CLINICAL STUDY PROTOCOL

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

Amendment 4

Compound:	ATI-501
US IND Number:	129, 539
Protocol Number:	ATI-501-AUAT-201
Phase:	2

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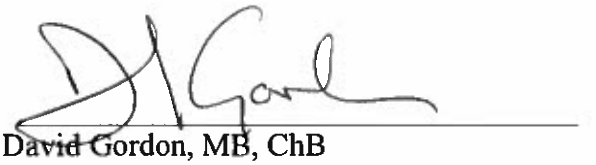
PROTOCOL APPROVAL SIGNATURE PAGE

Sponsor Signatures:



4-9-2019

David Gordon, MB, ChB
Chief Medical Officer
Aclaris Therapeutics, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ATI-501. I have read the ATI-501-AUAT-201 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I will conduct the trial in accordance with the principles of ICH Good Clinical Practice and the Declaration of Helsinki.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, case report forms, investigator's brochure, material supplied at investigator meetings, minutes of teleconferences, etc. Such materials will only be provided as necessary to site personnel involved in the conduct of the trial, involved IRBs or local regulatory authorities.

I will obtain written informed consent from each prospective trial subject or each prospective trial subject's legal representative prior to conducting any protocol-specified procedures. The Informed Consent Document used will have the approval of the IRB appropriate for my institution.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial subjects in their medical records. I will accurately complete the case report forms supplied by the Sponsor in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of the Sponsor, the IRB, and/or local regulatory authorities. I will ensure that I and my staff are available to meet with Sponsor representatives during regularly scheduled monitoring visits.

I will notify the Sponsor within 24 hours of any serious adverse events. Following this notification, an initial written report describing the serious adverse event will be provided to the Sponsor within 24 hours of Investigator awareness of the event.

_____

Printed Name of Investigator

_____ _____

Signature of Investigator Date

AMENDMENT HISTORY

Amendment 1.0 (Protocol Version 2.0 dated 20Jul2018): The primary reason for Amendment 1.0, Protocol Version 2.0 dated 20Jul2018 was to decrease the number of subjects enrolled in the study which are sufficient to explore the efficacy and safety in this initial Phase 2 study. In addition, a substudy was added to determine the trough levels of ATI-502 in the blood and pharmacodynamic effects at trough.

Amendment 2.0 (Protocol Version 3.0 dated 19Sep2018): The primary reason for Amendment 2.0, Protocol Version 3.0, dated 19SEP2018 was to add additional safety assessments, specifically – clinical laboratory testing (chemistry and hematology) at Visit 5, Visit 7 and Visit 8 and to remove pharmacodynamic testing in a subset of subjects at Visit 2, Visit 4, Visit 6 and Visit 9.

Amendment 3.0 (Protocol Version 4.0 dated 08Nov2018): The primary reason for Amendment 3.0, Protocol Version 4.0, dated 08NOV2018 is to give subjects the option to initiate treatment with ATI-502 Topical Solution, 0.46% to explore if hair regrowth can be maintained or continued following cessation of treatment with ATI-501 Oral Suspension. Eligible subjects will be given the option at Visit 9 to enter an open-label study ATI-502-AA-203.

AMENDMENT RATIONALE

The purpose of Protocol Version 5.0 dated 09APR2019 (Protocol Amendment 4.0) is to clarify the primary endpoint will be conducted on the ITT population. In addition, other clarifications were made to the statistical methods as detailed in the following table. All previous amendments have been incorporated into the protocol dated 09APR2019.

MAJOR PROTOCOL CHANGES

Protocol Version	Date	Section	Revisions
Version 5.0	09APR2019	Statistical Methods -Synopsis, -Section 9.4.1	-Specified that the primary analysis would be on the ITT population, using LOCF for missing data and based upon a mixed effect model repeated measures (MMRM). -Clarified: efficacy variable is “percent change from baseline” and not “mean percent change from baseline”.
		Secondary Efficacy Analyses -Synopsis -Section 9.4.2	-Included a secondary sensitivity analysis on the primary endpoint using the PP population. -Added secondary responder efficacy endpoints to be specified in the SAP -Specified that all secondary efficacy endpoints would be analyzed using the ITT population Deleted: Dichotomous variables will be analyzed using Chi-square tests. Ordinal and continuous variables will be analyzed using appropriate Analysis of Variance models.
		Section 9.4	-Deleted the statement that the PP population would be used for all efficacy analyses -Clarified that Hair regrowth is determined based on both percent change from baseline and absolute change from baseline.
		Synopsis, Section 9.5	Dropped the chi-square test for the overall incidence of AE

SYNOPSIS

Name of Sponsor/Company: Aclaris Therapeutics, Inc.

Name of Investigational Product: ATI-501 Oral Suspension

Name of Active Ingredient: ATI-501

Title of Study: 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

Study center(s): Approximately 25 US study centers

Studied period (years):	**Phase of development:** 2
Estimated date first patient enrolled: June 2018 Estimated date last patient completed: July 2019	

Objectives:

Primary:

- To evaluate the safety, tolerability and efficacy of ATI-501 Oral Suspension, 400 mg, 600 mg, 800 mg compared to Placebo Oral Suspension in subjects with alopecia areata (AA), alopecia universalis (AU) or alopecia totalis (AT)

Secondary:

- To evaluate the psychometric performance of the key clinical outcome assessments and 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
- To assess the level of ATI-502 in the blood at trough

Methodology:

This Phase 2, multicenter, randomized study will evaluate the safety, tolerability and efficacy of ATI-501 for the treatment of AA, AU, or AT in adult subjects. Subjects will be required to have a clinical diagnosis of stable AA, AU, or AT with 30% to 100% total scalp hair loss for a duration of at least 6 months up to and including 12 years. A total of 80 subjects will be randomized with approximately 40 subjects enrolled with AU or AT. Subjects will be randomized to a 1:1:1:1 ratio:

- 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)
- Placebo Oral Suspension, BID for 24 weeks (6 months)

During the screening period, subjects will be assessed for eligibility into the study. Subjects qualifying for protocol treatment based on the outcome of screening procedures will be randomized to take 400 mg, 600 mg, 800 mg or placebo suspension twice-daily within approximately 30 minutes following morning and evening meals for 24 weeks. Assessment of response to treatment will be performed at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and post-treatment Week 28.

Safety and tolerability will be evaluated at each study visit by assessment of adverse events, clinical laboratory tests, and vital signs, and at select visits, ECGs will be completed.

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.

Select Sites:

At approximately six sites, 24 subjects will have additional blood samples taken for pharmacokinetic analyses. Blood samples will be taken at predose at Visit 2 and at trough at Visit 4, Visit 6 and Visit 9 to determine the concentration of ATI-502 in the blood at trough.

Number of subjects (planned): Approximately 95 with approximately 45 subjects enrolled with AT or AU.

Male and female subjects, 18 years of age or older, with a clinical diagnosis of stable AA, AU or AT of the scalp, who meet all the inclusion criteria and none of the exclusion criteria, will be eligible to enroll in this study.

Inclusion Criteria:

Subjects must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and willing to sign an Informed Consent Form (ICF).
2. Male or non-pregnant, non-nursing female ≥ 18 years old at the time of informed consent.
3. Have a clinical diagnosis of stable AA, AU or AT (Stable is defined as no current areas of spontaneous terminal scalp hair regrowth).
4. Have a Severity of Alopecia Tool (SALT) score of at least 30% to 100% total scalp hair loss determined by the study investigator at Screening (Visit 1) and Baseline (Visit 2).
5. Subjects with 30% to 95% scalp hair loss (based on SALT score) must have an assessment of "no hair" or "a little hair" in the target scalp patch based on both the Clinician and Subject Alopecia Scalp Appearance Assessment (ASAA). The target patch is defined as the most bothersome patchy area of hair loss as identified by the subject (Refer to Section 7.1).
6. Have a duration of the current episode of stable scalp hair loss for a minimum of 6 months and a maximum duration of hair loss of 12 years (inclusive). [Current episode is defined as the period of the current presentation of hair loss (AA, AU or AT)].
7. If the subject is a woman of childbearing potential (WOCBP), she must have:
    - Negative serum pregnancy tests at Screening (Visit 1); and
    - A negative urine pregnancy test at Baseline (Visit 2); and
    - Agree to not be planning a pregnancy during the study duration and use a highly effective method of contraception for the duration of the study and 30 days after the last dose of study medication. (Refer to Section 8.4.2).
8. Be in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair evaluation of the subject or which might expose the subject to an unacceptable risk by study participation.
9. Be willing to maintain the same hair style and hair dyeing throughout the study period. Subjects who shave their scalp must be willing to refrain from shaving their scalp for at least two weeks prior to each study visit, as determined by the investigator based on the ability to assess visible scalp hair growth. Hair trimming outside the treatment areas to maintain the current hair style is permitted.

10. Be willing and able to follow all study instructions and to attend all study visits.
11. Subjects taking hormonal replacement therapies must be on stable doses for 6 months prior to enrollment and remain on a maintenance dose throughout the study.
12. Subjects taking thyroid replacement medication must be on stable doses for 6 months prior to enrollment and remain on a maintenance dose throughout the study.
13. Sexually active male subjects must agree to use a barrier method of contraception with any WOCBP partner(s) from the first dose of study medication to at least 30 days after the last dose of study medication.

Exclusion Criteria:

Subjects are excluded from this study if any 1 or more of the following criteria is met:

1. Females who are nursing, pregnant, or planning to become pregnant for the duration of the study and up to 30 days after the last dose of study medication.
2. Diffuse alopecia areata. [Diffuse alopecia areata is defined as the absence of the typical patchy distribution of hair loss (in subjects with ≤95% total scalp hair loss) with hair thinning distributed throughout the scalp.]
3. Concomitant hair loss disorder (by history or physical exam) such as androgenetic alopecia (AGA) or scarring alopecia (*e.g.*, cicatricial alopecia, frontal fibrosing alopecia, etc.). Subjects without a prior known history of AGA or other patterned hair loss disorder who exhibit AGA or other patterned hair loss with regrowth during the study will be allowed to continue in the study.
4. Active skin disease on the scalp (such as psoriasis or seborrheic dermatitis) or a history of skin disease on the scalp that in the opinion of the investigator would interfere with study assessments of efficacy or safety.
5. Active scalp trauma or other condition affecting the scalp that, in the investigator's opinion, may affect the course of AA, AU or AT or interfere with the study conduct or evaluations.
6. The presence of a permanent or difficult to remove hairpiece or wig that will, in the opinion of the investigator, interfere with study assessments if not removed at each visit.
7. History of, or current, severe, progressive or uncontrolled autoimmune, metabolic, hepatic, endocrine, renal, gastrointestinal, pulmonary, cardiovascular, genitourinary, or hematological disease, neurologic or cerebral disorders, or coagulation disorders that, as determined by the Investigator, would preclude participation in and completion of study assessments.
8. History of, current or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than subjects with a history of adequately treated and well healed and completely cleared non-melanoma skin cancers (e.g. basal or squamous cell carcinoma) treated successfully at least 1 year prior to study entry with no evidence of disease.
9. Evidence of active or latent bacterial (including tuberculosis) or viral infections at the time of enrollment, or history of incompletely treated or untreated tuberculosis. Subjects who have completed therapy for latent tuberculosis may participate. Refer to Exclusion Criterion 12 for herpes zoster, herpes simplex, or cytomegalovirus infections.
10. History of serious local infection (*e.g.*, cellulitis, abscess) or systemic infection including but not limited to a history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to Baseline. Subjects on an antibiotic for a nonserious, acute local infection must complete the course prior to enrollment into the study.
11. Positive for HIV, Hepatitis B or C. Subjects with serologic evidence of Hepatitis B vaccination (HepB surface Ab without the presence of Hep B surface Ag) will be allowed to participate.
12. History of recurrent herpes zoster (more than one episode) or disseminated herpes zoster (a single episode) or disseminated herpes simplex (single episode) or cytomegalovirus (CMV)

that resolved less than 2 months before study enrollment. Subjects with a history of frequent outbreaks of Herpes Simplex Virus (defined as 4 or more outbreaks a year).

