STATISTICAL ANALYSIS PLAN

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of ATI-501 Oral Suspension Compared to Placebo in Adult Subjects with Alopecia Areata, Alopecia Universalis or Alopecia Totalis
Phase:	II
Protocol No.:	ATI-501-AUAT-201
Protocol Date(s):	Version 1.0, 26APR2018 Version 2.0, 20JUL2018 Version 3.0, 19SEP2018 Version 4.0, 08NOV2018 Version 5.0, 09APR2019
Analysis Plan Version and Date:	Version 1.0 Draft, 28MAY2019
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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
AAP	Patchy Alopecia Areata
AFHA	Alopecia Facial Hair Appearance Assessment
AT	Alopecia Totalis
AU	Alopecia Universalis
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
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
NSHA	Non-Scalp Hair Loss Assessment
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	Scalp-ClinRO for AAP[1]
Scalp-PRO	Scalp-PRO for AAP[2]
SGIC	Subject Global Impression of Change
SGIS	Subject Global Impression of Severity
SGITS	Subject Global Impression of Treatment Satisfaction
SGSHQ	Subject Global Satisfaction with Hair Quality

SR	Subject Rating
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-Clinician Rating (ASAA-CR) in the protocol. Subjects with Patchy AA complete Item 1 and Item 2 (target patch and whole scalp assessment). Subjects with Alopecia Totalis or Alopecia Universalis complete the assessment for the whole scalp only.
[2]This assessment is named Alopecia Scalp Appearance Assessment-Subject Rating (ASAA-SR) in the protocol. Subjects with Patchy AA complete Item 1 and Item 2 (target patch and whole scalp assessment). Subjects with Alopecia Totalis or Alopecia Universalis complete the assessment for the whole scalp only.

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol ATI-501-AUAT-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 evaluation of the psychometric properties of the newly developed patient-reported and clinician-reported outcome (PRO and ClinRO) questionnaires. Additionally, the generation of score interpretation estimates for the clinical outcome assessments to guide the definition of responders in pivotal trials is also not within the scope of this SAP.

1.1. STUDY OVERVIEW

ATI-501-AUAT-201 is a Phase 2, multicenter, randomized, double-blind study designed to evaluate the safety, tolerability and efficacy of ATI-501 Oral Suspension in subjects with alopecia areata (AA), alopecia universalis (AU), or alopecia totalis (AT). Subjects will be required to have a clinical diagnosis of stable AA, AU, or AT with at least 30% up to 100% total scalp hair loss for a duration of at least 6 months up to and including 12 years.

Treatment Assignment:
A total of approximately 95 subjects will be randomized in a 1:1:1:1 ratio:

- Placebo Oral Suspension, twice daily (BID) for 24 weeks (6 months)
- ATI-501 Oral Suspension, 400 mg, BID for 24 weeks (6 months)
- ATI-501 Oral Suspension, 600 mg, BID for 24 weeks (6 months)
- ATI-501 Oral Suspension, 800 mg, BID for 24 weeks (6 months)

During the screening period, subjects will be assessed for eligibility into the study. Subjects will receive ATI-501 Oral Suspension, 400 mg, 600 mg, or 800 mg or Placebo Oral Suspension twice-daily for up to 24 weeks. Assessment of response to treatment will be performed at Week 4 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 24 (Visit 9), and post-treatment (Visit 10). Safety and tolerability will be evaluated at each study visit by assessment of adverse events (AEs), clinical lab tests, vital signs, and at select visits, ECGs. The primary analysis will be conducted after all subjects complete Visit 9 or Visit 10.

Subjects who complete Visit 9 (Week 24) will be eligible to enter a 28-week open-label study ATI-502-AA-203. Subjects who decline or are not eligible for ATI-502-AA-203 should be seen for the Visit 10 (Post-treatment) assessments.

