STATISTICAL ANALYSIS PLAN

Study Title:	A Randomized, Double-Blind, Vehicle-Controlled Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of ATI-50002 Topical Solution Administered Twice-Daily for 6 Months in Adolescents and Adult Subjects with Stable Patchy Alopecia Areata with Optional Long-Term Open-Label Extension
Phase:	II
Protocol No.:	ATI-50002-AA-201
Protocol Date(s):	Version 1.0, 12JUL2017 Version 2.0, 26JUL2017 Version 3.0, 04JAN2018 Version 4.0, 26APR2018 Version 5.0, 11JUN2018 Version 6.0, 08AUG2018 Version 7.0, 10AUG2018 Version 8.0, 26SEP2018 Version 9.0, 09APR2019
Analysis Plan Version and Date:	Version 2.0, Final 19APR2019
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
AA	Alopecia Areata
AE	Adverse Event
AIA-PRO	Alopecia Impact Assessment-Patient Reported Outcome
ALODEX	Alopecia Density and Extent Score
BID	Twice daily
CBC	Complete Blood Count
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
CRF	Case Report Form
CR	Clinician Rating
DB	Double-Blind
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ICF	Informed Consent Form
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LS Mean	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect for Repeated Measures
mL	Milliliter
msec	Millisecond
OLE	Open Label Extension
PE	Physical Examination
PhGIC	Physician Global Impression of Change
PhGIS	Physicians Global Impression of Severity
PP	Per- protocol
PRO	Patient-Reported Outcome
SAE	Serious Adverse Event
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan
Scalp-ClinRO	Item 1 and Item 2 Scalp-ClinRO for AAP[1]
Scalp-PRO	Item 1 and Item 2 Scalp-PRO for AAP[2]
SGIC	Subject Global Impression of Change
SGIS	Subject Global Impression of Severity
SGITS	Subject Global Impression of Treatment Satisfaction
TEAE	Treatment Emergent Adverse Events
UPT	Urine Pregnancy Test
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

[1]This assessment is named Alopecia Scalp Appearance Assessment for Patchy AA-Clinician Rating in the protocol.
[2]This assessment is named Alopecia Scalp Appearance Assessment for Patchy AA-Subject Rating in the protocol.

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol ATI-50002-AA-201. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

The scope of this document excludes the analysis of biomarker data being collected at specific sites and the evaluation of the psychometric properties of the newly developed patient-reported (PRO) and clinician-reported outcome (ClinRO) questionnaires.

1.1. STUDY OVERVIEW

This Phase 2, multicenter, randomized study is designed to evaluate the safety, tolerability and efficacy of ATI-50002 Topical Solution in subjects with stable patchy alopecia areata (AA). Subjects will be required to have a clinical diagnosis of AA with at least 15% up to 95% total scalp hair loss for a duration of at least 6 months up to and including 12 years.

This study has a double-blind period and an open-label extension period.

Double-blind (DB) Period:
A total of 120 subjects will be randomized in a 1:1:1 ratio:

- Vehicle Topical Solution BID for 24 weeks (6 months)
- ATI-50002 Topical Solution, 0.12%, BID for 24 weeks (6 months)
- ATI-50002 Topical Solution, 0.46%, BID for 24 weeks (6 months)

During the screening period, subjects will be assessed for eligibility into the study. Subjects will apply up to 4 mL of study medication to the entire scalp or patchy areas with a ½" margin twice a day for 24 weeks. Assessment of response to treatment will be performed at Week 4 (Visit 5), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (Visit 8), Week 20 (Visit 9), Week 24 (Visit 10), and post-treatment Week 28 (Visit 11). Safety and tolerability will be evaluated at each study visit by assessment of adverse events and vital signs, and at select visits, ECGs and clinical laboratory tests will be completed. The primary analysis will be conducted after all subjects complete Visit 10 or Visit 11 of the double-blind period.

Subjects who complete Visit 10 or Visit 11 (Week 24 or 28) will be eligible to enter a 28 week OLE. Subjects who decline or are not eligible for the OLE should be seen for the Visit 11 (Post-treatment) assessments.

Open-Label Extension (OLE):
In the OLE, safety, tolerability and efficacy will be assessed. All subjects enrolled in the OLE will apply ATI-50002 Topical Solution, 0.46% to the entire scalp or patchy areas with a ½" margin, twice daily for 24 weeks (6 months). In addition, subjects with eyebrow loss may apply study

medication to the entire eyebrow(s) twice daily for 24 weeks. Subjects will be followed for safety, tolerability and efficacy as detailed in Section 1.2 Schedule of Assessments. Subjects who entered the OLE and for administrative reasons had a gap of > 30 days between completion of Visit 10 or Visit 11 and entry into the open-label should return for the OLE Visit 1 and have the procedures detailed in the Schedule of Assessments.