13. Clinically significant laboratory abnormalities at screening that, in the opinion of the Investigator, would make the subject a poor candidate for the study. [Subjects with any Screening laboratory values meeting the Study Medication Interruption Criteria found in Table 2 must have repeat lab testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2)].
14. Subjects with absolute neutrophil count <1,800/μL, or platelet count <130,000/μL.
15. Subjects who have received any of the following treatments for the timeframes specified below:
    - Disease Modifying Anti-Rheumatic Drugs (DMARDS), Biologics or immunosuppressants, including but not limited to: anakinra, adalimumab, azathioprine, corticosteroids, cyclosporine, etanercept, infliximab, methotrexate, TNF inhibitors, ustekinumab within 1 month or 5 half-lives (whichever is greater) of Baseline (Visit 2).
    - Plaquenil within 2 months of Baseline (Visit 2).
    - JAK inhibitors (oral or topical) within 6 months of Baseline (Visit 2).
    - Intralesional steroids or platelet rich plasma injections in the scalp within 1 month of Baseline (Visit 2).
    - Topical treatments on the scalp with anthralin, bimatoprost, corticosteroids, diphencyprone, diphenylcyclopropenone (DPCP), squaric acid dibutylester (SADBE), minoxidil, pimecrolimus, or tacrolimus within 1 month of Baseline (Visit 2).
    - Phototherapy (narrow band Ultraviolet B [NB UVB] or broadband therapy) within 4 weeks of Baseline (Visit 2).
16. Participation in an investigational drug or device trial in which administration of an investigational drug or device occurred within 30 days or 5 half-lives (whichever is longer) of Baseline (Visit 2).
17. Any condition possibly affecting oral drug absorption, e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding are not exclusionary.
18. Sensitivity to any of the ingredients in the study medications.
19. Unwillingness to refrain from weaves, hair extensions, or shaving of the scalp for at least two weeks prior to a study visit, at the discretion of the investigator, based on the ability to assess hair growth.
20. Screening ECG findings of:
    - QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose)
    - Heart rate ≤45 or ≥ 100 beats/minutes (A subject with a heart rate ≤ 45 beats/min may be enrolled if in the opinion of the investigator the heart rate is not clinically significant).
    - Rhythm disturbance other than sinus arrhythmia or ectopic supraventricular rhythm (ectopic atrial rhythm)
    - Conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
    - Acute or chronic signs of ischemia
    - Left Bundle Branch Block
    - Prior myocardial infarction
21. Vaccination with a live or attenuated vaccine within 6 weeks prior to Baseline (Visit 2) or planned vaccination with these vaccines at any time during treatment or within 6 weeks following discontinuation of study medication.

22. Participation in an investigational study with ATI-502 Topical Solution.
23. Subjects unwilling to have photographs taken for study purposes.

Investigational product, dosage and mode of administration:

ATI-501 Oral Suspension, 400 mg, 600 mg, 800 mg or placebo will be taken approximately 30 minutes after morning and evening meal followed by a large glass of water, twice-daily for 24 weeks.

Duration of treatment:

All subjects will take 400 mg, 600 mg, 800 mg or placebo oral suspension twice daily for 24 weeks followed by a 4-week post-treatment follow up period.

Reference therapy, dosage and mode of administration:

Placebo suspension, twice daily, oral

Criteria for evaluation:

Primary Efficacy:

- The primary efficacy endpoint is the mean percent change from Baseline in the Severity of Alopecia Tool (SALT) score at Week 24 (Visit 9).

Secondary Efficacy*:*

- Mean percent change from Baseline in the Alopecia Density and Extent Score (ALODEX) score at Week 24.
- Change from Baseline in the SALT score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Alopecia Density and Extent Score (ALODEX) score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Proportion of subjects in each treatment arm achieving at least a 50% reduction in ALODEX score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available compared to Baseline.
- Proportion of subjects in each treatment arm achieving at least a 50% reduction in SALT score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available compared to Baseline.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Patient-reported outcome [PRO]) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Clinician-reported outcome [ClinRO]) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Physician Global Impression of Severity (PhGIS) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in Alopecia Facial Hair Appearance Assessment (AFHA) (Clinician and Subject) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Subject Global Impression of Severity (SGIS) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the subject reported Alopecia Impact Assessment (AIA) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Subject Global Impression of Treatment Satisfaction (SGITS) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Subject Global Satisfaction with Hair Quality (SGSHQ) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.

- Change in Dermatology Life Quality Index (DLQI) total score between Baseline and Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Global Impression of Change (Clinician and Subject) at Week 24 (Visit 9).

Other Assessments:

- Hair quality assessment including normalization of exclamation point hairs and hair shedding will be described.
- Vellus and Indeterminate scalp hair will be described.
- Non-scalp hair assessments (body and nasal hair) will be described.

Pharmacokinetic:

The concentration of ATI-502 in the blood predose at Visit 2 and at trough at Visit 4, Visit 6 and Visit 9 will be measured by a bioanalytical lab using fully validated analytical methods.

Safety:

- Safety variables to be assessed include: adverse events, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, respiration rate, heart rate, and oral body temperature), and electrocardiograms.

Statistical Methods:

Sample Size/ Power Calculations

The planned sample size is approximately 95 enrolled subjects with approximately 45 subjects enrolled with AT or AU. The sample size estimate was based on published results from a similar study (Crispin et al. 2016) where 32% of subjects receiving active drug achieved at least a 50% relative reduction in hair loss ($SALT_{50}$) under similar conditions. For the current study, the primary efficacy analysis is mean % change in hair loss, evaluated using SALT scores. That analysis is expected to have greater statistical sensitivity than the $SALT_{50}$ responder analysis, which is also a secondary efficacy analysis in the current study.

We assume the pooled results of 600mg and 800mg treatment groups in the current study will achieve the same or higher $SALT_{50}$ response rate (32%) as the published results above, and pooled Vehicle plus 400mg treatment groups will not achieve more than a 6% $SALT_{50}$ response rate. Based on a comparison of those two pooled groups, the current study is anticipated to have no less than 80% power with a 10% subject dropout rate for the $SALT_{50}$ analysis. Because the primary efficacy analysis of mean percent reduction 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 80%.

Statistical Methods

The primary efficacy variable will be the percent change from Baseline in the SALT score at Week 24 (Visit 9). This represents the percentage of hair regrowth. It will be calculated as the change from baseline (Visit 2) to Week 24 (Visit 9), divided by the baseline and expressed as a percentage. Missing data for the primary endpoint will be imputed using Last Observation Carried Forward (LOCF) methodology. The analysis will be conducted on the percent change from baseline over time including all visits using a mixed effect model repeated measures (MMRM). The adjusted mean (LS Mean) for percent change from baseline in the SALT score at each visit, estimated from the MMRM, 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. No adjustment for multiplicity will be made. The model

will include fixed effect terms for treatment, study visit, baseline SALT score group (<50, >=50), and treatment by baseline SALT group interaction. The primary analysis will be based on the Intent-to-Treat (ITT) population. Statistical significance for primary efficacy endpoint will be declared if at least one treatment group comparison at the Week 24 visit has a two-sided p-value less than or equal to 0.05.

Secondary Efficacy Analyses

A secondary sensitivity analysis of the primary endpoint will be conducted using the PP population. This analysis will use the same methodology as described for the primary analysis just applied to the PP population.

The secondary efficacy endpoints include the change from Baseline in the ALODEX score, ASAA (CR & SR), AFHA (CR & SR), PhGIS, SGIS, AIA, SGSHQ, and DLQI as well as the proportion of subjects achieving a ≥ 50% hair growth compared with Baseline based upon the SALT score and ALODEX score, separately. SGITS responses at Week 12, 24, and 28 will be summarized. Various secondary responder efficacy endpoints will be defined based upon the SALT score, the ALODEX score and the AAA (Clinician and Subject) questionnaires. Details of these responder definitions will be specified in the statistical analysis plan (SAP). Global Impression of Change (Clinician and Subject) at Week 24 (Visit 9) will be used in the psychometric evaluation of the scores from the ASAA (CR and SR), respectively. Non-Scalp Hair Loss Assessment, Vellus and Indeterminate Hair Assessment and Hair Quality Assessment including normalization of exclamation point hairs and hair shedding will be described. The analysis for percent change in ALODEX score will used the same methodology as specified for the primary efficacy analysis. Other parameters will be analyzed as detailed in the statistical analysis plan.

Data collected in this trial will be used to evaluate the psychometric properties of the newly developed patient-reported and clinician-reported outcome (PRO and ClinRO) questionnaires. A measurement-focused statistical analysis plan will detail the data analytic strategy used to achieve the measurement property and score interpretation objectives. The anticipated psychometric evaluation analyses for the newly developed PRO and ClinRO questionnaires may include the following: score description, score reliability, score construct-related validity and score interpretation.

Pharmacokinetic Analyses

The concentration of ATI-502 in the blood will be summarized (mean [SD], minimum, median maximum) predose at Visit 2 and at trough at Visit 4, 6, and 9.

Safety Data

Safety analyses will include descriptive statistics calculated on the safety parameters using the safety population. The proportion of subjects with treatment-emergent adverse events will be tabulated and presented by treatment and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class. Vital signs and clinically significant abnormal laboratory results will also be tabulated and presented by treatment group.

Data from all randomized and treated subjects will be presented and summarized. Safety summaries by study treatment group will include listings by study medication of adverse events incidences within each MedDRA System Organ Class, and changes from pre-dose values in vital signs. Adverse event summaries will be presented by study medication showing the proportion of subjects experiencing adverse events, both overall and by MedDRA System Organ Class.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AA	Alopecia Areata
AAP	Alopecia Areata Patchy
AE	Adverse Event
AFHA	Alopecia Facial Hair Appearance Assessment
AGA	Androgenic Alopecia
AIA	Alopecia Impact Assessment
ALADIN	Alopecia Areata Disease Activity Index
ALODEX	Alopecia Density and Extent Score
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
ASAA	Alopecia Scalp Appearance Assessment
AST	Aspartate Aminotransferase
AT	Alopecia Totalis
AU	Alopecia Universalis
BID, b.i.d.	Twice-daily
BUN	Blood Urea Nitrogen
°C	Degrees Centigrade
CD	Cluster of Differentiation
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
CMV	Cytomegalovirus
CR	Clinician's Rating
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Clinically Significant
CTL	Cytotoxic T-lymphocytes
DLQI	Dermatology Life Quality Index
DMARDs	Disease Modifying Anti-Rheumatic Drugs
DPCP	Diphenylcyclopropenone
e.g.	for example (Latin; *exempla gratia*)
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
°F	Degrees Fahrenheit
FACS	Fluorescence Acquisition Cell Sorting
FDA	Food and Drug Administration
G/g	Gram
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
H&E	Hematoxylin and Eosin
HLA-DR	Human Leukocyte Antigen- antigen D Related
ICAM-1	Intercellular Adhesion Molecule 1
ICF	Informed Consent Form

Abbreviation or Specialist Term	Explanation
ICH	International Conference on Harmonization
i.e.	that is (Latin; *id est*)
IFN	Interferon
IHC	Immunohistochemical
IL	Interleukin
ITT	Intent-to-Treat
IRB	Institutional Review Board
JAK	Janus Kinase
KER	Hair keratin panel
KRT	Hair Keratin
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
mL	Milliliter
mm	Millimeter
MMRM	Mixed Effect Model Repeated Measures
NCS	Not Clinically Significant
NK/ NKG	Natural Killer/ Natural Killer Group
NMSC	Nonmelanoma Skin Cancer
OTC	Over-The-Counter
PDT	Photodynamic Therapy
PhGIC	Physician Global Impression of Change
PhGIS	Physician Global Impression of Severity
PP	Per-protocol
PRO	Patient-Reported Outcome
PUVA	Psoralen and Ultraviolet A
SADBE	Squaric Acid Dibutyl Ester
SAE	Serious Adverse Event
SALT	Severity of Alopecia Tool
SALT50	50% Absolute Change in SALT (Hair Loss at Baseline – Hair loss At Follow-up)
$SALT_{50}$	50% Change in Hair Loss or 50% regrowth
SGIC	Subject Global Impression of Change
SGIS	Subject Global Impression of Severity
SGSHQ	Subject Global Satisfaction with Hair Quality
SGITS	Subject Global Impression of Treatment Satisfaction
SI	Subject identifier
SN	Subject Number
SOP	Standard Operation Procedure
SR	Subject's Rating
STAT	Signal Transducer and Activator of Transcription
TEAE	Treatment Emergent Adverse Event
Th1	Type 1 Helper T Cell
TNK	Tumor Necrosis Factor
Tyk2	Tyrosine Kinase 2
UPT	Urine Pregnancy Test
US	United States
UVA	Ultraviolet A
UVB	Ultraviolet B
WOCBP	Women of childbearing potential

1. INTRODUCTION

Aclaris Therapeutics, Inc. is developing ATI-501 for the treatment of alopecia areata, alopecia universalis, and alopecia totalis. ATI-501 is a potent highly selective inhibitor of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3).

1.1. Overview of Alopecia Areata

Alopecia areata (AA) is an autoimmune dermatologic condition, which, in its mildest form, is typically characterized by patchy non-scarring hair loss on the scalp and/or body. More severe forms of AA include total scalp hair loss, known as alopecia totalis (AT), and total loss of all the hair on the scalp and body- importantly, including loss of eyebrows, eyelashes, and intranasal hair- known as alopecia universalis (AU). While spontaneous regrowth of hair is common in the milder form of AA (patchy), where the hair loss may wax and wane, in patients with the extensive hair loss of AT or AU, spontaneous hair regrowth is rare. AA affects both males and females across all ethnic groups and ages, and with a lifetime risk of 1.7% (Safavi 1995). About two-thirds of affected individuals are 30 years old or younger at the time of disease onset.

The course of AA is unpredictable and while up to 50% of patients may recover within 1 year even without treatment, most patients will have more than one episode of hair loss (Price 2008). Factors portending a poorer prognosis for regrowth are more extensive hair loss presentations (extensive AA, AT, AU), an ophiasis pattern of hair loss, a long duration of hair loss, a positive family history, the presence of other autoimmune diseases, nail involvement, and young age of first onset (Tosti 2006, Weise 1996). In children, the disease may have a tendency towards worsening with time even if the initial presentation was mild, and the progressively disfiguring nature of the disease can be psychologically devastating. AA is highly associated with numerous psychiatric comorbidities including adjustment disorders, anxiety disorders and depression in both children and adults, and an effective treatment for AT and AU, the more severe forms of the disease, represents a significant unmet medical need (Bilgic 2014, Ruiz-Doblado 2003, Alkhalifah 2010).