1.2. SCHEDULE OF ASSESSMENTS

		Screening	Baseline	Treatment							Post-Treatment
		Visit 1	Visit 2	Visit 3[1]	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 (ET)	Visit 10[19]
Week			0	2	4	8	12	16	20	24	28
Treatment Day		-30 to 0	1	15	29	57	85	113	141	169	197
Treatment window (days)		N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3
Informed consent[2]		X									
Inclusion/exclusion criteria		X	X								
Physical exam[3]		X								X	
Demographics & medical history		X									
Alopecia Areata History		X									
Vital signs[4]		X	X	X	X	X	X	X	X	X	X
Clinical Complete Blood Count (CBC), Chemistry, Virology, Serum Pregnancy, Urinalysis[5]		X[4]	X	X	X	X	X	X	X	X	X
Blood for PK (Select Sites Only)[6]			X (Pre-dose)		X		X			X	
Urine pregnancy test7		X	X		X	X	X	X	X	X	X
ECG		X		X						X	
Subject[8]	Target Patch identification (Patchy AA Subjects Only)		X								
	Scalp-PRO Target Patch, Whole Scalp[9]		X	X			X			X	X
	Alopecia Facial Hair Appearance Assessment (AFHA: SR)		X	X			X			X	X
	Subject Global Impression of Severity (SGIS-AAP (patchy alopecia areata) or SGISAT/AU)		X	X			X			X	X
	Alopecia Impact Assessment (AIA): Subject Rating		X	X			X			X	X
	Subject Global Impression of Change (SGIC)									X	
	Subject Global Impression Treatment Satisfaction (SGITSAAP or SGITSAT/AU)[10]						X			X	X
	Subject Global Satisfaction with Hair Quality (SGSHQAAP or SGSHQAT/AU)		X	X			X			X	X
	DLQI[11]		X	X			X			X	X

		Screening	Baseline	Treatment							Post-Treatment
		Visit 1	Visit 2	Visit 3[1]	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 (ET)	Visit 10[19]
Week			0	2	4	8	12	16	20	24	28
Treatment Day		-30 to 0	1	15	29	57	85	113	141	169	197
Treatment window (days)		N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3
Investigator[12]	Scalp-ClinRO Target Patch, Whole Scalp[13]		X	X			X			X	X
	Alopecia Facial Hair Appearance Assessment (AFHA: CR)		X	X			X			X	X
	Non-Scalp Hair Loss Assessment (NSHA)		X	X			X			X	X
	Physician Global Impression of Severity (PhGIS-AAP or PhGIS-AT/AU)		X	X			X			X	X
	Physician Global Impression of Change (PhGIC)									X	
	Hair Quality Assessment (Patchy AA Subjects Only)		X				X			X	X
	SALT Score (prior to ALODEX)[14]	X	X	X	X	X	X	X	X	X	X
	ALODEX Score (after SALT)[15]	X	X	X	X	X	X	X	X	X	X
	Vellus and Indeterminate Hair Assessment	X	X	X	X	X	X	X	X	X	X
Photography (complete scalp)			X		X	X	X	X	X	X	
Subject randomization			X								
Subject instructions[16]			X		X	X	X	X	X	X	
Dispense study medication[17]			X	X[18]	X	X	X	X	X		
Collect study medication and assess compliance[17]			X	X	X	X	X	X	X	X	X
Concomitant therapies			X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X

Abbreviations: CR= Clinician Rating; ET= Early termination Visit; SR= Subject Rating

[1] Efficacy assessments completed at Visit 3 are to test the reliability of the clinician and patient reported outcome tools.

[2] A written, signed informed consent form (ICF) 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).

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

[4] Vitals signs include: oral or ear temperature, blood pressure, heart rate, respiration rate (height and weight at Screening only).

[5] Clinical laboratory non-fasting sampling includes: CBC, Chemistry with lipids, Urinalysis. Quantiferon Gold, Human Immunodeficiency Virus (HIV), Hepatitis B and C, TIBC, Serum Iron, Serum Ferritin, T3, free T4, TSH and Serum Pregnancy should be done at screening visit only.

[6] At Select sites: A single 4.5 mililiters (mL) sodium citrate vacutainer should be drawn at Visit 2 (predose) and Visits 4, 6, and 9, 12 hours (± 30 minutes) after the prior evening dose. Subjects participating in the PK analysis should be called the day prior to Visit 4, 6, and 9 to remind them to take their evening dose approximately 11 hours prior to the visit time and to document the time of the evening dose.