1.2. SCHEDULE OF ASSESSMENTS

Double-Blind Treatment Period	Screening	Baseline	Treatment								Post-Treatment
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Week		0	1	2	4	8	12	16	20	24	28
Treatment Day	-30 to 0	1	8	15	29	57	85	113	141	169	197
Treatment window (days)	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3
Informed consent/assent[1]	X									X[14]	X[14]
Inclusion/exclusion criteria	X	X									
Physical exam[2]	X									X	
Demographics & medical history	X										
Alopecia Areata History	X										
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X
Clinical CBC, Chemistry, Virology, Serum Pregnancy, Urinalysis[4]	X[4]	X		X	X	X	X	X	X	X	X
Urine pregnancy test[5]		X			X	X	X	X	X	X	X
ECG	X	X		X	X	X	X	X	X	X	X
SALT Score (prior to ALODEX)[6]		X			X	X	X	X	X	X	X
ALODEX Score (after SALT)[7]		X			X	X	X	X	X	X	X
Target Scalp Patch Identification[8]		X									
Assessment of hair quality[9]		X			X	X	X	X	X	X	X
Scalp-ClinRO **All Patches, Target Patch**[10]		X			X		X			X	
Scalp-PRO **All Patches, Target Patch**[10]		X			X		X			X	
Physician Global Impression of Severity (PhGIS) [10]		X			X		X			X	
Physician Global Impression of Change (PhGIC)										X	
Subject Global Impression of Severity (PhGIS) [10]		X			X		X			X	
Subject Global Impression of Change (PhGIC)										X	
Subject Global Impression Treatment Satisfaction (SGITS)							X			X	
DLQI[10]		X			X		X			X	
Alopecia Impact Assessment-Patient Reported Outcome (AIA-PRO) [10]		X			X		X			X	
Photography (complete scale and target patch) [10]		X			X	X	X	X	X	X	X
Subject Randomization		X									
Subject instructions[11]		X	X	X	X	X	X	X	X	X	
Dispense collect, weigh study medications[12]		X	X	X	X	X	X	X	X	X	
In office study medication applications[13]		X									
Concomitant therapies		X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X

Open-Label Extension	Open-Label Treatment							Post Treatment
	OLE Visit 1			OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	OLE Visit 6
Week	OLE Visit 1 occurs at Visit 10 or 11	Visit 11 (Week 28) was:		2	4	12	24	28
Treatment Day		≤ 30 Days	>30 Days	15	29	85	169	197
Treatment window (days)	NA	NA	NA	±3	±3	±7	±7	±7
Informed consent/assent[1]	X	X	X					
Inclusion/exclusion criteria	X	X	X					
Physical exam[2]			X					X
Medical History Update			X					
Vital Signs[3]		X	X	X	X	X	X	X
Clinical CBC, Chemistry, Virology, Serum Pregnancy, Urinalysis[4]			X	X	X	X	X	X
Urine pregnancy test[5]		X	X	X	X	X	X	X
ECG								X
SALT Score (prior to ALODEX)[6]		X[15]	X		X	X	X	X
ALODEX Score (after SALT)[7]		X[15]	X		X	X	X	X
Scalp-ClinRO (All Patches, Target Patch)						X	X	X
Scalp-PRO (All Patches, Target Patch)						X	X	X
SGITS							X	
Photography (complete scalp and target patch)		X[15]			X	X	X	X
Subject Instructions[11]	X	X		X	X	X	X	
Dispense and weigh study medication[12]	X	X		X	X	X	X (Weigh only)	
Collect study medication, assess compliance				X	X	X	X	
Concomitant therapies		X		X	X	X	X	X
Adverse events		X		X	X	X	X	X

[1] A written, signed ICF/ assent must be obtained from each subject prior to performing any study related procedure (i.e., prior to performing vital signs, standardized photography, biopsies, clinical laboratory sampling or urine pregnancy tests.) An OLE ICF must be obtained prior to performing any OLE assessments.
[2] A physical exam includes: general appearance, extremities, examination of head, eyes, ears, nose and throat, 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] Clinical laboratory sampling include: CBC, Chemistry with lipids, Urinalysis. Quantiferon Gold, HIV, Hepatitis B and C, and Serum Pregnancy
[5] UPT must be performed in WOCBP prior to randomization at Baseline (Visit 2) and must be negative for the subject to continue in the study. UPTs in WOCBP must also be obtained at Visits 5, 6, 7, 8, 9, 10, 11 and if applicable, OLE Visit 1, and OLE Visit 2-6. WOCBP must have a negative serum pregnancy test at Screening (Visit 1) and a negative UPT at baseline (Visit 2) prior to randomization. WOCBP must have a negative UPT prior to continuation into the OLE.

[6] SALT score must be determined prior to ALODEX using device provided. At Baseline (Visit 2), SALT score should be determined prior to application of study medication.
[7] ALODEX score determined after SALT score using device provided. At Baseline (Visit 2), ALODEX score should be determined prior to application of study medication.
[8] The subject will be instructed to identify the most bothersome patchy area- this will be the Target Patch. At Baseline (Visit 2), the Target Patch should be identified prior to application of study medication.
[9] The investigator will assess active hair loss through the hair pull test and the presence of exclamation point hairs. At Baseline (Visit 2), the assessment should be determined prior to application of study medication.
[10] At Baseline (Visit 2), study assessments must be performed prior to application of study medication.
[11] The study staff must instruct the subject to apply study medication according to the instructions in APPENDIX 1, 2 and 3.
[12] The study staff must weigh the study medication bottle(s) with cap prior to dispensing to the subject and after the study medication bottles are returned to the investigational site. Staff should review the usage based on the weight of the bottle and counsel the subject as necessary.
[13] At Baseline (Visit 2), the first application of study medication should be performed by the subject under the supervision of the study staff and the subject should be observed for 20 minutes after the initial application.
[14]At Week 24 (Visit 10) or Week 28 (Visit 11), the subject may be given the option to move into the OLE treatment.