The clinical development of innovative therapies in AA has lagged far behind other autoimmune conditions and there are currently no evidence-based treatments for AA. A Cochrane database review highlighted that few therapies for AA have been comprehensively evaluated in randomized clinical trials and that no treatment has demonstrated significant benefit compared to placebo according to evidence-based assessments (Delamere, 2008). This lack of good evidence-based data remains a challenge for physicians attempting to select efficacious treatments for their patients and, as a result, numerous approaches to treatment exist and are typically based on considerations such as the age of the patient, the extent and/or duration of the disease, patient expectations, cost considerations (both time and financial resources) and physician preferences and experience.

Common treatments for the less severe (patchy) form of AA include corticosteroids, either topically applied or injected intralesionally into the alopecic areas, or the induction of an allergic reaction at the site of hair loss using a topical contact sensitizing agent- an approach known as topical immunotherapy- typically with the topical contact sensitizers diphenylcyclopropenone (DPCP), squaric acid dibutyl ester (SADBE), or treatment with topical anthralin. While these same treatment options may be utilized for the more severe forms of AA, their use in the more

severe forms of AA is limited not only due to limited efficacy, but also because of the impracticality of using them over extensive body surface areas. Additional treatments used for extensive forms of AA (AT, AU) have included systemic steroids (pulsed or chronically administered), immunosuppressive agents such as cyclosporine or methotrexate, phototherapy with psoralen +UVA (PUVA), narrow-band UVB, photodynamic therapy (PDT), laser therapy (e.g., excimer laser, fractional photothermolysis lasers), prostaglandin analogs, etanercept, bexarotene and others, all with varying degrees of success and each with its inherent risk of adverse effects and unproven efficacy (Alkhalifah 2010, Price 1999, Hordinsky 2015, Strober 2005). Most recently, however, a breakthrough in the understanding of the pathophysiology of AA and several case reports in the literature have suggested that a group of inhibitors of the JAK-STAT pathway, the Janus Kinase (JAK) inhibitors, or "jakinibs" may be efficacious in the treatment of AA even in its most severe phenotypes, AT and AU (Jabbari, 2015, Pieri, 2015, Xing 2014).

The JAKs are members of a family of tyrosine kinases that are involved in cytokine receptor signaling. The JAK family of enzymes (JAK1, JAK2, JAK3, Tyk2) plays an essential role in regulating the signaling process of most cytokines in cells by linking the cytokine-induced signaling from the cell surface membrane receptors to signal transducers and activators of transcription, or STATs, within the cells. Once these JAK receptors are activated by the binding of a cytokine to the appropriate receptor, they initiate a JAK-STAT signaling pathway which can modify gene expression and modulate important regulatory functions in the cell, including regulating immune and inflammatory responses. JAK1 and JAK3 are constitutively associated with the alpha chain and the common gamma chain (γc), respectively, of the receptors for interleukin-2 (IL2), interleukin-4 (IL-4), interleukin-7 (IL-7) interleukin-9 (IL-9), interleukin-15 (IL-15), and interleukin-21 (IL-21). When these cytokines bind to their respective receptors, JAK1 and JAK3 are activated and initiate a signaling cascade that drives key inflammatory events, including lymphocyte activation and proliferation. The JAK inhibitors can block the cytokine receptor signaling pathways, (in this instance JAK1 and JAK3) blocking JAK-STAT transcription activation, and can therefore modulate inflammatory or immune responses, which can be beneficial in a variety of disease states, particularly, as recently reported, AA (Xing 2014). In that report, pharmacologic inhibition of JAK kinase signaling (JAK-STAT signaling) was reported to promote hair growth in both genetic mouse models of alopecia and in human patients.

1.2. Immunopathology & Pathophysiology of AA

Alopecia areata (AA) results from an autoimmune attack on the hair follicles that results in growing anagen-phase terminal hairs being induced to prematurely enter the telogen-phase and then shed. In its most acute state, AA demonstrates a histopathologically characteristic white cell infiltrate- the so called "swarm of bees"- encircling the human hair follicle, though more chronic forms typically demonstrate a sparser infiltrate (Jabbari 2016, Whiting 2003). Though the exact autoantigens expressed in the perifollicular epithelium that allow these specific T-cells to infiltrate the normally immunologically privileged hair follicle have been previously unknown, the T-cells that home to the hair follicle have been demonstrated to consist of both CD4 and CD8 cells. Most recent studies have further characterized a specific subpopulation of activated NKG2D-bearing CD8+ T-cells as being prominent in the peribulbar infiltrate, and it is

now currently felt that these CD8+NKG2D+ effector T-cells preferentially localize to dermal sheath cells aberrantly expressing high levels of major histocompatibility complex (MHC) molecules and NKG2D ligands. Interferons, as key activators of the MHC locus and of the cellular immune response, appear to play a key role in eliminating the immunologic privilege of the hair follicle and in inducing and maintaining the pathologic inflammatory response in AA. This is also seen in the C3H-HeJ mouse model of AA, in which IFN-γ is required for pathogenesis, and in which administration of IFN-γ accelerates disease. (Gilhar 2005, Hirota 2003).

AA has been viewed as a Th1-driven disease and, consistent with a pathogenic cellular immune response, elevated Th1 cytokines/ chemokines (IFN-induced chemokines [IP-10/CXCL10]) are seen in the peripheral blood of AA patients and IFN-inducible gene signatures have been described in the skin of AA patients and may correlate with disease activity (Arca 2004, Barahmani 2009, Kuwano 2007). Additionally, transcriptional profiles in human AA patients have shown a Type I IFN response in lesional biopsies and Th1 skewing and elevated IFN response cytokines/chemokines in both the peripheral blood and in reviewed scalp biopsies (Jabbari 2015, Xing 2014, Jabbari 2016). The cellular source of IFN-γ is hypothesized to be the T-cells, as in the AA mouse model IFN-gamma producing CD8+NKG2D+ cells dominate the dermal hair follicle infiltrate, and in human AA, IFN-γ producing cells were identified in 4 of 5 dermal crawl-out assays (Christiano 2016). Additionally, data implicate IL- 15 in driving activation of IFN-producing CD8 T-cells (Xing 2014).

Thus, preclinical and preliminary clinical information, as discussed above, strongly suggests that the primary pathophysiologic mechanism in AA (including AT and AU) is a cytokine mediated (primarily through T-lymphocyte induced upregulation of IL-15 and IFN gamma) induction of and prolonged maintenance of the telogen stage of the hair cycle. Inhibitors of the JAK/STAT pathway, particularly JAK1 and JAK3, are known to downregulate the effects of both IFN-gamma (through the inhibition at JAK1), and IL-15 (through inhibition at both JAK1 and JAK 3), and several published case reports have demonstrated the potential for compounds that are JAK1/3 inhibitors to induce hair growth in patients with AA (Kim 2017, Craiglow 2014 and 2017, Gupta 2016, Scheinberg 2016). As ATI-501 is a potent inhibitor at JAK 1 and JAK 3, it is strongly suggested that ATI-501 may be effective in the treatment of AA.

Among patients with AA, patients with higher disease burdens are unlikely to have satisfactory outcomes with current therapies. Aclaris Therapeutics, Inc. is developing ATI-501 as a treatment for stable patchy AA, AU or AT. ATI-501 is an oral prodrug that is rapidly converted presystemically to ATI-502, a potent highly selective inhibitor of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3). This study will evaluate whether or not the orally administered JAK1/JAK3 inhibitor prodrug, ATI-501, will attenuate both IL-15 and IFN-gamma signaling, thereby blocking re-activation of CD8+NKG2D+ memory T-cells, and aborting the cytotoxic T-cell inflammatory response underlying AA.

1.3. Previous Clinical Study Experience with ATI-501

Eight Phase 1 clinical studies were conducted with ATI-501 oral doses ranging from single ascending doses of ATI-501 of 50 mg to 500 mg and multiple ascending doses of 200, 400 mg, 600 mg and 800 mg BID for 14 days. A total of 186 healthy volunteers were exposed to oral

doses of ATI-501. Single and twice-daily doses of ATI-501 were well-tolerated. There were no SAEs reported in the eight completed clinical studies.

In study ATI-50001-AUAT-106, the multiple ascending dose study, 54 subjects received doses up to 800 mg BID for 14 days. The most frequently reported treatment related adverse events (TRAE) reported in more than 1 subject were: headache (14.8%), abdominal discomfort (9.3%), decreased appetite (9.3%), dizziness (7.4%), somnolence (7.4%), diarrhea (5.6%), dry skin (5.6%), nausea (5.6%), constipation (3.7%), dyspepsia (3.7%), feeling hot (3.7%) and paresthesia (3.7%).

No clinically significant laboratory abnormalities were observed. There were no clinically significant findings from 12-lead ECGs. One subject experienced a transient elevation in blood pressure (pre-dose 126/85mmHg, 4 hours post dose 142/104 mm/Hg) which was assessed as clinically significant by the investigator. The subjects blood pressure returned to within normal limits at all other assessed timepoints throughout the study. There were no other clinically significant findings from vital signs assessments.

In study, ATI-50001-AUAT-106, ATI-501 was not detected in plasma and there was a dose-related increase in plasma of the active metabolite ATI-502. Systemic levels of ATI-502, following oral doses of ATI-501 in healthy volunteers transiently reduced pSTAT5 activity in ex vivo IL-2 stimulated lymphocytes, indicating inhibition of the JAK signaling pathway. Upon multiple dosing, pSTAT5 activity showed a more sustained inhibition during the dosing period.

Non-clinical studies conducted with oral administration of ATI-501 support the oral administration of ATI-501 (ATI-501 Investigator Brochure).

1.4. Study Rationale

Preclinical and preliminary clinical information, as discussed above, strongly suggests that the primary pathophysiologic mechanism in AA (including AT and AU) is a cytokine-mediated (primarily through T-lymphocyte induced upregulation of IL-15 and IFN gamma) induction of and prolonged maintenance of the telogen stage of the hair cycle. Inhibitors of the JAK/STAT pathway, particularly JAK1 and JAK3, are known to downregulate the effects of both IFN-gamma (through the inhibition at JAK1), and IL-15 (through inhibition at both JAK1 and JAK 3), and several published case reports have demonstrated the potential for compounds that are JAK1/3 inhibitors to induce hair growth in patients with AA. As ATI-501 is a potent inhibitor at JAK 1 and JAK 3, it is strongly suggested that ATI-501 may be effective in the treatment of AA.

This study will evaluate the safety, tolerability and efficacy of ATI-501 Oral Suspension, 400 mg, 600 mg, or 800 mg compared to Placebo Oral Suspension taken with food, twice-daily for 24 weeks.

Subjects with hair loss due to AA, AU or AT ranging from 30% to 100% based on the SALT score will be included in this study. In prior published studies, assessment of efficacy of treatment of AA was based on hair regrowth as determined by changes in the SALT score (Olsen 2016). Both the SALT and ALODEX scores will be measured electronically using an iPad. The SALT score is a measurement based on the SALT I diagram, that quantifies the amount of scalp without any hair. The ALODEX score is a measurement of the amount of scalp with hair loss and is based on the SALT II diagram (Olsen, submitted). The SALT II diagram breaks the scalp

surface area from the SALT I diagram into 1% scalp surface areas and allows the investigator to assign a 10-point density rating to each area from 0 = no hair loss to 10 = complete baldness. The ALODEX score is a summation of all density ratings in each 1% scalp area. By assessing hair density in each of the 1% scalp areas, the use of the SALT II visual aid allows the following to be tracked: amount of absolute hair loss (ALODEX score), specific areas of baldness (all 1% areas are numbered), small changes in density that may otherwise go undetected with original SALT I score, percentage of scalp surface involved with any hair loss and thus needing to be treated topically, new areas of hair loss present since Baseline of any given treatment, and lesional scoring by identifying target areas.

Hair loss will be quantified using both the SALT and ALODEX assessments at Baseline and monthly during treatment. The change from Baseline in the SALT and ALODEX scores will be used to determine hair regrowth. In addition to the SALT and ALODEX assessment tools, Aclaris is developing Clinician and Patient Reported outcome tools (ClinRO and PRO) to assess hair regrowth that is clinically meaningful to subjects. These ClinRO and PRO tools will measure the signs, symptoms, and impacts of AA for use as secondary efficacy and exploratory endpoints.

Subjects will be enrolled with 30% to 100% hair loss over the entire scalp surface area based on the SALT score at Screening (Visit 1) and Baseline (Visit 2). Screening (Visit 1) and Baseline (Visit 2) ALODEX scores will also be obtained but will not be used as an inclusion criterion. The scalp appearance assessments in development (ClinRO and PRO) will assess hair loss on a scale from “no hair” to a “full head of hair”. A target patch (identified by the subject as their most bothersome area of hair loss) will be identified at Baseline (Visit 2). By identifying a target patch, subjects with less extensive hair loss overall can be enrolled using the same rating on the Alopecia Scalp Appearance Assessment of “no hair” or “a little hair” at Baseline (Visit 2). Subjects with patchy AA will have ClinRO and PRO assessments completed for a scalp target patch and for scalp hair loss over the subject’s whole scalp surface area.