[7] Subjects who are women of child-bearing potential (WOCBP) should have a urine pregnancy test (UPT) performed early in the screening procedures (following informed consent) which shows negative results in order to avoid the continuation of what would then be unnecessary screening testing. Subjects who are WOCBP must also have a negative serum pregnancy test result from Screening (Visit 1) to continue in the study, and a negative UPT at Baseline (Visit 2) prior to randomization. UPTs in WOCBP must also be obtained at Visits 4, 5, 6, 7, 8, 9 and 10 and must be negative for the subject to continue in the study.
[8] The subject should perform assessments prior to the Investigator assessments. The investigator may assist the subject in locating a Target Patch.
[9] Subjects with 30% to 95% scalp hair loss will identify the most bothersome patchy area at Baseline (Visit 2). A score of "no hair" or "a little hair" in the target patch is required. For subjects with AU or AT, the target patch identification at Baseline (Visit 2) will be recorded as "Not Applicable" in the source document and eCRF.
[10] The study staff should remind the subject that this question is in relation to the satisfaction with the result of the hair regrowth.
[11] The study staff should remind the subject that the questions are in relation to hair loss and not skin.
[12] Investigator assessments should be performed after the Subject Assessments.
[13] In subjects with patchy AA, the assessment of hair quality will be performed at the edge of the target patch. For subjects with AU/AT, the assessment of hair quality will be recorded as Not Applicable in the source document and eCRF. At Baseline (Visit 2), the assessment should be determined prior to the first dose of study medication.
[14] SALT score must be determined prior to ALODEX using device provided.
[15]ALODEX score determined after SALT score using device provided.
[16] The study staff must instruct the subject to dose study medication according to the instructions in Appendix 15.
[17]Staff should review the usage based on the number of used and unused bottles and counsel the subject as necessary.
[18]At Visit 3, the subject's Month 1 drug supply carton should be reviewed by site staff as part of compliance activities and then released back to the subject for continued use.
[19] Subjects who complete study visits through Visit 9 will have the option to roll over into an open-label study ATI-502-AA-203. Subjects who withdraw consent or meet study medication discontinuation criteria (Section 3.4.1.2) on study ATI-501-AUAT-201 will not be eligible for roll-over to study ATI-502-AA-203. Subjects who complete the assessments for Visit 9 and then meet study ATI-502-AA-203 entry criteria and provide written consent will skip post-treatment Visit 10. Subjects who are not eligible for ATI-502-AA-203 or who decline to participate should return for the final Visit 10 assessments.

2. OBJECTIVES

Primary Objective:

The primary objective is to assess the safety, tolerability and efficacy of ATI-501 Oral Suspension, 400 mg, 600 mg, or 800 mg compared to Placebo Oral Suspension in subjects with AA, AU, or AT.

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. This objective is not within the scope of the SAP.
- To generate score interpretation estimates for the clinical outcome assessments to guide the definition of responders in pivotal trials. This objective is not within the scope of the SAP.
- To assess the concentration level of ATI-502 in the blood at trough.

3. EFFICACY AND SAFETY ASSESSMENTS

Efficacy assessments include the following scores and/or scales (Note: Target Patch and Entire Scalp assessments are performed for AAP subjects. Only Entire Scalp assessments are performed for AT/AU subjects):

- Severity Alopecia Tool (SALT) Score
- Alopecia Density and Extent Score (ALODEX)
- Item 1 and Item 2 Scalp-ClinRO for AAP (Scalp-AAP-ClinRO), referred to as Alopecia Scalp Appearance Assessment (ASAA-AAP:CR) in the protocol
- Scalp-ClinRO for AT/AU (Scalp-AT/AU-ClinRO), referred to as Alopecia Scalp Appearance Assessment (ASAA-AT/AU:CR) in the protocol
- Item 1 and Item 2 Scalp-PRO for AAP (Scalp-AAP-PRO), referred to as Alopecia Scalp Appearance Assessment (ASAA-AAP:SR) in the protocol
- Scalp-PRO for AT/AU (Scalp-AT/AU-PRO), referred to as Alopecia Scalp Appearance Assessment (ASAA-AT/AU:SR) in the protocol
- Physician Global Impression of Severity (PhGIS-AAP or PhGIS-AT/AU)
- Alopecia Facial Hair Appearance Assessment (AFHA-PRO and AFHA-ClinRO)
- Subject Global Impression of Severity (SGIS-AAP or SGIS-AT/AU)
- Alopecia Impact Assessment (AIA) – Subject Rating
- Subject Global Impression of Treatment Satisfaction (SGITS-AAP or SGITS-AT/AU)
- Subject Global Satisfaction with Hair Quality (SGSHQ-AAP or SGSHG-AT/AU)
- Dermatology Life Quality Index (DLQI) total score
- Physician Global Impression of Change (PhGIC)
- Subject Global Impression of Change (SGIC)
- Hair Quality Assessment (Hair Pull Test, AAP subjects only)
- Vellus and Indeterminate scalp hair
- Non-scalp hair assessments (body and nasal hair) (NSHA)

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 (ECGs)

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. SAMPLE SIZE AND POWER

The planned sample size is 95 enrolled subjects with approximately 45 subjects enrolled with AT or AU. It is assumed that the proportion of subjects who achieve at least a 50% reduction in hair loss ($SALT_{50}$) for the pooled 600mg and 800mg treatment groups will be at least 32%, and the $SALT_{50}$ for the pooled placebo and 400mg treatment groups will be at most 6%. Assuming a 10% dropout rate, this results in >80% power for the $SALT_{50}$ analysis. Because the primary efficacy analysis of mean percent change in hair loss using SALT scores is expected to be more sensitive than the $SALT_{50}$ responder analysis, the power for the primary analysis is also expected to be no less than 84%.