- If the subject declines the OLE, Visit 11 (Post-treatment) will be the last double-blind study visit.
- If the subject chooses to continue into the OLE, she/he must sign an OLE ICF, complete Visit 10 or Visit 11 as appropriate and OLE Visit 1, prior to being dispensed openlabel drug and receiving study medication application instructions. The subject will be scheduled for OLE Visit 2.
- If the subject enrolls in open-label treatment within 30 days of completion of Week 24 (Visit 10) or Week 28 (Visit 11), OLE Visit 1 will be conducted to obtain consent/assent and perform the procedures in the Schedule of Assessments. This will be considered the official date that the subject initiated OLE treatment.
- If the subject enrolls in open-label treatment > 30 days after completion of Week 28, OLE Visit 1 will be conducted to obtain consent/ assent, and complete the procedures detailed in the Scheduled of Events. This will be considered the official date that the subject initiated OLE treatment and the scheduling of subsequent visits will be based on this date.

[15] SALT, ALODEX and Photography is performed at OLE Visit 1 (if Week 28 is < 30 days) only if there is a significant change from the last double-blind study visit.

2. OBJECTIVES

Primary Objective:

The primary objective of this study is to assess the safety, tolerability and efficacy of ATI-50002 Topical Solution, 0.46% and 0.12% compared to vehicle in subjects with stable patchy alopecia areata (AA).

Efficacy assessments include the following scores and/or scales:

- Severity Alopecia Tool (SALT) Score
- Alopecia Density and Extent Score (ALODEX)
- Assessment of Hair Qual
- Item 1 and Item 2 Scalp-ClinRO for AAP (Scalp-ClinRO), referred to as Alopecia Scalp Appearance Assessment for Patchy AA – Clinician Rating in protocol for target patch and entire scalp.
- Item 1 and Item 2 Scalp-PRO for AAP (Scalp-PRO), referred to as Alopecia Scalp Appearance Assessment for Patchy AA – Subject Rating in protocol for target patch and entire scalp.
- Physician Global Impression of Severity (PhGIS)
- Subject Global Impression of Severity (SGIS)
- Alopecia Impact Assessment – Patient Reported Outcome (AIA-PRO)
- Subject Global Impression of Treatment Satisfaction (SGITS)
- Dermatology Life Quality Index (DLQI) total score
- Physician Global Impression of Change (PhGIC)
- Subject Global Impression of Change (SGIC)

Safety assessments include:

- Adverse events
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Vital sign measurements (systolic and diastolic blood pressure, respiration rate, heart rate, and temperature)
- Electrocardiograms

Secondary Objective:

The secondary objectives are as follows:

- To evaluate the psychometric performance of the key clinical outcome assessments questionnaires with respect to reliability, construct-related validity, and sensitivity to change
- To generate score interpretation estimates for the clinical outcome assessments to guide the definition of responders in pivotal trials

The secondary objectives are not within the scope of this SAP.

Exploratory Objectives (Select Sites Only): At select clinical sites, to explore the effects of ATI-50002 induced Janus kinase (JAK) 1/3 inhibition on the ALADIN scores, peribulbar infiltrate and other inflammatory biomarkers.

The exploratory objectives are not within the scope of this SAP.

Long-term Objective To assess the safety, tolerability and efficacy of ATI-50002 Topical Solution, 0.46% in subjects with stable patchy alopecia areata.

This objective will be assessed at the end of the Open Label Extension period.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

The planned sample size is 120 subjects. Since this is the first multicenter study evaluating the effect of ATI-50002 Topical Solution in subjects with stable patchy alopecia areata, the sample size was based upon feasibility issues rather than on a formal power calculation. However, data from 120 subjects (40 per group), utilizing LOCF for missing data, provides 80% power to detect a 24-point difference in percent change from baseline in SALT score between any two treatment groups. This power computation was based upon the assumed standard deviation of 38%. Data from a previous study NCT02197455 showed that the standard deviation in percent change from baseline in the SALT score is 30.3%. The 38% standard deviation assumption used for this power computation was chosen to account for the increase in variance due to the lower baseline SALT entry criteria for this study as compared to NCT02197455.

3.2. RANDOMIZATION AND MASKING

Prior to the start of the study, Aclaris Therapeutics, Inc. or a designated third party will generate a list of randomization numbers that shall be transmitted to the assigned clinical packaging organization for study medication labeling. The randomization list will be stored with access limited to designated personnel for study medication labeling. The randomization list will be made available, as appropriate, to unblind the database.

In the double-blind period, subjects will be assigned to 1 of the 3 treatment groups in a random manner and at a 1:1:1 ratio. At Baseline (Visit 2), an investigational center staff member will assign study medication to eligible subjects by selecting an appropriate Subject Kit. The staff member must select Subject Kits in chronological sequence and in an ascending numerical order starting with the lowest available Subject Kit number. No Subject Kit number may be omitted or reused. The Subject Kit number is the randomization number.