Because this trial will not be stratified in terms of ethnic background or gender of subjects, there is no consistent measure of hair color, caliber, growth rate or hair density that can be used across such a diverse population of subjects. Each of these parameters is intrinsically determined within a given subject, and in subjects with more severe hair loss, there will be little to no normal hair at the start of the study. Therefore, it will be impossible to establish each subject’s individual Baseline measure of healthy hair in order to monitor restoration of these parameters over the study. Further, it is not possible to compare these parameters across individuals in the study.

The ALODEX and SALT assessments are based on terminal hair growth. Another parameter that will be considered will be the normalization of exclamation point hairs. These two features should be trackable irrespective of the subjects’ intrinsic hair color, caliber or density, and should give a meaningful indicator of response to treatment.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. 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 alopecia areata (AA), alopecia universalis (AU) or alopecia totalis (AT).

2.2. Secondary Objectives

Secondary objectives are:

- To evaluate the psychometric performance of the key clinical outcome assessments and 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
- To assess the level of ATI-502 in the blood at trough

2.3. Primary Efficacy Endpoint

The primary efficacy endpoint is the mean percent change from Baseline in the Severity of Alopecia Tool (SALT) score at Week 24 (Visit 9).

2.4. Secondary Efficacy Endpoints

- Mean percent change from Baseline in the Alopecia Density and Extent Score (ALODEX) score at Week 24.
- Change from Baseline in the SALT score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Alopecia Density and Extent Score (ALODEX) score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Proportion of subjects in each treatment arm achieving at least a 50% reduction in ALODEX score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available compared to Baseline.
- Proportion of subjects in each treatment arm achieving at least a 50% reduction in SALT score at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available compared to Baseline.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Patient-reported outcome [PRO]) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Clinician-reported outcome [ClinRO]) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Physician Global Impression of Severity (PhGIS) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.

- Change from Baseline in Alopecia Facial Hair Appearance Assessment (AFHA) (Clinician and Subject) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Subject Global Impression of Severity (SGIS) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the subject reported Alopecia Impact Assessment (AIA) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Subject Global Impression of Treatment Satisfaction (SGITS) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change from Baseline in the Subject Global Satisfaction with Hair Quality (SGSHQ) at Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Change in Dermatology Life Quality Index (DLQI) total score between Baseline and Week 24 (Visit 9) with additional analyses at each applicable post-baseline visit where data are available.
- Global Impression of Change (Clinician and Subject) at Week 24 (Visit 9).

2.5. Other Assessments

- Hair quality assessment including normalization of exclamation point hairs and hair shedding will be described.
- Vellus and Indeterminate scalp hair will be described.
- Non-scalp hair assessments (body and nasal hair) will be described.

2.6. Pharmacokinetic Endpoints

The concentration of ATI-502 in the blood predose at Visit 2 and at trough at Visit 4, Visit 6 and Visit 9 will be measured by a bioanalytical lab using fully validated analytical methods.

2.7. Safety Endpoints

Safety variables to be assessed include: adverse events, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, respiration rate, heart rate, and oral body temperature), and electrocardiograms.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This Phase 2, multicenter, randomized, double-blind study is designed to evaluate the safety, tolerability and efficacy of ATI-501 Oral Suspension in subjects with AA, AU or AT. Subjects will be required to have a clinical diagnosis of stable AA, AU or AT with 30% to 100% total scalp hair loss for a duration of at least 6 months up to and including 12 years (inclusive). Stable AA, AU or AT is defined as no areas of spontaneous terminal scalp hair growth.

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, Week 8, Week 12, Week 16, Week 20, Week 24, and post-treatment Week 28. Safety and tolerability will be evaluated at each study visit by assessment of adverse events, clinical laboratory tests, and vital signs, and at select visits, ECGs.

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.

3.2. Number of Subjects

A total of approximately 95 subjects will be enrolled at approximately 25 US sites.

3.3. Treatment Assignment

Subjects will be randomized 1:1:1:1 to ATI-501 Oral Suspension 400 mg, 600 mg, 800 mg or Placebo Oral Suspension twice-daily for 24 weeks followed by a 4-week post-treatment follow up period.

3.4. Dose Adjustment Criteria

Subjects should not modify the study medication dosage or frequency without the investigator's prior approval. All study medication modifications must be reported on the appropriate eCRF. If study medication intolerance or safety issue occurs, after consulting with the Aclaris Therapeutics, Inc. Medical Monitor (see page 1), the investigator or designee may direct the subject to modify the study medication frequency from twice-daily to once-a-day. If the subject cannot take the study medication twice-daily for more than 4 consecutive days, other dose modifications and continuation in the study must be reviewed with the Medical Monitor.

3.4.1. Safety Criteria for Adjustment or Stopping Doses

3.4.1.1. Study Medication Interruption

Treatment with ATI-501 Oral Suspension should be temporarily interrupted in the event of severe adverse events considered related to ATI-501, or in the event of one or more of the abnormal laboratory values listed in Table 2.

Table 2: Study Medication Interruption Criteria

Laboratory Test	Hold Study Medication if:	Resume Study Medication if:
WBC count	$< 2 \times 10^3/\mu L$	$\geq 2.5 \times 10^3/\mu L$
ANC	$< 1 \times 10^3/\mu L$	$\geq 1.5 \times 10^3/\mu L$
Lymphocyte count	$< 0.5 \times 10^3/\mu L$	$\geq 0.75 \times 10^3/\mu L$
Platelet count	$< 75 \times 10^3/\mu L$	Returns to Baseline values
Hemoglobin	< 8 g/dL or a decrease > 2g/dL	≥ 10 g/dL
AST or ALT	> 3 x ULN	< 2 x ULN or within 20% of Baseline values
Serum creatinine	>2 x ULN	<1.5 x ULN or within 10% of Baseline value

Subjects with one or more of the Screening (Visit 1) laboratory values meeting the Study Medication Interruption Criteria found in Table 2 must have repeat lab testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2).

During treatment, if a subject has one or more of the abnormal laboratory values noted in Table 2, the investigator or designee upon receipt and review of the central laboratory report should instruct the subject to hold study medication dosing. The investigator or designee should ask the subject about symptoms, concomitant illnesses and medications and repeat the test(s) as soon as possible. The Medical Monitor must be notified of dose interruptions due to SAEs considered related to study medication or laboratory abnormalities noted in Table 2.

If the retest confirms the abnormal laboratory value, then the study medication should continue to be held followed by repeat testing once a week or sooner at the discretion of the investigator. The subject should be followed until the laboratory abnormality(s) returns to normal or to Baseline values.

3.4.1.2. Study Medication Discontinuation

Study medication should be permanently discontinued in the event of any of the following:

- Subject's study medication blinding is broken
- Severe infection requiring parenteral antimicrobial therapy or hospitalization
- Symptomatic herpes zoster

- Malignancy
- Anaphylactic or severe allergic reaction
- WBC Count: < 1 x 10^3/µL or second occurrence of < 2 x 10^3/µL
- ANC: < 0.5 x 10^3/µL or second occurrence of < 1 x 10^3/µL
- Lymphocyte count: < 0.3 x 10^3/L or second occurrence of < 0.5 x 10^3/µL
- Platelet count: < 50 x 10^3/µL or second event of < 75 x 10^3/µL – in each case, value should be confirmed by retesting before treatment discontinuation
- Hemoglobin: < 6.5 g/dL or second occurrence of < 8 g/dL – in each case, value should be confirmed by retesting before treatment discontinuation
- AST or ALT:
    - > 5 x ULN persisting for 2-weeks of study medication interruption or second event of > 5 x ULN
    - > 3 x ULN with total bilirubin >2 x ULN or symptoms of hepatocellular injury [fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/ or eosinophilia (>5%)].
- Serum creatinine: > 2 x ULN persisting for >2 weeks of treatment discontinuation or second occurrence of > 2 x ULN

The continued treatment of subjects who experience other serious or severe adverse events considered related to study treatment should be discussed with the Sponsor's medical monitor.

Any subject who develops any of the following ECG findings during the active treatment phase will be instructed to stop study medication and will be withdrawn from the study:

- A post-study medication ECG result where the evaluator's interpretation shows any of the following:
    - Clinically significant rhythm disturbance other than sinus rhythm or ectopic supraventricular rhythm (ectopic atrial rhythm)
    - Clinically significant conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
    - New finding of QRS >120ms (if not present at screening. For example, subjects with right bundle branch block at screening would not need to be withdrawn from the study if their subsequent ECGs remained unchanged).
    - Evidence of QT-interval prolongation, defined as an increase in the QT_cF interval >60ms from Visit 1
    - Acute signs of ischemia or infarction
    - Any ECG abnormality which may, in the opinion of the investigator, represent a new medical issue of concern

Site staff must perform protocol-required procedures for trial discontinuation and follow-up.

3.5. Criteria for Study Termination

This study may be terminated prematurely in whole or in part due to a change in the benefit/risk profile for ATI-501 Oral Suspension such that continuation of the study would not be justified on medical or ethical grounds. This determination may be made by the Study Investigators in conjunction with the Sponsor, or by IRB or the U.S. Food and Drug Administration (FDA). The

Sponsor may also elect to terminate the study if enrollment is sufficiently slow to prevent the completion of the study in an acceptable timeframe, or if ATI-501 development is discontinued.

If the study is terminated prematurely, the Sponsor will notify the Study Investigators and the FDA. The Investigator must promptly notify all enrolled subjects and the IRB of study termination.

3.6. Study Procedures

The investigator, a designated and appropriately trained staff member, or the subject, will perform the study assessments according to the Schedule of Assessments (Table 3). The same staff member should perform the assessments for a given subject throughout the study. If this becomes impossible, an appropriate designee with overlapping experience with the subject and study should perform the assessments. The same lighting conditions and subject positioning should be used for all evaluations for a given subject.

Table 3: 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 CBC, Chemistry, Virology, Serum Pregnancy, Urinalysis[5]		X	X	X	X	X	X	X	X	X	X
Blood for PK (Select Sites Only)[6]			X (Pre-dose)		X		X			X	
Urine pregnancy test[7]		X	X		X	X	X	X	X	X	X
ECG		X		X						X	
Subject[8]	Target Patch identification (Patchy AA Subjects Only)		X								
	Alopecia Scalp Appearance Assessment (ASAA-AAP: SR or ASAA-AT/AU: SR) [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 or SGIS-AT/AU)		X	X			X			X	X
	Alopecia Impact Assessment (AIA): Subject Rating		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
	Subject Global Impression of Change (SGIC)									X	
	Subject Global Impression Treatment Satisfaction (SGITS-AAP or SGITS-AT/AU)[10]						X			X	X
	Subject Global Satisfaction with Hair Quality (SGSHQ-AAP or SGSHQ-AT/AU)		X	X			X			X	X
	DLQI[11]		X	X			X			X	X
Investigator[12]	Alopecia Scalp Appearance Assessment (ASAA: -AAP:CR of ASAA-AT/AU:CR)[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

	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
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 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, 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 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 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.

	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

[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.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Male and female subjects, 18 years of age or older, with a clinical diagnosis of stable AA, AU or AT of the scalp, who meet all the inclusion criteria and none of the exclusion criteria, will be eligible to enroll in this study.

4.1. Subject Inclusion Criteria

Subjects must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and willing to sign an Informed Consent Form (ICF).
2. Male or non-pregnant, non-nursing female ≥ 18 years old at the time of informed consent.
3. Have a clinical diagnosis of stable AA, AU or AT (Stable is defined as no current areas of spontaneous terminal scalp hair regrowth).
4. Have a Severity of Alopecia Tool (SALT) score of at least 30% to 100% total scalp hair loss determined by the study investigator at Screening (Visit 1) and Baseline (Visit 2).
5. Subjects with 30% to 95% scalp hair loss (based on SALT score) must have an assessment of "no hair" or "a little hair" in the target scalp patch based on both the Clinician and Subject Alopecia Scalp Appearance Assessment (ASAA). The target patch is defined as the most bothersome patchy area of hair loss as identified by the subject (Refer to Section 7.1).
6. Have a duration of the current episode of stable scalp hair loss for a minimum of 6 months and a maximum duration of hair loss of 12 years (inclusive). [Current episode is defined as the period of the current presentation of hair loss (AA, AU or AT)].
7. If the subject is a woman of childbearing potential (WOCBP), she must have:
    - Negative serum pregnancy tests at Screening (Visit 1); and
    - A negative urine pregnancy test at Baseline (Visit 2); and
    - Agree to not be planning a pregnancy during the study duration and use a highly effective method of contraception during the study and for 30 days after the last dose of study medication. (Refer to Section 8.4.2).
8. Be in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair evaluation of the subject or which might expose the subject to an unacceptable risk by study participation.
9. Be willing to maintain the same hair style and hair dyeing throughout the study period. Subjects who shave their scalp must be willing to refrain from shaving their scalp for at least two weeks prior to each study visit, as determined by the investigator based on the ability to assess visible scalp hair growth. Hair trimming outside the treatment areas to maintain the current hair style is permitted.
10. Be willing and able to follow all study instructions and to attend all study visits.
11. Subjects taking hormonal replacement therapies must be on stable doses for 6 months prior to enrollment and remain on a maintenance dose throughout the study.
12. Subjects taking thyroid replacement medication must be on stable doses for 6 months prior to enrollment and remain on a maintenance dose throughout the study.

