3.4 ECG assessments

The core laboratory's interpretation of the ECGs will be summarized as "shift" from baseline to "worst" overall interpretation recorded after baseline where the order of severity of the interpretations from best to worst will be "Normal", "Abnormal, NCS" and "Abnormal, CS".

4.3.5 Laboratory Evaluations

Chemistry and Hematology parameters will be summarized using descriptive statistics for each visit. Both actual values and changes from baseline will be summarized.

The number and percentage of subjects meeting criteria for hepatobiliary abnormalities and for potential renal impairment will also be provided.

4.4 Sample Size

Sample size for this study was not based upon formal statistical criteria. A total of 30 subjects is planned.

4.5 Changes in/ Clarifications to the Conduct of the Study or Planned Analysis

In addition to the EASI-75 planned in the protocol, an EASI-50 has been added.

Sensitivity assessments of key efficacy analyses was included that was not specified in the protocol.

5. STATISTICAL SOFTWARE

All data summaries and listings will be performed using SAS® Version 9.2 or higher, under Windows operating system.