The investigational staff member randomizing the subject will enter the subject identifier, subject initials, and date randomized on both parts of the Subject Kit label, remove the tear-off part, attach

it to the subject's study medication eCRF label page and record the Subject Kit number in the subject's eCRF.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

The baseline SALT score group (<50, >=50) will be used a stratum in the planned primary efficacy models. The strata will not be used in the subset analyses.

3.3.2. Examination of Subject Subsets

The baseline SALT score group (< 50, >=50) and the subjects who treat the whole scalp will be used for subset analyses. The details of the subset analyses are given in the statistical analysis section.

3.3.3. Multiple Testing and Comparisons

There are no planned adjustments for multiple comparisons.

3.3.4. Missing Data and Outliers

For missing clinical assessments, the method of last observation carried forward (LOCF) will be used to impute values. The last non-missing value prior to the missing assessment will replace the missing values. For subjects who terminate early, missing assessment after the date of early termination will be replaced by the LOCF method.

3.3.5. Imputation of Incomplete Dates

A missing date is one in which the day, month or year are all unknown. For adverse events, if a date is missing entirely then the date will be set to equal Day 1.

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

To minimize bias, the project statistician will impute dates in a systematic, but reasonable manner. If the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. For nonexistent dates occurring at the end of a month created by this imputation method, the first date of the next month will be used (e.g. Day 1 = 31JAN2017, incomplete date = XXFEB2017 -> imputed date = 01MAR2017).

3.3.6. Definitions and Terminology

Day 1 (DB)
Day 1 (DB) is defined as the date of the initial study medication application as reported on the study medication usage page of the CRF.

Day 1 (OLE)
Day 1(OLE) is defined as the date of the Visit 10 assessment for all subjects entering the OLE period.

Study Day
Study Day is defined relative to Day 1(DB). Thus, the study day of an event is calculated as:

Study Day = ((event date – date of Day 1(DB)) + 1) for dates on or after Day 1(DB)

Study Day = (event date – date of Day 1) for dates prior to Day 1(DB)

Period Day
Period Day is defined separately for the DB and OLE periods. Period day will be relative to the defined Day 1 of each period.

Study Visit
Study Visit is the nominal visit as recorded on the CRF.

Days on Study
Days on Study is calculated as: study discontinuation date - informed consent date + 1

Last Dose of Study Medication
Last Dose of Study Medication is defined as the last date that the subject applied study medication as determined by last date of recorded on the study medication usage page of the CRF.

Study Medication Exposure (days) in DB
Study drug exposure is defined as the (date of last DB dose – date of first dose + 1).

Dose Interruptions
Dose interruption is defined as 2 or more consecutive days where 'None' was checked for the number of applications per day field on the study medication page of CRF.

Missed Dose
A missed dose is defined as a single day where 'None' was checked for the number of applications per day field on the study medication page of CRF.

Study medication compliance (%) based on number of applications
The compliance with the dosing regimen will be calculated based on the subject-specific application regimen as, [(study medication exposure days - number of days with less than the subject-specific expected number of applications) / (study medication exposure days)] x 100.

Age
The age of a subject is defined as the number of whole calendar years from the subject's date of birth to the date of informed consent.

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to initiation of study medication.

Change from Baseline
Change from Baseline for a given endpoint is defined as the value at the analysis visit minus the baseline value.

Duration of alopecia
Date of Informed Consent minus the original onset date of alopecia as reported on the History of Alopecia page of eCRF.

Duration of current episode of patchy alopecia
Date of Informed Consent minus the onset date of current episode of Patchy Alopecia as reported on the History of Alopecia page of eCRF.

Prior Medications
Prior medications are those medications taken prior to the initiation of study medication, regardless of whether it continues into the blinded treatment period.

Concomitant Medications
Concomitant medications are those medications taken on or after the initiation of study medication. This definition includes medications started prior to the initiation of study medication but continuing concomitantly with the study medication.

DLQI Total Score - The scoring of each question is as follows:
Very much=scored 3, A lot=scored 2, A little= scored 1, Not at all= scored 0, Not relevant=scored 0, Question 7, 'prevented work or studying'=scored 3.
The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Adverse Event (AE)
An AE is any untoward medical occurrence in a subject administered a study medication(s) and which does not necessarily have a causal relationship with the study medication. An AE can therefore be any unfavorable and unintended sign or symptom associated with the use of a study medication (including an abnormal laboratory finding), whether related to the study medication. Thus, any new, clinically significant worsening of an existing sign, symptom or disease, should be considered an AE. Every new episode or clinically significant worsening of a chronic condition (*e.g.*, headaches, seasonal allergies, depression, or hypertension) should be reported as a separate AE, even if the condition is reported in the subject's medical history.

Treatment-Emergent Adverse Event (TEAE)
For the interim analysis of the DB treatment period, any recorded AE that occurs on or after the initiation of study medication and within 31 days after the date of Visit 10 or after the date of last DB dose of study medication will be considered treatment-emergent. For the OLE period analysis, an AE that occurs on or after the initiation of OLE study medication and within 31 days after the date of last dose of study medication will be considered treatment-emergent.

Treatment-emergent Laboratory Abnormalities
A treatment-emergent laboratory abnormality is defined as a result in which the baseline value is within normal laboratory limits and the post-baseline value is outside normal laboratory limits. If the relevant baseline assessment is missing, then any post-baseline value outside normal laboratory limits is treatment-emergent.