13. Sexually active male subjects must agree to use a barrier method of contraception with any WOCBP partner(s) from the first dose of study medication to at least 30 days after the last dose of study medication.

4.2. Subject Exclusion Criteria

Subjects are excluded from this study if any 1 or more of the following criteria is met:

1. Females who are nursing, pregnant, or planning to become pregnant for the duration of the study and up to 30 days after the last dose of study medication.
2. Diffuse alopecia areata. [Diffuse alopecia areata is defined as the absence of the typical patchy distribution of hair loss (in subjects with ≤95% total scalp hair loss) with hair thinning distributed throughout the scalp.]
3. Concomitant hair loss disorder (by history or physical exam) such as androgenetic alopecia (AGA) or scarring alopecia (*e.g.*, cicatricial alopecia, frontal fibrosing alopecia, etc.). Subjects without a prior known history of AGA or other patterned hair loss disorder who exhibit AGA or other patterned hair loss with regrowth during the study will be allowed to continue in the study.
4. Active skin disease on the scalp (such as psoriasis or seborrheic dermatitis) or a history of skin disease on the scalp that in the opinion of the investigator would interfere with study assessments of efficacy or safety.
5. Active scalp trauma or other condition affecting the scalp that, in the investigator's opinion, may affect the course of AA, AU or AT or interfere with the study conduct or evaluations.
6. The presence of a permanent or difficult to remove hairpiece or wig that will, in the opinion of the investigator, interfere with study assessments if not removed at each visit.
7. History of, or current, severe, progressive or uncontrolled autoimmune, metabolic, hepatic, endocrine, renal, gastrointestinal, pulmonary, cardiovascular, genitourinary, or hematological disease, neurologic or cerebral disorders, or coagulation disorders that, as determined by the Investigator, would preclude participation in and completion of study assessments.
8. History of, current or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than subjects with a history of adequately treated and well healed and completely cleared non-melanoma skin cancers (e.g. basal or squamous cell carcinoma) treated successfully at least 1 year prior to study entry with no evidence of disease.
9. Evidence of active or latent bacterial (including tuberculosis) or viral infections at the time of enrollment, or history of incompletely treated or untreated tuberculosis. Subjects who have completed therapy for latent tuberculosis may participate. Refer to Exclusion Criterion 12 for herpes zoster, herpes simplex, or cytomegalovirus infections.
10. History of serious local infection (*e.g.*, cellulitis, abscess) or systemic infection including but not limited to a history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to Baseline. Subjects on an antibiotic for a nonserious, acute local infection must complete the course prior to enrollment into the study.
11. Positive for HIV, Hepatitis B or C. Subjects with serologic evidence of Hepatitis B vaccination (HepB surface Ab without the presence of Hep B surface Ag) will be allowed to participate.

12. History of recurrent herpes zoster (more than one episode) or disseminated herpes zoster (a single episode) or disseminated herpes simplex (single episode) or cytomegalovirus (CMV) that resolved less than 2 months before study enrollment. Subjects with a history of frequent outbreaks of Herpes Simplex Virus (defined as 4 or more outbreaks a year).
13. Clinically significant laboratory abnormalities at screening that, in the opinion of the Investigator, would make the subject a poor candidate for the study. [Subjects with any Screening laboratory values meeting the Study Medication Interruption Criteria found in Table 2 must have repeat lab testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2)].
14. Subjects with absolute neutrophil count <1,800/μL, or platelet count <130,000/μL.
15. Subjects who have received any of the following treatments for the timeframes specified below:
    - Disease Modifying Anti-Rheumatic Drugs (DMARDS), Biologics or immunosuppressants, including but not limited to: anakinra, adalimumab, azathioprine, corticosteroids, cyclosporine, etanercept, infliximab, methotrexate, TNF inhibitors, ustekinumab within 1 month or 5 half-lives (whichever is greater) of Baseline (Visit 2).
    - Plaquenil within 2 months of Baseline (Visit 2).
    - JAK inhibitors (oral or topical) within 6 months of Baseline (Visit 2).
    - Intralesional steroids or platelet rich plasma injections in the scalp within 1 month of Baseline (Visit 2).
    - Topical treatments on the scalp with anthralin, bimatoprost, corticosteroids, diphencyprone, diphenylcyclopropenone (DPCP), squaric acid dibutylester (SADBE), minoxidil, pimecrolimus, or tacrolimus within 1 month of Baseline (Visit 2).
    - Phototherapy (narrow band Ultraviolet B [NB UVB] or broadband therapy) within 4 weeks of Baseline (Visit 2).
16. Participation in an investigational drug or device trial in which administration of an investigational drug or device occurred within 30 days or 5 half-lives (whichever is longer) of Baseline (Visit 2).
17. Any condition possibly affecting oral drug absorption, e.g., gastrectomy, clinically significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass. Procedures such as gastric banding are not exclusionary.
18. Sensitivity to any of the ingredients in the study medications.
19. Unwillingness to refrain from weaves, hair extensions, or shaving of the scalp for at least two weeks prior to a study visit, at the discretion of the investigator, based on the ability to assess hair growth.
20. Screening ECG findings of:
    - QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose)
    - Heart rate ≤45 or ≥ 100 beats/minutes (A subject with a heart rate ≤ 45 beats/min may be enrolled if in the opinion of the investigator the heart rate is not clinically significant).
    - Rhythm disturbance other than sinus arrhythmia or ectopic supraventricular rhythm (ectopic atrial rhythm)

- Conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
- Acute or chronic signs of ischemia
- Left Bundle Branch Block
- Prior myocardial infarction

21. Vaccination with a live or attenuated vaccine within 6 weeks prior to Baseline (Visit 2) or planned vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of study medication.
22. Participation in an investigational study with ATI-502 Topical Solution.
23. Subjects unwilling to have photographs taken for study purposes.

4.3. Subject Withdrawal Criteria

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The investigator may remove a subject from the study if, in the investigator's opinion, it is not in the best interest of the subject to continue the study. Examples of other reasons subjects may be discontinued from the study are: a change in compliance with an inclusion or exclusion criterion, occurrence of AEs, occurrence of pregnancy, use of a prohibited therapy or subject is unwilling or refuses to continue with the protocol defined study visits and/or subject withdraws consent (Refer to Section 3.5 for study medication discontinuation or termination criteria).

In case of premature discontinuation from study participation, all efforts will be made to perform all Week 24 (Visit 9) assessments. The date the subject is withdrawn from the study and the reason for discontinuation must be recorded in the subject's electronic case report forms (eCRFs). All withdrawn subjects with ongoing AEs will be followed until the event has resolved or stabilized, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study medication or study procedures is made.

5. TREATMENT OF SUBJECTS

5.1. Study Medication Administration

Study medication will be self-administered by the subject. Study staff should instruct the subject not to take study medication on an empty stomach. Subjects will be instructed to take one single-dose bottle of study medication followed by a full glass of water, within approximately 30 minutes after the morning meal and after approximately 8 to 12 hours, to take the second dose within approximately 30 minutes after the evening meal as detailed in study medication instructions in Appendix 15. Subjects should not mix/dilute the medication in other liquids, rather they should take the study medication as indicated in the directions provided.

The investigational site staff will dispense a sufficient supply of study medication at the visits detailed in the Schedule of Assessments (Table 3) and will review the study medication instructions as detailed in Appendix 15. The investigational site staff dispensing and reconciling the study medication should not be involved in the investigator or subject efficacy assessments. Subjects will be given a compliance record to complete. At each study visit, subjects should bring the study medication including used and unused bottles and the completed compliance record. The study staff will review the compliance record, used and unused bottles and the study medication instructions.

5.2. Concomitant Medications

Concomitant therapies are any new or existing therapies received from Screening (Visit 1) until discharge from the study. Concomitant therapies include drug (e.g. prescription and over the counter [OTC]), and non-drug (e.g., chiropractic, physical therapy, energy-based treatments).

Subjects will be allowed to take medications not restricted by the protocol as long as they have been reviewed by the investigator and will not affect efficacy or safety. Vitamins, minerals, and dietary supplements are permitted while on study if the subject has been on a stable dose prior to study entry and, in the opinion of the Investigator, will not affect the safety or efficacy of the subject during the study. Topical hair and scalp products (shampoos, conditioners, styling products) should be reviewed by the Investigator and are permitted if, in the Investigator's opinion, they will not affect the safety or efficacy of the subject during the study. Use of hair dyes is permitted during the study if the subject uses the same hair dye throughout the study. If in the opinion of the Investigator, the hair dye interferes with study assessments the subject may be directed to wait until after the study visit to dye his or her hair. Efforts should be made to keep the hair care regimen the same throughout the duration of the study.

Topical therapies such as topical corticosteroids are permitted if they are not applied on or near the scalp and are not used for hair growth in other areas. Inhaled or intranasal corticosteroids are allowed in the study.

Prior permitted concomitant medications taken within 30 days of beginning treatment with ATI-501 Oral Suspension will be documented in the subject's source document and eCRF. In addition, any new permitted medications administered during protocol treatment and through Week 28 (Visit 10) will be documented in the subject's source document and eCRF.

5.3. Grooming

Routine shaving of beard or body hair is allowed during the study as long as the subject refrains from shaving for a period sufficient to show hair growth prior to Visits 6, 9, and 10. Shaving of the scalp must conform to the requirements specified in Inclusion Criterion #9. Subjects are allowed to grow their hair longer than the length at baseline visit, as long as the investigator can assess hair loss and regrowth during the study and hair regrowth is pinned out of the way to show the areas with hair loss at baseline for photographs.

5.4. Prohibited Medications

Any medication, shampoo or hair product known to affect hair growth in AA, AU or AT is prohibited throughout the study period. Subjects who are on a chronic stable dose of finasteride for benign prostatic hypertrophy for greater than 1 year are eligible for enrollment in the study as long as they maintain the same stable dose throughout the study. Since subjects with known AGA are excluded from the study, treatment with finasteride for alopecia during the study or within one year prior to study enrollment is prohibited.

The following medications and therapies require a specific washout period prior to study entry and are not permitted during the study:

- Disease Modifying Anti-Rheumatic Drugs (DMARDS), Biologics or immunosuppressants, including but not limited to: anakinra, adalimumab, azathioprine, corticosteroids, cyclosporine, etanercept, infliximab, methotrexate, TNF inhibitors, ustekinumab within 1 month or 5 half-lives (whichever is greater) of Baseline (Visit 2).
- Plaquenil within 2 months of Baseline (Visit 2).
- JAK inhibitors (oral or topical) within 6 months of Baseline (Visit 2).
- Intralesional steroids or platelet rich plasma treatment in the scalp within 1 month of Baseline (Visit 2).
- Topical treatments on the scalp with anthralin, bimatoprost, corticosteroids, diphencyprone, diphenylcyclopropenone (DPCP), squaric acid dibutylester (SADBE), minoxidil, pimecrolimus, or tacrolimus within 1 month of Baseline (Visit 2).
- Phototherapy (narrow band Ultraviolet B [NB UVB] or broadband therapy) within 4 weeks of Baseline (Visit 2).

Any prohibited medications taken by a subject in violation of the protocol requirements will be documented in the source record and eCRF. Discussion with the Sponsor's Medical Monitor must also take place in order to determine if the subject's continuation in the study is allowed.

5.5. Vaccine Guidelines

Vaccination with live or attenuated components is prohibited during the study and for 6 weeks after the last dose of study medication. Similarly, current routine household contact with children and others vaccinated with live or attenuated vaccine components should be avoided during treatment and for 6 weeks following completion of the study. Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine.

Following vaccination with live or attenuated component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted. General guidelines suggest that exposure should be avoided following vaccination with these vaccines for the stated time period:

- Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination;
- Oral polio vaccination for 6 weeks following vaccination;
- Attenuated rotavirus vaccine for 10 days following vaccination;
- Inhaled flu vaccine for 1 week following vaccination.

5.6. Treatment Compliance

The investigator or designee will be responsible for monitoring subject compliance through questioning the subject, reviewing the subject completed compliance record and documenting missed doses, if any, and visual inspection of the study medication bottles (used and unused). Study staff will counsel the subjects, as required to make sure subjects are compliant with study medication dosing.

5.7. 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.

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 as detailed in the Pharmacy Manual.

Blinding of study medication is important for validity of this study. This study uses a double-blind design. The study medications are indistinguishable in appearance, as packaged and labeled.

5.7.1. Unblinding the Study Medication

The blinding may be broken ONLY in the event of a medical emergency, in which knowledge of the study medication identity is critical to the management of the subject's course of treatment. Before breaking the blind, the investigator shall determine that the information is necessary (*i.e.*, that is, will alter the subject's immediate course of treatment). In many cases, particularly when the emergency is clearly not study medication-related, the problem may be effectively managed by assuming that the subject is receiving an active study medication without the need for unblinding.