4.2. RANDOMIZATION AND BLINDING

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 treatment period, subjects will be assigned to 1 of the 4 treatment groups in a random manner and at a 1:1:1:1 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.

This study uses a double-blind design. The study medications are indistinguishable in appearance, as packaged and labeled.

4.3. HANDLING OF DATA

4.3.1. Strata and Covariates

No stratified analyses are planned.

4.3.2. Examination of Subject Subsets

The baseline SALT score group (< 50, ≥50) will be used for subset analyses. Additionally, duration of current episode (< 4 years, ≥ 4 years) will be used for subset analyses. The details of the subset analyses are given in the statistical analysis section.

4.3.3. Multiple Testing and Comparisons

There are no planned adjustments for multiple comparisons.

4.3.4. 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.

4.3.5. Imputation of Incomplete Dates

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.

For purposes of imputation, all events with an incomplete end date are assumed to have ended on or before the day the form was completed. 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).

4.3.6. Definitions and Terminology

Day 1
Day 1 is defined as the date of the initial study medication dose as reported on the study medication usage page of the CRF.

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

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

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

Study Day
Study day will be relative to the defined Day 1.

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 took oral medication in the treatment period as determined by last date of recorded on the study medication usage page of the CRF.

Study Medication Exposure (days)
Study drug exposure is defined as the (date of last 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 doses per day field on the study medication page of eCRF.

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

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

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

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
An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product.
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. Hair growth in unexpected areas, such as facial hair in women, should be reported as an adverse event

Treatment-Emergent Adverse Event (TEAE)
Any recorded AE that occurs on or after the initiation of study medication and within 30 days after the date of Visit 9 or 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.

4.3.7. Presentations by Study Visit

Results from efficacy assessments and safety will be summarized by study visit and treatment group. 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 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 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 – 182]

For the post-treatment visit 10, the analyses will be based on the nominal study visit as reported on the CRF.

4.4. TIMING OF ANALYSES

When all subjects have completed study AA-501-AUAT-201 or terminated early from the blinded treatment period and the database has been locked and forwarded for analysis, the study will be unblinded and the safety and efficacy analysis will be performed according to this SAP.

No interim analysis is planned for this study

5. ANALYSIS POPULATIONS

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

5.1. 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.

5.2. SAFETY POPULATION

The Safety population is defined as all randomized subjects who received at least one dose 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.

5.3. 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 administer at least 75% of study medication

4. Did not complete Week 24 (Visit 9).

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

5.4. PHARMACOKINETICS (PK) POPULATION

The Pharmacokinetics (PK) population is defined as all subjects who receive at least one dose of study medication and have at least one measurable ATI-502 concentration value. Subjects in this population will be analyzed according to the treatment which they receive. All PK analyses will be based on this population.

6. 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.

The term 'treatment group' refers to ATI-501 active groups and matching Placebo Oral Suspension 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-501 treatment groups will be tested versus Placebo Oral Suspension 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 prior to issuance of the draft statistical report. All documents will be reviewed by the lead statistician to ensure accuracy and consistency.

6.1. 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 diagnosis type (Areata, Universalis, Totalis), ophiasis pattern of hair loss, duration of alopecia, duration of current episode of alopecia (continuous and dichotomized (< 4 years, ≥ 4 years)), baseline hair pull test results (dislodged hairs and broken hairs), baseline vellus and indeterminate hair assessment, baseline SALT score group (<50%, >50%) and baseline Scalp-ClinRO (target patch and entire scalp) and Scalp-PRO (target patch and entire scalp) 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 (NCS) and abnormal clinically significant (CS).

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.

6.2. EFFICACY ANALYSIS

6.2.1. Primary Efficacy Endpoint

The primary efficacy variable will be the mean percent change from baseline in the SALT score at Week 24 (Visit 9).

6.2.2. Primary Efficacy Analysis

Descriptive statistics for the SALT score, change, and percent change from baseline will be presented by 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, and treatment by study visit 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.

6.2.3. 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 PP population and the ITT population.