3.3.7. Presentations by Study Visit

Results from efficacy assessments and safety will be summarized by study visit and treatment group. For the DB period, all assessments will be assigned to an analysis visit window using the study day ranges described in Table 1. All study days up to and including Day 1 (DB) are considered the baseline eligible analysis visit window. The last non-missing assessment in the baseline analysis visit window will be used for the baseline summary presentations. If assessments are collected multiple times within a given analysis visit window, the result closest to the target study day, regardless of whether scheduled or unscheduled, will be used for summary presentations. If two measurements have the same distance to the target study day, the first assessment will be used in the summary presentations. All assessments will be presented in the listings.

Table 1: Visit Windows

Nominal Visit	***Target Study Day***	***Analysis Visit***	***Study Day Range***
Screening	-30 to -1	Baseline	<=1
Day 1	1		
Week 1	8	Week 1	[2 – 11]
Week 2	15	Week 2	[12 – 22]
Week 4	29	Week 4	[23 – 42]
Week 8	57	Week 8	[43 – 70]
Week 12	85	Week 12	[71 – 98]
Week 16	113	Week 16	[99 – 126]
Week 20	141	Week 20	[127 – 154]
Week 24	169	Week 24	[155 to 182]

For the OLE, the analyses will be based on the nominal study visit as reported on the CRF.

3.4. TIMING OF ANALYSES

3.4.1. Interim Analysis

When all subjects have completed the blinded treatment period or terminated early from the blinded treatment period and data have been cleaned and forwarded for analysis, the study will be unblinded and the safety and efficacy analysis will be performed according to this SAP. See Section 8.1. for the list of proposed summary table and figures and data listings for the End of Double-Blind Treatment Period analysis.

3.4.2. End of Open Label Analysis

A final analysis will also be performed at the end of the open-label extension period. See Section 8.2. for the list of proposed summary table and figures and data listings for the End of Open Label Period analysis.

4. ANALYSIS POPULATIONS

The populations for analysis will include the intent-to-treat population (ITT), the safety population (SAF), and the per protocol (PP) population.

4.1. INTENT-TO-TREAT (ITT) POPULATION

The ITT population is the population of all subjects who are randomized into a treatment group. Subjects in this population will be analyzed according to the treatment group to which they were randomized. The ITT population will be used for all efficacy analyses.

4.2. SAFETY POPULATION

The Safety population is defined as all randomized subjects who applied at least 1 application of study medication. Subjects in this population will be analyzed according to the treatment which they receive. All safety analyses will be based on this population.

4.3. PER PROTOCOL (PP) POPULATION

The Per-Protocol (PP) population is defined as all subjects who are randomized and do not have any major protocol violations. Major protocol violations that will lead to exclusion from the PP are defined as:

1. Inclusion or Exclusion criteria not met

2. Concomitant medications taken during the study that interfere with efficacy

3. Did not apply at least 75% of study medication

4. Did not complete Week 24 (Visit 10).

This population will be used for supportive analyses of key efficacy analyses.

5. STATISTICAL METHODS

Descriptive statistical methods will also be used to summarize the data from this study, with hypothesis testing performed for the primary and key secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects, mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. For categorical variables, the denominator of percentages will be the number of subjects in the treatment group, except for those collected by study visit and/or scheduled time point, in which case the denominator of percentages will be the number of subjects with a non-missing value at the visit and/or the scheduled time point. If a different denominator is used, this will be identified in the summary table.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number. Assessments indicated as 'Not Done' will not be includes in the listings.

The term 'treatment group' refers to ATI-50002 active groups and matching Vehicle group.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05 unless otherwise stated. P-values will be presented to three decimal places. For the efficacy endpoints, the ATI-50002 treatment groups will be tested versus vehicle via statistical inference.

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be independently verified by a second programmer/statistician or independently hand-checked prior to issuance of the draft statistical report. All documents will be reviewed by the lead statistician to ensure accuracy and consistency.

5.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject disposition will be presented for all subjects in the ITT population. The number of subjects who completed the study or early terminated from the study during the blinded treatment period will be provided. The reasons for early termination will be presented by treatment group. Additionally, the number of weeks on study will be summarized for all treated subjects.

Demographic data, including age, gender, race, ethnicity, and Fitzpatrick skin type, and screening weight (kg) and height(cm) will be summarized using descriptive statistics by treatment group. This information will be reviewed for baseline differences, but no statistical testing will be performed.

Baseline characteristics, including duration of alopecia, duration of current episode of patchy alopecia (continuous and dichotomized (< 2 years, >= 2 years), baseline hair pull test results (dislodged hairs and broken hairs), baseline SALT score group (<50%, >50%) and baseline Scalp-ClinRO and Scalp-PRO will be reported.

Alopecia treatment history will be summarized. The count and percent of subjects using the therapies pre-specified on the History of Alopecia CRF page will be reported.

Medical history will be summarized using the pre-specified CRF body system categories. The count and percent of subjects reporting a condition in the body system will be reported.

Findings from the baseline physical examination (PE) will also be summarized using the pre-specified body system categories and include reporting of abnormal not clinically significant and abnormal clinically significant.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version WHO-DD – March 2019) for the entire period of the study. Prior and concomitant medications will be summarized in tables and may be presented in data listings.