If the investigator deems it necessary to break the blind for a study subject, he/she will attempt to contact the Medical Monitor (protocol page 1) to obtain permission. If it is not possible to contact the Medical Monitor beforehand, contact her/him as soon as possible after breaking the blind for a subject.

To identify a subject's study medication, locate the second panel of the tear-off label from the Subject Kit attached to the subject's study medication label page and follow the instructions on the label. Record the date of unblinding, the reason for unblinding, and the initials of the investigational staff member who performed the unblinding on the subject's study medication label page. Any subject whose blind has been broken must be discontinued from the study (Section 3.4.1.2). At the end of the study, the original study medication label pages will be returned to Aclaris Therapeutics, Inc. with a photocopy placed in the investigator's study file. The original study medication label pages will be available, upon request, to the site if needed to respond to a regulatory audit.

6. STUDY MEDICATION MATERIALS AND MANAGEMENT

6.1. Study Medication

The study medications for this study are ATI-501 Oral Suspension in dosage strengths of 400 mg, 600 mg, 800mg or Placebo Oral Suspension. The study medications are formulated as an oral suspension that are indistinguishable as packaged and labelled. The inactive ingredients include: Povidone (Kollidon 30); Sodium Lauryl Sulfate (Kolliphor SLS); Sodium Phosphate, Dibasic, 7-Hydrate; Citric Acid, monohydrate; Hydrochloric Acid; Sodium Benzoate; and Purified Water.

Table 4: Investigational Product

STUDY MEDICATION INFORMATION				
Study medication name	**ATI-501**	**ATI-501**	**ATI-501**	**Placebo**
Dosage Strength	400 mg	600 mg	800 mg	-
Manufacturer	Alliance Contract Pharma, Harleysville, PA 19438			
Pharmaceutical Form	Oral Suspension			
Container	30 mL amber plastic bottle			
Storage Conditions	59°F to 77°F (15°C to 25°C)			
Dose regimen				
Route	Oral			
Frequency	Twice-daily			
Duration of administration	24 weeks			

6.2. Packaging and Labeling

The study medication must be used by the study subjects only. The study medication will be supplied in single-dose bottles. Investigational site staff will explain the administration of study medication to subjects. Study medication will be provided by Aclaris Therapeutics, Inc. and labeled according to regulations as detailed in the Pharmacy Manual.

6.3. Study Medication Storage

Study medications must be stored in a secure area with limited access under appropriately controlled and monitored storage conditions. Study medication should be stored at controlled room temperature 59°F – 77°F (15°C – 25°C). Subjects will be instructed to store the study medication in the kit at room temperature, away from heat, moisture, direct light, and to keep it from freezing and out of the reach of children.

6.4. Study Medication Accountability and Disposal

The Principal Investigator or designee is responsible for ensuring accountability for the investigational agent, including reconciliation of medications and maintenance of medication records. Upon receipt of study medication, the clinical site will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided. A copy of

this document will be submitted to Aclaris Therapeutics, Inc. (or designee) by facsimile or e-mail (scanned copy) and the original will be maintained in the study file. In addition, an accurate study medication disposition record will be kept, specifying the amount dispensed for each subject and the date of dispensing. This inventory record will be available for inspection at any time. At the completion of the study, the original inventory record will be available for review by Aclaris Therapeutics, Inc. upon request. Final medication accountability will be performed by the study monitor at the completion of the study and all used and unused study medication bottles will be disposed of as detailed in the Pharmacy Manual.

7. ASSESSMENT OF EFFICACY

Note that all subject assessments should be performed in the order detailed in Table 5 prior to any investigator assessments. The investigator may assist in determining the location of the target patch prior to subject assessments but should not review the subject's assessments prior to completing the investigator assessments. The investigator should perform the assessments in the order detailed in Table 6. Detailed instructions for completing the subject and investigator assessments will be provided to the investigational center prior to the initiation of subject enrollment.

7.1. Alopecia Target Scalp Patch Identification

At Baseline (Visit 2), the investigator will ask the subjects with patchy AA (30% to 95% scalp hair loss), to identify the most bothersome patchy area of the scalp, which will be identified as the target patch. Subjects must have an assessment of "no hair" or "a little hair" in the target scalp patch based on both the Clinician's and Subject's Alopecia Scalp Appearance Assessment (ASAA). The target patch will be documented photographically at Baseline (Visit 2) and monthly throughout the study at the visits detailed in Schedule of Assessments (Table 3).

In subjects with extensive hair loss, the target patch may be a large scalp surface area. In subjects with total scalp hair loss (AU or AT), this assessment should be completed as not applicable in both the source documentation and the eCRF.

7.2. Subject Reported Outcome Assessments

The subject will complete the assessments (questionnaires) in the order detailed in Table 5. The subject must sign/initial and date the completed questionnaire to indicate he/she performed the assessment as instructed. The staff member administering the questionnaires must document proper completion of the assessments in the subject's source notes.

Table 5: Subject Assessments

Order	Subjects with Patchy AA (30% – 95%) Scalp Hair Loss	Subjects with AU or AT (>95% hair loss)
1.	Alopecia Scalp Appearance Assessment for Patchy AA: Subject Rating (ASAA-AAP: SR) Appendix 3	Alopecia Scalp Appearance Assessment for AT/AU: Subject Rating (ASAA-AT/AU: SR) Appendix 10
2.	Alopecia Facial Hair Appearance Assessment: Subject Rating (AFHA: SR) Appendix 4	
3.	Subject Global Impression of Severity for Patchy AA (SGIS-AAP) Appendix 5	Subject Global Impression of Severity for AT/AU (SGIS-AT/AU) Appendix 11
4.	Alopecia Impact Assessment (AIA) Appendix 6	
5.	Subject Global Impression of Change (SGIC)* Appendix 14	
6.	Subject Global Impression of Treatment Satisfaction for Patchy AA (SGITS-AAP) Appendix 7	Subject Global Impression of Treatment Satisfaction for AT/AU (SGITS-AT/AU) Appendix 12
7.	Subject Global Satisfaction with Hair Quality (SGSHQ) Appendix 8	Subject Global Satisfaction with Hair Quality (SGSHQ) Appendix 13
8.	Dermatology Life Quality Index Appendix 9	

*Only assessed at final study treatment visit

7.2.1. Alopecia Scalp Appearance Assessment (ASAA)

Subjects with patchy AA (30 – 95% scalp hair loss) at Baseline (Visit 2), will assess appearance of hair loss in the target scalp patch and the whole scalp by completing Item 1 and 2 of the ASAA-AAP: SR at Baseline (Visit 2) and at the visits detailed in Schedule of Assessments (**Table 3)**. At Baseline (Visit 2), the response for Item 1 of the ASAA-AAP: SR must be "no hair" or "a little hair" for the subject to be eligible for randomization. The ASAA-AAP: SR is located in **Appendix 3.**

Subjects with AU and AT (>95% scalp hair loss) at Baseline (Visit 2) will assess the appearance of the whole scalp using the ASAA-AT/AU: SR by the subject at the visits listed in the Schedule of Assessments (**Table 3**). The ASAA-AT/AU: SR is located in Appendix 10**.**

7.2.2. Alopecia Facial Hair Appearance Assessment (AFHA) for AA, AT and AU: Subject Rating (SR) (AFHA: SR)

All subjects (AA, AT or AU) will complete the AFHA: SR. An investigational staff member will instruct the subject to assess the facial hair areas (eyebrows, eyelashes and if male, beard), educate the subject on the AFHA: SR before each evaluation at Baseline (Visit 2) and at the visits detailed in Schedule of Assessments (Table 3). The staff member should not influence the subject's assessment.

The AFHA: SR is in Appendix 4.

7.2.3. Subject Global Impression of Severity (SGIS)

The severity of the subject's AA, AU or AT will be assessed by the all subjects at Baseline (Visit 2) and at the visits detailed in Schedule of Assessments (Table 3) by the subject using the Global Impression of Severity Questionnaire in Appendix 5 for subjects with AA or Appendix 11 for subjects with AT/AU.

7.2.4. Alopecia Impact Assessment (AIA): Subject Rating

The Investigator or study staff will instruct subjects with AA, AT or AU to answer the AIA (Appendix 6) during the study visit at Baseline (Visit 2), and the visits detailed in the Schedule of Assessments (Table 3).

7.2.5. Subject Global Impression of Change (SGIC)

The investigator or study staff will instruct subjects with AA, AU or AT to answer the SGIC questionnaire at their final study treatment visit to report their overall impression of change for their condition. Subjects will assess change in the severity of their condition on a 7-point scale from "Very much improved" to "Very much worse"; the SGIC can be found in Appendix 14.

7.2.6. Subject Global Impression of Treatment Satisfaction (SGITS)

The investigator or study staff will instruct subjects with AA, AU or AT to answer the SGITS questionnaire in relation to their satisfaction with the scalp hair regrowth. Subjects will assess their satisfaction with the outcome of the study treatment on a 7-point satisfaction scale from "extremely satisfied" to "extremely dissatisfied" at the visits detailed in the Schedule of Assessments (Table 3). Subjects with patchy AA (30%-95% scalp hair loss) will complete the SGITS-AAP found in Appendix 7. Subjects with AT or AU (> 95% scalp hair loss) will complete the SGITS-AT/AU found in Appendix 12.

7.2.7. Subject Global Satisfaction with Hair Quality (SGSHQ)

The investigator or study staff will instruct the subject to answer the SGSHQ questionnaire in relation to their satisfaction with the quality of scalp hair right now. Subjects will assess their satisfaction with the quality of their scalp hair on a 7-point satisfaction scale from extremely satisfied to extremely dissatisfied at the visits detailed in the Schedule of Assessments (Table 3). Subjects with patchy AA (30%-95% scalp hair loss) will complete the SGSHQ-AAP found in Appendix 8. Subjects with AT or AU (> 95% scalp hair loss) will complete the SGSHQ-AT/AU found in Appendix 13.

7.2.8. Dermatology Life Quality Index (DLQI)

The impact of AA, AU, or AT on the quality of life of subject will be assessed using the DLQI (Appendix 9) at the visits detailed in Schedule of Assessments (Table 3). The investigator or study staff will instruct the subject to answer the questions based on the scalp hair loss instead of skin.

7.3. Investigator Efficacy Assessments

The investigator will complete the assessments detailed in Table 6 in the order listed.

Table 6: Investigator Assessments

Order	Subjects with Patchy AA (30% – 95%) Scalp Hair Loss	Subjects with AU or AT (>95% hair loss)
1.	Alopecia Scalp Appearance Assessment for Patchy AA: Clinician Rating (ASAA-AAP: CR)	Alopecia Scalp Appearance Assessment for AT/AU: Clinician Rating (ASAA-AT/AU: CR)
2.	Alopecia Facial Hair Appearance Assessment: Clinician Rating (AFHA: CR)	
3.	Non-Scalp Hair Loss Assessment (NSHA)	
4.	Physician Global Impression of Severity for Patchy AA (PhGIS-AAP)	Physician Global Impression of Severity for AT/AU (PhGIS-AT/AU)
5.	Physician Global Impression of Change (PhGIC)*	
6.	Hair Quality Assessment	N/A
7.	SALT	
8.	ALODEX	
9.	Vellus and Indeterminate Hair Assessment	

*Only assessed at final study treatment visit

7.3.1. Alopecia Scalp Appearance Assessment (ASAA) Clinician Rating (CR)

The investigator will complete the ASAA-AAP: CR for subjects with patchy AA (30%-95% scalp hair loss) or the ASAA-AT/AU: CR for subjects with AT or AU (>95% scalp hair loss) at the visits listed in Table 3, Schedule of Assessments.

For subjects with patchy AA (30% to 95% scalp hair loss), the appearance of the target scalp patch and the whole scalp will be assessed by the Investigator by completing Items 1 and 2 of the ASAA-AAP:CR (Section 7.3.1.1).

For subjects with AT or AU (scalp hair loss > 95%), the appearance of the whole scalp will be assessed by the investigator by completing Item 1 of the ASAA-AT/AU: CR (Section 7.3.1.2).

At Baseline (Visit 2), the score for ASAA-AAP: CR Item 1 for subjects with patchy AA (30% to 95% scalp hair loss) must be “no hair” or “a little hair” for the subject to be eligible for randomization.

7.3.1.1. Alopecia Scalp Appearance Assessment (ASAA) for Patchy AA: Clinician Rating (CR) (ASAA-AAP: CR)

Instructions for item 1: Please mark an "X" in the box (☐) that best describes the appearance of the **subject's target patch** right now. Please select the one response that best represents your answer.

- ☐ Full hair, scalp of the target patch completely covered with hair
- ☐ Most hair, scalp of the target patch mostly covered with hair
- ☐ Some hair, scalp of the target patch somewhat covered with hair
- ☐ A little hair, scalp of the target patch mostly exposed
- ☐ No hair, scalp of the target patch completely exposed

Instructions for item 2: Please mark an "X" in the box (☐) that best describes the appearance of the subject's **whole scalp** right now. Please select the one response that best represents your answer.