6.2.4. Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Percent change from baseline in the ALODEX score at Week 24 (Visit 9), also described as mean percent regrowth,
- Mean change from baseline in SALT score at Week 24 (Visit 9)
- Mean change from baseline in ALODEX score at Week 24 (Visit 9)
- 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-AAP-PRO and Scalp-AT/AU-PRO at Week 24 (Visit 9)
- Change from baseline in the Scalp-AAP-ClinRO and Scalp-AT/AU-PRO at Week 24 (Visit 9)
- Change from baseline in the PhGIS-AAP and PhGIS-AT/AU at Week 24 (Visit 9)
- Change from baseline in AFHA-ClinRO at Week 24
- Change from baseline in AFHA-PRO at Week 24
- Change from baseline in the SGIS-AAP and SGIS-AT/AU at Week 24 (Visit 9)
- Change from baseline in SGSHQ-AAP and SGSHQ-AT/AU at Week 24
- Change from baseline in the subject reported AIA at Week 24 (Visit 9)

- SGITS-AAP and SGITS-AT/AU at Week 24 (Visit 9)
- Change in DLQI total score between Baseline and Week 24 (Visit 9)
- PhGIC at Week 24 (Visit 9)
- SGIC at Week 24 (Visit 9)

6.2.5. 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 (patchy AA subjects only)
- Proportion of subjects with ≥ 2-point improvement in Scalp-PRO for the Target Area (patchy AA subjects only)
- 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 a factor for treatment. The p-value for the overall global test that $\beta = 0$ for this factor will be presented. The adjusted odds ratios (95% CI) for being a responder (active/placebo oral suspension) will be presented along with the associated p-value.

The questionnaires Scalp-PRO, Scalp-ClinRO, PhGIS, AFHA, and SGIS are collected on a 1-5 scale. The SGSHQ questionnaire is collected on a 1-7 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 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 placebo oral suspension.

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 placebo oral suspension.

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.

6.2.6. Other Efficacy

Results from the Hair Quality Assessment (hair pull test) will be summarized. The summary will show the shift relative to baseline in the categories of dislodged hairs and broken hairs at Week 24 (Visit 9).

Results from the Vellus and Indeterminate Hair Assessment will be summarized. The summary will show the shift relative to baseline at Week 24 (Visit 9) in the categories of vellus hair present and indeterminate hair present.

NSHA results will also be summarized. The summary will show the shift relative to baseline at Week 24 (Visit 9) in the Body Hair Loss categories of no body hair loss, some hair loss, and total body hair loss and in the Nasal Hair Loss categories of no nasal hair loss to some to total hair loss.

6.2.7. Subset Analyses

- Subgroups of Baseline SALT score group (< 50, ≥50)
- Subgroups of duration of current alopecia episode (<4 years, ≥4 years)

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.

6.2.8. 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.

6.3. 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).

6.3.1. 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 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.

6.3.2. 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.

6.3.3. 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 (CS and NCS) 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 milliseconds (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

6.4. PHARMAKOKINETICS

6.4.1. Pharmacokinetic Analyses

The concentration of ATI-502 in the blood will be summarized for the treatment period at pre-dose (Visit 2) and approximately 12-hr post dosing at Visits 4, 6 and 9.

7. 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.

8. 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. The number of missing observations, if any, will be noted.
    - 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. The number of missing observations, if any, will be noted.
- 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.
- 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).

9. PROPOSED TABLES, LISTINGS, AND FIGURES

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128. Table 14.3.5.1.3 Proportion of Subjects with Noteworthy QT and QTcF Values and Changes from Baseline by Visit
129. Table 14.3.5.2.1 Summary of Vital Signs and Change from Baseline, Safety Population

Section 14.4 Pharmacokinetics

130. Table 14.4.1 Summary ATI-502 Concentrations and Change from Baseline, PK Population

Section 16.2 Data Listings

1. Disposition - Early Termination/Study Completion
2. Protocol Violations
3. Study Populations
4. Inclusion/Exclusion Criteria
5. Demographics
6. Medical History
7. History of Alopecia and Previous Therapies for Alopecia
8. Prior and Concomitant Medications
9. Study Drug Administration
10. Study Drug Accountability
11. SALT Score, ALODEX Score, Scalp-ClinRO, Scalp-PRO
12. PhGIS and SGIS
13. AFHA
14. SGSHQ
15. SGITS
16. DQLI Questions and Total Score
17. AIA-PRO Scale Items and Total Score
18. PhGIC and SGIC
19. Hair Quality Assessments – Hair Pull Test
20. Vellus and Indeterminate Hair Assessment (AAP Subjects)
21. NSHA
22. Adverse Events
23. Serious Adverse Events
24. Adverse Events Leading to Discontinuation
25. Laboratory Tests – Panel
26. Lab Abnormalities
27. Vital Signs
28. Physical Examination
29. ECG
30. ATI-502 Concentrations