Study drug exposure and compliance will be summarized by treatment. The study drug duration along with summaries of missed doses, dose reductions, and treatment compliance will be reported.

5.2. EFFICACY ANALYSIS

5.2.1. Primary Efficacy Endpoint

The primary efficacy variable will be the mean percent change from baseline in the SALT score at Week 24 (Visit 10).

5.2.2. Primary Efficacy Analysis

Descriptive statistics for the SALT score, change, and percent change from baseline will be presented for each scheduled analysis visit. Percent change from baseline in SALT over time up to Week 24 will be analyzed using a mixed effect for repeated measures (MMRM) model. This primary analysis will utilize the score with imputation for LOCF and will be based on the ITT population. The model will include fixed effect terms for treatment, study visit, baseline SALT score group (<50, >=50), and treatment by SALT group interaction. Within-subject variability will be modeled using a compound symmetry covariance structure. The least squares mean (LS Mean) percent change from baseline in the SALT score at each visit, estimated from the MMRM model, with the estimated standard error and 95% confidence interval (CI), will be presented in tabular and graphic format. The difference in the adjusted means between treatment groups and the associated 95% CI of the difference will be provided.

5.2.3. Additional Analyses of the Primary Endpoint

The statistical methods for the main analysis will be repeated using the PP population. The analysis will also be performed using the observed data without imputation for missing in both the ITT population and the PP population.

Another exploratory MMRM analysis for the primary endpoint will be performed with factors for the duration of current episode of patchy alopecia (< 2 years, >= 2 years) and the treatment by duration of episode interaction replacing the baseline SALT score group and treatment by SALT group interaction factors. This analysis will be performed in both the ITT population and the PP population using data with LOCF imputation.

5.2.4. Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Mean percent change from baseline in the ALODEX score at Week 24 (Visit 10), also described as mean percent regrowth,
- Mean change from baseline in SALT score at Week 24 (Visit 10)
- Mean change from baseline in ALODEX score at Week 24 (Visit 10)
- Proportion of subjects in each treatment arm achieving ≥ 50% hair regrowth compared with baseline using a separate model for SALT and for ALODEX scores
- Change from baseline in the Scalp-PRO at Week 24 (Visit 10)
- Change from baseline in the Scalp-ClinRO at Week 24 (Visit 10)
- Change from baseline in the PhGIS of Patchy AA at Week 24 (Visit 10)
- Change from baseline in the SGIS of Patchy AA at Week 24 (Visit 10)
- Change from baseline in the subject reported AIA-PRO at Week 24 (Visit 10)
- SGITS at Week 24 (Visit 10)
- Change in DLQI total score between Baseline and Week 24 (Visit 10)
- PhGIC at Week 24 (Visit 10)
- SGIC at Week 24 (Visit 10)

5.2.5. Secondary Efficacy Analysis

Descriptive statistics will be presented for all secondary efficacy endpoints.

The mean percent change from baseline in the ALODEX score (percent regrowth); the mean change from baseline in SALT and the mean change from baseline in ALODEX will be analyzed using the methods planned for the primary efficacy analysis. The calculated DLQI total score ranges from 0 to 30. This mean change from baseline in DLQI will also utilize the MMRM analysis as planned for the primary efficacy analysis.

Responder-type analyses are planned based on the SALT, ALODEX, Scalp-ClinRO, and Scalp-PRO. The responder definitions include:

- The proportion of subjects achieving a ≥ 50% hair regrowth compared with baseline for SALT and for ALODEX scores
- Proportion of subjects achieving an absolute SALT score <= 10
- Proportion of subjects with >= 2-point improvement in Scalp-ClinRO for the Target Area
- Proportion of subjects with >= 2-point improvement in Scalp-PRO for the Target Area
- Proportion of subjects with >= 1-point improvement in Scalp-ClinRO for the entire scalp
- Proportion of subjects with >= 1-point improvement in Scalp-PRO for the entire scalp

The observed proportion of responders and associated 95% CI will be presented. Adjusted rates and 95% CI will be obtained from a logistic regression model with factors for treatment and baseline SALT score group. The p-value for the overall global test that $\beta = 0$ for each factor will be presented. The adjusted odds ratios (95% CI) for being a responder (active/vehicle) will be presented along with the associated p-value.

The questionnaires Scalp-PRO, Scalp-ClinRO, PhGIS, and SGIS are collected on a 1-5 scale. The frequency of responses for each value will be reported by visit and treatment group. Additionally, change status will be categorized as "Better by x points" when the score decreases from baseline by x points, and as "Worse by x points" when the score increases by x points. For these scales, a stratified Wilcoxon rank sum test will be used at each visit to obtain a p-value to compare the change status of each active treatment group to the vehicle.

For SGITS, PhGIC, and SGIC, the frequency of responses will be summarized for each scheduled collection timepoint. A stratified Wilcoxon rank sum test will be used at each visit to obtain a p-value to compare the results of each active treatment group to the vehicle.

The AIA-PRO consists of 13 questions each rated on a scale of 1 to 10 and mean total score. The mean total score is taken as the average of the 13 items. If any of the items is missing the mean total score will not be calculated. Descriptive statistics for actual and change from baseline for the mean total score and each individual item will be presented.