- ☐ Full hair, whole scalp completely covered with hair
- ☐ Most hair, whole scalp mostly covered with hair
- ☐ Some hair, whole scalp somewhat covered with hair
- ☐ A little hair, whole scalp mostly exposed
- ☐ No hair, whole scalp completely exposed

7.3.1.2. Alopecia Scalp Appearance Assessment (ASAA) for AT and AU: Clinician Rating (CR) (ASAA-AT/AU: CR)

Instructions: Please mark an "X" in the box (☐) that best describes the appearance of the subject's **whole scalp** right now. Please select the one response that best represents your answer.

- ☐ Full hair, whole scalp completely covered with hair
- ☐ Most hair, whole scalp mostly covered with hair
- ☐ Some hair, whole scalp somewhat covered with hair
- ☐ A little hair, whole scalp mostly exposed
- ☐ No hair, whole scalp completely exposed

7.3.2. Alopecia Facial Hair Appearance Assessment (AFHA) for AA, AT and AU: Clinician Rating (CR) (AFHA: CR)

For subjects with AA, AU or AT, the appearance of the subject's facial hair (eyebrows, eyelashes and if male, beard) will be assessed using the AFHA: CR by the investigator at Baseline (Visit 2) and the visits listed in the Schedule of Assessments (Table 3).

The AFHA: CR is the investigator's assessment of the subject's facial hair (eyebrow(s), eyelashes, and if male, beard) at a particular point in time. The investigator should NOT refer to any other assessments to assist with these assessments. The investigator or designee will assess the affected facial hair areas (eyebrows, eyelashes and if male, beard) using the scales below and report the one response that best describes the amount of eyebrow, eyelash and if applicable beard hair present. Right and left eyebrow and eyelashes should be evaluated separately. The AFHA is a tool to assess the presence of hair in expected areas of growth. As such, unexpected hair growth (e.g. facial/beard hair in women) should be documented as an adverse event rather than on the AFHA.

Instructions for item 1a: Please mark an "X" in the box (☐) that best describes the appearance of the subject's **left** eyebrow hair right now. Please select the one response that best represents your answer.

- ☐ Full eyebrow hair
- ☐ Most eyebrow hair
- ☐ Some eyebrow hair
- ☐ A little eyebrow hair
- ☐ No eyebrow hair

Instructions for item 1b: Please mark an "X" in the box (☐) that best describes the appearance of the subject's **right** eyebrow hair right now. Please select the one response that best represents your answer.

- ☐ Full eyebrow hair
- ☐ Most eyebrow hair
- ☐ Some eyebrow hair
- ☐ A little eyebrow hair
- ☐ No eyebrow hair

Instructions for item 2a: Please mark an "X" in the box (☐) that best describes the appearance of the subject's **left** eyelashes right now. Please select the one response that best represents your answer.

☐ Full eyelashes
☐ Most eyelashes
☐ Some eyelashes
☐ A little eyelashes
☐ No eyelashes

Instructions for item 2b: Please mark an "X" in the box (☐) that best describes the appearance of the subject's **right** eyelashes right now. Please select the one response that best represents your answer.

☐ Full eyelashes
☐ Most eyelashes
☐ Some eyelashes
☐ A little eyelashes
☐ No eyelashes

Instructions for item 3: Please mark an "X" in the box (☐) that best describes the appearance of the subject's beard hair right now. Beard hair can include hair on the chin, cheeks, neck, and above the upper lip. Please select the one response that best represents your answer.

☐ Full beard hair
☐ Most beard hair
☐ Some beard hair
☐ A little beard hair
☐ No beard hair

7.3.3. Non-Scalp Hair Loss Assessment (NSHA)

The investigator will assess body hair (axillary, truncal, genital, extremities) and facial hair including nasal hair using a 3-point scale; no hair loss, some hair loss and total hair loss. Nasal hair will be assessed by presence or absence only. These assessments will be completed at Baseline (Visit 2) and the visits listed in the Schedule of Assessments (Table 3) (Olsen, 2011).

Instructions: Please mark an "X" in the box (☐) that best describes the appearance of the subject's body hair loss right now. Please select the one response that best represents your answer.

Mark "X"	**Body Hair Loss (**axillary, truncal, genital, extremities)	
☐	**B0**	No body hair loss
☐	**B1**	Some hair loss
☐	**B2**	Total body hair loss

Instructions: Please mark an "X" in the box (☐) that best describes the appearance of the subject's nasal hair loss right now. Please select the one response that best represents your answer.

Mark "X"	**Nasal Hair Loss**	
☐	NH0	No nasal hair loss
☐	NH1	Some to total nasal hair loss

7.3.4. PHYSICIAN GLOBAL IMPRESSION OF SEVERITY (PhGIS)

The severity of the subject's AA, AU or AT will be assessed at Baseline and at the visits detailed in Schedule of Assessments (Table 3), by the investigator using either the PhGIS-AAP for subjects with patchy AA (30% - 95% scalp hair loss) (Section 7.3.4.1) or the PhGIS-AT/AU for subjects with AT or AU (> 95% scalp hair loss) (Section 7.3.4.2).

7.3.4.1. PHYSICIAN GLOBAL IMPRESSION OF SEVERITY (PhGIS-AAP)

Please mark an "X" in the box (☐) that best describes the severity of the subject's patchy alopecia areata right now.

Overall, how severe is the subject's patchy alopecia areata right now?
☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

☐ Extremely Severe

7.3.4.2. PHYSICIAN GLOBAL IMPRESSION OF SEVERITY (PhGIS-AT/AU)

Please mark an "X" in the box (☐) that best describes the severity of the subject's alopecia totalis or alopecia universalis right now.

Overall, how severe is the subject's alopecia totalis or alopecia universalis right now?

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

☐ Extremely Severe

7.3.5. Physician Global Impression of Change (PhGIC)

The investigator will assess the global impression of change in the subject's hair loss (AA, AT or AU) at Week 24 (Visit 9) using the PhGIC detailed below.

Compared to the subject's hair loss at Baseline [prior to study medication initiation], the subject's AA, AT or AU is (Please mark an "X" in the box ☐):

☐ 1=Very much improved since the initiation of treatment;

☐ 2=Much improved;

☐ 3=Minimally improved;

☐ 4=No change from baseline (the initiation of treatment);

☐ 5=Minimally worse;

☐ 6= Much worse;

☐ 7=Very much worse since the initiation of treatment.

7.3.6. Hair Quality Assessments

Hair quality will be assessed by the investigator using the hair pull test including the presence of exclamation point hairs at Baseline and then monthly during the study. For subjects with AU or AT, the hair pull test will not be conducted.

7.3.6.1. Hair Pull Test

The hair pull test is performed at the edge of the alopecic (target) patch as follows:

- Pinch 25 to 50 hairs between non-gloved thumb and forefinger and exert slow, gentle traction while sliding fingers up.
- Resulting extracted hairs should be examined with magnification and counted.
  - Normal: 1 to 2 hairs dislodged
  - Abnormal: >2 hairs dislodged
  - Broken hairs (structural disorder)
  - Broken-off hair at the borders of an alopecic patch that are easily removable (in alopecia areata) (exclamation point hair)

7.3.7. Severity Alopecia Tool (SALT) Score

The SALT score is a measurement of the amount of terminal scalp hair loss. The investigator will assess the SALT score using an iPad provided by Aclaris at screening, Baseline, Day 15 (Visit 3) and at the visits detailed in Schedule of Assessments (Table 3). The SALT score must be determined prior to the ALODEX score. At Baseline (Visit 2), the SALT score must be determined prior to randomization and the score must be within 30% to 100% total scalp hair loss for the subject to receive study treatment. Equipment, supplies, training and the detailed Reference Guide will be provided to the investigational site prior to the initiation of subject enrollment.

7.3.8. Alopecia Density and Extent Score (ALODEX)

The ALODEX score is a measurement of the amount of terminal scalp hair loss. The investigator will calculate the ALODEX score using the iPad provided by Aclaris at Screening, Baseline, Day 15 (Visit 3), and at the visits detailed in Schedule of Assessments (Table 3). The ALODEX score must be determined after the SALT score. At Baseline (Visit 2), the ALODEX score must be determined prior to randomization. Equipment, supplies, training and the detailed Reference Guide will be provided to the investigational site prior to the initiation of subject enrollment.

7.3.9. Vellus and Indeterminate Hair Assessment

The investigator will assess if vellus and indeterminate hair are present on the scalp by completing the question:

Is vellus hair present in the areas of hair loss? Y, N

Is indeterminate hair present in the areas of hair loss? Y, N

Hair types are characterized by the diameter and length of the hair shafts. Vellus hair is soft, hypopigmented, unmedullated and less than 0.03 mm in diameter and less than 1 cm in length.

Terminal hair is longer, coarser, often medullated, pigmented, and > 0.06 mm in diameter and > 1 cm in length. Indeterminate hairs are intermediate in size between terminal and vellus hairs (>0.03 mm and <0.06 mm in diameter).

7.4. Photographic Assessment

A qualified investigational staff member will take standardized photographs of the scalp at Baseline and then monthly during the study. The photographs are to document the Baseline hair loss and hair growth during treatment. Photography is a required element of the study procedures and is not considered optional. During initial study discussion as part of consent procedures, site staff should ensure that subjects are fully aware of this aspect of study participation.

Subjects should be instructed to maintain the same hairstyle and color throughout the study. It is important for the staff member to clip the hair as detailed in the instructions provided, so the areas of hair loss and possible regrowth are visible at baseline and monthly throughout the study. Equipment, supplies, training and detailed instructions for obtaining and managing photographs and clipping the hair will be provided to the investigational center prior to the initiation of subject enrollment.

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

Safety will be assessed throughout the study by the investigator or a designated and appropriately trained staff member.

8.1.1. Demographic/Medical History/ Alopecia Areata History

During the screening visit, the investigator or designee will interview each subject to obtain demographic information including date of birth, sex at birth, Fitzpatrick skin type, race and, if appropriate, ethnicity. The investigator or designee will interview each subject to obtain medical history information related to all medical conditions, surgeries and disease states that, at screening: are ongoing, require concomitant therapy or are, in the opinion of the investigator, relevant to the subject's study participation. In addition, the medical history of women who are not of childbearing potential should reflect the reason e.g. post-menopausal for 1 year or greater, bilateral tubal ligation, or hysterectomy. The investigator or designee will also obtain an alopecia history at screening (Appendix 1). The subject's alopecia history is captured on a separate source document and eCRF and is not documented as part of the subject's general medical history.

8.1.2. Vital Signs

Vital signs will be measured at each visit during the study. The following items will be measured:

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height (at Visit 1 only)
- Weight (at Visit 1 only)

Any measure that is, in the opinion of the investigator, abnormal AND clinically significant (CS) must be recorded as medical history if found prior to the first study medication administration, or as an AE if found after the first dose of study medication.

A systolic blood pressure >140mm Hg or a diastolic blood pressure >90 mmHg is considered abnormal and therefore must be defined as CS or not clinically significant (NCS) in the eCRF. A weight >300 lbs. is considered abnormal and therefore must be defined as CS or NCS in the eCRF.

8.1.3. Physical Examination

The investigator or designee will perform a physical examination for all body systems at Screening (Visit 1) and end of treatment Week 24 (Visit 9). The skin assessment portion of the Physical Examination does not require documentation of alopecia as an abnormality since it is

the indication of interest for this study and required for participation. In the absence of any other abnormalities, skin should be considered "Normal" for these subjects.

8.1.4. Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed by a qualified staff member at Screening (Visit 1), Visit 3, and Visit 9 as detailed in Schedule of Assessments (Table 3). The ECGs must be obtained using a standard 12-lead ECG with a 10mm/mV amplitude, at 25mm/sec and a 5 to 10 second duration. To ensure a steady heart rate the subject must rest quietly in the supine position for at least 5 minutes prior to performing the ECG.

A central lab, eResearchTechnology, Inc. (ERT), will provide ECG equipment, supplies and site training. In addition, ERT will process ECGs received by the sites and report results via a secure study portal. The ECG results will be interpreted by a qualified health professional (evaluator) and the interpretation reported on a separate report which includes a copy of the tracing. The evaluator will interpret the results of every ECG and define the ECG as "normal" or "abnormal". Variations such as minor ST changes (i.e., <0.5mm depression) and early re-polarization are considered normal.

The investigator must review the evaluator's interpretation of each subject's screening ECG prior to Baseline (Visit 2). The investigator will review the evaluator's interpretation of all ECG reports in a timely manner and comment on the clinical relevance of any result that is defined by the evaluator as abnormal.

Any abnormalities that are, in the opinion of the investigator, clinically significant, must be reported as medical history if found prior to the start of the first dose of study medication or as an AE if found after the start of the first dose of study medication (see Section 8.2).