5.2.6. Other Efficacy

Results from the hair pull test at scheduled visits will be summarized. The summary will show the shift relative to baseline in the categories of dislodged hairs and broken hairs at each post-baseline analysis visit.

5.2.7. Subset Analyses

Subgroups of Baseline SALT score group (< 50, >=50)

The primary analysis of the percent change in SALT score over time, the analysis of percent change in ALODEX score over time, and all planned responder-type analyses will be repeated in

each subgroup. For these analyses, the baseline SALT score group will be removed from the planned MMRM model and logistic regression model.

Subgroup of subjects who applied Whole Scalp Treatment

This subset will consist of all subjects who indicated on the End of Blinded Treatment page of the eCRF that the whole scalp is treated twice per day. The primary efficacy analysis of the percent change in SALT score will be repeated in this subset.

5.2.8. Graphical Displays

For SALT and ALODEX, the LS mean percent change and 95% CI will be plotted over time by treatment group. For the binary efficacy endpoint of proportion of subjects achieving >=50% hair regrowth relative to baseline based on the SALT and ALODEX scores, the percentage and 95% CI will be plotted over time by treatment group.

5.2.9. Open-Label Extension

For the open label extension period, efficacy will be evaluated based on the SALT, ALODEX, Scalp-ClinRO, Scalp-PRO, and SGITS. Descriptive summary statistics will be reported for the following:

- SALT score and change from baseline
- ALODEX Score and change from baseline
- Number (%) of subjects for each category of the Scalp-ClinRO (target patch and entre scalp)
- Number (%) of subjects for each category of the Scalp-PRO (target patch and entre scalp)
- Number (%) of subjects for each category of SGITS.

Summaries will include changes from baseline (study day 1) and changes from the end of the DB study (Visit 10). All by visit summaries will utilize the normal study visit based on CRF collection.

The efficacy summaries will be presented for the following subject groups based on the DB treatment assignments and the duration since end of DB period:

- Subjects who were randomized to Vehicle in the double-blind portion of the study
- Subjects who were randomized to ATI-50002 12% in the double-blind portion of the study who also entered the OLE less than 7 days from the end of their DB treatment period
- Subjects who were randomized to ATI-50002 12% in the double-blind portion of the study who also entered the OLE more than 7 days, but less than 60 days from the end of their DB treatment period
- Subjects who were randomized to ATI-50002 12% in the double-blind portion of the study who also entered the OLE at least 60 days from the end of their DB treatment period
- Subjects who were randomized to ATI-50002 46% in the double-blind portion of the study who also entered the OLE less than 7 days from the end of their DB treatment period

- Subjects who were randomized to ATI-50002 46% in the double-blind portion of the study who also entered the OLE more than 7 days, but less than 60 days from the end of their DB treatment period
- Subjects who were randomized to ATI-50002 46% in the double-blind portion of the study who also entered the OLE at least 60 days from the end of their DB treatment period.

5.3. SAFETY

All safety analyses will be performed on the Safety Population. Values for all safety variables will be listed by subject and visit (as applicable).

5.3.1. Adverse Events

Adverse events will be mapped to a preferred term and system organ classification by Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

An overall summary will be presented which includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE. This summary will also include:

- Any TEAE
- Any Serious TEAE
- Any Mild TEAEs
- Any Moderate TEAEs
- Any Severe TEAEs
- Any Related TEAEs
- Any TEAEs leading to discontinuation
- Any Related TEAEs leading to discontinuation

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by system organ class (SOC), preferred term (PT) and maximum severity. If a participant reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC for that participant. As with the PT, if a participant reports multiple conditions within the same SOC, that SOC will only be counted once for that participant. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all participants within each SOC.

The occurrence of TEAEs related to study medication (possibly/probably) will be tabulated by SOC, PT and maximum severity. Serious adverse events (SAE) will be presented by system organ class (SOC), preferred term (PT) and maximum severity. SAE related to study medication will also be presented by SOC and PT.

All AEs reported will be listed by individual subject, showing both verbatim and preferred terms. All AEs reported with a start date prior to the initiation of study medication will be excluded from the TEAE tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 3.3.5 as required to determine TEAEs.

5.3.2. Clinical Laboratory Assessments, Vital Signs, and Physical Examination Findings

Descriptive summaries of quantitative clinical laboratory results (hematology, chemistry, and urinalysis) and their change from baseline values will be presented by study visit and treatment group. Observed values of categorical urinalysis data will be displayed with frequencies and percentages. All laboratory data will be listed for individual subjects.

Treatment-emergent abnormal laboratory assessments will be based on the lab provided normal ranges. If the baseline laboratory assessment is normal and shifts to Low or High post-baseline, then the laboratory value is considered a TE abnormal laboratory value. For each protocol specified lab test, the number and percent of subjects reporting a TE abnormal lab will be reported.

All laboratory summaries will be limited to the tests specified in the protocol.

Descriptive summaries of vital signs and their change from baseline will be presented by study visit and treatment group and all vital signs will be listed.

Post-baseline PE findings will be listed.

5.3.3. Other Safety Analyses

ECG measurements will include heart rate, QT interval, Fredericia-corrected QT interval (QTcF), PR interval, and QRS interval. Change from baseline will be summarized descriptively by treatment group at each scheduled evaluation and all ECG data will be listed. Proportion of subjects with abnormal ECG interpretations will be summarized at each study visit and by treatment group. Proportion of subjects who meet each of the following criteria from International Conference on Harmonization Guideline E14 "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (October 2005) for QT and corrected QT intervals will be summarized across treatment groups:

- QT or QTcF >450 msec
- QT or QTcF >480 msec
- QT or QTcF >500 msec
- QT or QTcF increases from baseline by ≥30 msec
- QT or QTcF increases from baseline by ≥60 msec

5.3.4. Open-Label Extension Safety Analyses

Adverse events, laboratory values, and vital signs will be used in the OLE period to assess safety. Results occurring in just the OLE period will be reported based on the same treatment groups used for reporting during the DB portion of the study. The same analyses planned for the DB period will be generated for the OLE. Additionally, pooled AE displays will be developed. For the pooled analysis, only AEs in the OLE would apply to the patients randomized to vehicle during the DB

portion of the study. For patients randomized to ATI-502 during the DB portion, their complete AE profile for the entire study should be summarized in the pooled analysis.

6. CHANGES IN THE PROTOCOL-SPECIFIED ANALYSES

All analyses specified in the SAP are consistent with those specified in the protocol. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

7. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population due to missing data.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations.
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by treatment group, subject number and date, if applicable.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
    - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.

  - Means will be reported to one decimal place beyond the number of significant digits as the parameter.
  - Calculated percentages will be reported to one decimal place.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

8. PROPOSED TABLES, LISTINGS, AND FIGURES

8.1. END OF DOUBLE-BLIND TREATMENT PERIOD ANALYSIS

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2. Table 14.1.2 Primary Protocol Violations, ITT Population
3. Table 14.1.3 Analysis Populations, ITT Population
4. Table 14.1.3.1 Reasons for Exclusion from Per Protocol Population, ITT Population
5. Table 14.1.4 Demographics, ITT Population
6. Table 14.1.5 Baseline Characteristics, ITT Population
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10. Table 14.1.8.1 Prior Medications, Safety Population
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Section 14.2 Efficacy

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21. Table 14.2.1.8 Analysis of Change from Baseline in SALT Score (LOCF), ITT Population

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22. Table 14.2.2.1 Summary of ALODEX Score, Change from Baseline, and Percent Change from Baseline by Visit, ITT Population

23. Table 14.2.2.2 Analysis of Percent Change from Baseline in ALODEX (LOCF), ITT Population
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27. Table 14.2.3.3 Proportion of Subjects Achieving an Absolute SALT Score <= 10, ITT Population
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Scalp-ClinRO and Scalp-PRO

32. Table 14.2.4.1 Analysis of Change from Baseline in Scalp-ClinRO for Target Patch, ITT Population
33. Table 14.2.4.2 Analysis of Change from Baseline in Scalp-PRO for Target Patch, ITT Population
34. Table 14.2.4.3 Analysis of Change from Baseline in Scalp-ClinRO for Entire Scalp, ITT Population
35. Table 14.2.4.4 Analysis of Change from Baseline in Scalp-PRO for Entire Scalp, ITT Population

PhGIS and SGIS

36. Table 14.2.5.1 Analysis of Change from Baseline in Physician Global Impression of Severity (PhGIS), ITT Population
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48. Table 14.2.10.5 AIA–PRO, Confidence, ITT Population
49. Table 14.2.10.6 AIA–PRO, Self-Conscious, ITT Population
50. Table 14.2.10.7 AIA–PRO, Embarrassed, ITT Population
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60. Table 14.2.12.1 Analysis of Percent Change from Baseline in ALODEX Score (LOCF), ITT Population, Baseline SALT < 50
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62. Table 14.2.13.1 Proportion of Subjects Achieving >=50% Hair Regrowth Based on SALT Score, ITT Population, Baseline SALT < 50
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64. Table 14.2.14.1 Proportion of Subjects Achieving an Absolute SALT Score <= 10, ITT Population, Baseline SALT < 50
65. Table 14.2.14.2 Proportion of Subjects Achieving an Absolute SALT Score <= 10, ITT Population, Baseline SALT ≥ 50
66. Table 14.2.15.1 Proportion of Subjects with >= 2 Point Improvement in Scalp-ClinRO for Target Patch, ITT Population, Baseline SALT < 50
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81. Table 14.3.1.4 Treatment-Emergent Serious Adverse Events by SOC and PT, Safety Population
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7. History of Alopecia and Previous Therapies for Alopecia
8. Prior and Concomitant Medications
9. Study Drug Administration
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11. SALT Score, ALODEX Score, Scalp-ClinRO, Scalp-PRO
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13. PhGIC and SGIC
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15. DQLI Questions and Total Score
16. AIA-PRO Scale Items and Total Score
17. Hair Quality Assessments – Hair Pull Test
18. Adverse Events
19. Serious Adverse Events
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21. Laboratory Tests – Panel
22. Lab Abnormalities
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8.2. END OF OPEN LABEL EXTENSION PERIOD ANALYSIS

Section 14.1 Accountability and Baseline Characteristics

1. Subject Disposition, All Subjects
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3. Demographics, PP Population
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10. Summary of Scalp-ClinRO for Target Patch, ITT Population
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12. Summary of Scalp-PRO for Target Patch, ITT Population
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