8.1.5. Clinical Laboratory Assessments

A qualified staff member will collect non-fasting samples for clinical laboratory analysis at the visits detailed in Schedule of Assessments (Table 3). Samples will be sent to a central laboratory for analysis. Refer to the study specific laboratory manual for handling and shipping instructions. The following tests will be conducted:

Chemistry Panel	**Complete Blood Count**
Albumin	Hematocrit
Alkaline phosphatase	Hemoglobin
Alanine aminotransferase (ALT)	Platelet count
Aspartate aminotransferase (AST)	Red blood cell morphology
Blood urea nitrogen (BUN)	Red blood cell count
Bicarbonate	White blood cell count
Calcium	White blood cell differential
Chloride	% & absolute
Creatinine	Basophils
Glucose	Eosinophils
Lactate dehydrogenase (LDH)	Lymphocytes

Phosphorus	Monocytes
Potassium	Neutrophils
Sodium	
Total bilirubin	**Urinalysis**
Total protein	
Uric acid	**Screening Only**
	Virology (HepB, HCV, HIV)
Total cholesterol, LDL, HDL, Triglycerides	Quantiferon Gold
	Total Iron Binding Capacity (TIBC)
Urine Pregnancy Test for WOCBP (Screening, Baseline, at the visits detailed in Schedule of Assessments (Table 3).	Serum iron
	Serum Ferritin
	T3/ Free T4, TSH
	Serum pregnancy

The following clinical laboratory tests: TIBC, serum iron, serum ferritin, T3/ Free T4, TSH are drawn at screening to rule out any underlying conditions that could be causing alopecia. Total cholesterol, LDL, HDL and Triglycerides will be assessed at all visits. The results of the clinical laboratory tests will be reported on the central laboratory's standard reports. The investigator must note NCS or CS to define the clinical relevance of any result that is outside the normal range for the laboratory. The investigator must date and initial every laboratory report.

The investigator or subinvestigator must review all the Screening (Visit 1) laboratory test results against the study entry criteria and the Study Medication Interruption Criteria Table 2 for each subject prior to Baseline (Visit 2). Subjects with Screening laboratory values meeting the Study Medication Interruption Criterial found in Table 2 must have repeat laboratory testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2).

The investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator, CS as medical history if found prior to the first study medication treatment or as an AE if found after the first study medication treatment begins. The investigator must review all laboratory reports in a timely manner.

8.1.6. Pregnancy Testing

Subjects who are WOCBP should have a 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. In addition, the investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at the visits detailed in Schedule of Assessments (Table 3). The UPT kits provided by the Central lab have a minimum sensitivity of 25-mIU ß-HCG/milliliter (mL) of urine. If the result of any post-

treatment urine pregnancy test is positive, the subject will be withdrawn from the study and the subject's pregnancy documented and followed.

8.1.7. Pharmacokinetic Assessments

At selected sites, a qualified staff member will collect a 4.5 mL sodium citrate vacutainer for analysis of ATI-502 predose at Visit 2 and at Visits 4, 6, and 9, 12 hours (± 30 minutes) after the prior evening dose. Samples will be sent to a bioanalytical laboratory for analysis. Refer to the pharmacokinetic laboratory manual for handling and shipping instructions.

8.2. Adverse and Serious Adverse Events

Adverse events will be monitored throughout the study and reported on the appropriate Aclaris Therapeutics, Inc. AE eCRF.

8.2.1. Definition of Adverse Events

8.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product.

The investigator should, when certain, report a diagnosis rather than the signs, symptoms or clinically significant abnormal laboratory values associated with the AE. Otherwise, signs, symptoms or abnormal laboratory values may be used to describe the 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. Hair growth in unexpected areas, such as facial hair in women, should be reported as an adverse event.

Any CS abnormality discovered prior to the first study medication treatment should be reported as medical history, not as an AE.

All AEs that occur after any subject has been enrolled, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded in the subject's source documents and in the Aclaris' electronic case report form (eCRF). Changes to a subject's medical condition that occur between signing an ICF and beginning treatment should be captured in the medical history.

8.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., Baseline, Treatment, Washout, or Follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization

- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The term "life threatening" refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not be immediately life threatening, result in death or hospitalization, but are clearly of major clinical significance and may jeopardize the subject or require intervention to prevent one of the outcomes listed in the SAE definition above. These should also usually be considered serious.

All SAEs that occur from the time of informed consent until 30 days following the cessation of study medication dosing, whether or not they are related to the study, must be recorded on the SAE forms provided by Aclaris Therapeutics, Inc.

8.2.1.3. Unexpected adverse event

An AE is considered unexpected if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

8.3. Reporting Adverse Events

8.3.1. Adverse event reporting period

The investigator must start reporting non-serious AEs from the time of the subject's first dose of study medication until 30 days after the last dose of study medication. Reporting for SAEs must start when the subject signs the ICF and continue until 30 days past the subject's last dose of study medication, whether or not they are related to the study.

8.3.2. Severity

The investigator is to define the severity of each AE using the following definitions as a guideline. The investigator will consider the range of the possible severity of the event and identify the severity that is the most appropriate according to her/his medical judgment.

Mild – Awareness of signs or symptom, but easily tolerated

Moderate – Discomfort, enough to cause interference with usual activity

Severe – Incapacitating with inability to perform usual activity

8.3.3. Relationship to study medication

The investigator will determine if there is a reasonable causal relationship between the study medication and an AE or not. The investigator will use her/his best medical judgment and

consider all relevant factors (*e.g.*, temporal relationship, location of the event, the subject's relevant medical history, concomitant therapies and concurrent conditions) to determine the relationship of the AE to the study medication. The investigator will define the relationship of an AE to the study medication by selecting one of the following categories:

Related – There is a reasonable causal relationship between the study medication and the AE.

Not Related – There is not a reasonable causal relationship between the study medication and the AE.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (International Conference on Harmonization [ICH] E2A).

8.3.4. Procedures for reporting adverse events

At each post-enrollment visit, the investigator will question the subject to elicit AEs using a non-directive question such as "Has there been any change in your health since the previous study visit?" If appropriate, based on the subject's response to non-directed questioning to elicit AEs, the investigator will follow-up with directed questions and appropriate evaluations.

Any AE noted during the reporting period must be reported in the source documents and on the appropriate AE eCRF. AEs that are defined as "Not Related" to the study medications will be followed until they are resolved or until the subject's last study visit. AEs that are defined as "Related" to the study medications will be followed until they are resolved or, if not resolved after the subject's last study visit, until in the opinion of the investigator, the AE reaches a clinically stable outcome with or without sequelae.

8.3.5. Procedure for reporting a serious adverse event

Upon becoming aware of a SAE occurring during the AE reporting period, whether or not related to the study medications, the investigator must:

1. Take the appropriate medical action to ensure the subject's safety.
2. Immediately inform the Safety Monitor of the SAE by email, ensuring that the subject information is deidentified (only subject initials and subject number) to: **ProPharma, Email: clinicalsafety@propharmagroup.com.**
3. Print a copy of the email confirmation from ProPharma and place in the study file.
4. Within 24-hours complete, as fully as possible, an AE eCRF and an SAE form; e-mail the forms and any other relevant information (*e.g.*, concomitant medication eCRF, medical history eCRF, laboratory test results) to ProPharma (Aclaris Therapeutics, Inc. Safety Monitor).
5. Monitor and document the progress of the SAE until it resolves or, if not resolved after the subject's last study visit, until in the opinion of the investigator the SAE reaches a clinically stable outcome with or without sequelae AND the investigator and Aclaris Therapeutics, Inc. Safety and Medical Monitor agree that the SAE is satisfactorily resolved.

6. Inform the Aclaris Therapeutics, Inc. Safety Monitor of SAE updates, via telephone, followed by an SAE form update sent by e-mail.
7. Comply with the appropriate regulatory requirements and Aclaris Therapeutics, Inc. instructions regarding reporting of the SAE to the responsible Institutional Review Board (IRB) or Ethics Committee (EC).

8.4. PREGNANCY

8.4.1. Definition of Women of Child Bearing Potential (WOCBP)

WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (*e.g.*, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. WOCBP must have a negative serum pregnancy test at screening and a negative UPT at Baseline prior to randomization.

8.4.2. Highly Effective Methods of Birth Control

The Investigator or subinvestigator will discuss the potential risk factors associated with pregnancy and the importance of maintaining a highly effective method of contraception throughout the study with all WOCBP (for example, those which result in a low failure rate - i.e., less than 1% per year- when used consistently and correctly). All WOCBP must use a highly effective method of birth control during the study and for 30 days after the final dose of study medication in a manner such that risk of failure is minimized.

Highly effective methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomized partner[1]
- sexual abstinence[2]

[1]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

WOCBP must be on a highly effective method of birth control for the following timeframes prior to study entry:

- Implants (on a stable dose for ≥30 days)
- Injectables (on a stable dose for ≥30 days)
- Patches (on a stable dose for ≥30 days)
- Combined oral contraceptives (on a stable dose for ≥30 days)
- Intrauterine devices (inserted for ≥30 days).

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and of the potential risk factors associated with pregnancy while in the study. The subject must sign an informed consent form documenting this discussion. During the trial, all WOCBP will be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study medication administration, the study medication must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed, the subject must not receive study medication and must be discharged from the study.

If, following study medication administration, it is determined that the subject or partner of a male subject may have been or was pregnant at the time of study medication exposure (including 30 days after study medication administration) the investigator must immediately notify the Aclaris Therapeutics, Inc. Medical Monitor and record the event on a pregnancy surveillance form. While not an AE or SAE, the investigator must report every pregnancy using a pregnancy surveillance form and follow the reporting procedures described for SAE reporting.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (*e.g.*, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to Aclaris Therapeutics, Inc.'s Medical Monitor on the pregnancy surveillance form, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of six weeks.

9. STATISTICS

9.1. Sample Size and Power Calculations

The planned sample size is 95 enrolled subjects with approximately 45 subjects enrolled with AT or AU.

The sample size estimate was based on published results from a similar study (Crispin et al. 2016) where 32% of subjects receiving active drug achieved at least a 50% reduction in hair loss ($SALT_{50}$) under similar conditions. For the current study, the primary efficacy analysis is mean percent change in hair loss, evaluated using SALT scores. That analysis is expected to have greater statistical sensitivity than the $SALT_{50}$ responder analysis, which is also a secondary efficacy analysis in the current study.

We assume the pooled results of 600mg and 800mg treatment groups in the current study will achieve the same or higher $SALT_{50}$ response rate (32%) as the published results above, and pooled Vehicle plus 400mg treatment groups will not achieve more than a 6% $SALT_{50}$ response rate. Based on a comparison of those two pooled groups, the current study is anticipated to have no less than 80% power with a 10% subject dropout rate 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 80%.

9.2. Analysis Populations

The Intent to Treat (ITT) population is defined as all subjects who are randomized. The Safety population is defined as all randomized subjects who received at least 1 dose of study medication. The Per-Protocol (PP) population is defined as all subjects who are randomized and do not have any major protocol violations. Major protocol violations are defined as:

- Inclusion or Exclusion criteria not met
- Concomitant medications taken during the study that interfere with efficacy
- Did not administer at least 75% of study medication
- Did not complete Week 24 (Visit 9).

9.3. Demographic and Baseline Characteristics

Subject demographic and baseline characteristics, including medical and alopecia history, prior medications and therapies and physical examination findings will be summarized using descriptive statistics.

For continuous variables, descriptive statistics (number, mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented, if necessary.

9.4. Efficacy Analyses

Hair regrowth is determined based on both percent change from baseline (Baseline SALT – Follow-up SALT/Baseline SALT) and absolute change from baseline (Baseline SALT – Follow-up SALT).

9.4.1. Primary Efficacy Analyses

The primary efficacy variable will be the percent change from Baseline (Visit 2) in the SALT score at Visit 9 (Week 24). Missing data for the primary endpoint will be imputed using Last Observation Carried Forward (LOCF) methodology. The analysis will be conducted on the percent change from baseline over time including all visits using a mixed effect model repeated measures (MMRM). The adjusted mean (LS Mean) for percent change from baseline in the SALT score at each visit, estimated from the MMRM, 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. No adjustment for multiplicity will be made. The model will include fixed effect terms for treatment, study visit, baseline SALT score group (<50, >=50), and treatment by SALT group interaction. The primary analysis will be based on the Intent-to-Treat (ITT) population. Statistical significance for primary efficacy endpoint will be declared if at least one treatment group comparison at the Week 24 visit has a two-sided p-value less than or equal to 0.05.

9.4.2. Secondary Efficacy Analyses

A secondary sensitivity analysis of the primary endpoint will be conducted using the PP population. This analysis will use the same methodology as described for the primary analysis just applied to the PP population.

The secondary efficacy endpoints include the change from Baseline in the ALODEX score, ASAA (CR & SR), AFHA (CR & SR), PhGIS, SGIS, SGSHQ, AIA, and DLQI as well as the proportion of subjects achieving a ≥ 50% hair growth compared with Baseline based upon the SALT score and ALODEX score, separately. SGITS responses at Week 12, 24, and 28 will be summarized. Various secondary responder efficacy endpoints will be defined based upon the SALT score, the ALODEX score and the AAA (Clinician and Subject) questionnaires. Details of these responder definitions will be specified in the statistical analysis plan (SAP). Global Impression of Change (Clinician and Subject) at Week 24 (Visit 9) will be used in the psychometric evaluation of the scores from the ASAA (CR and SR), respectively. Non-Scalp Hair Loss Assessment, Vellus and Indeterminate Hair Assessment and Hair Quality Assessment including normalization of exclamation point hairs and hair shedding will be described. The analysis for the percent change in ALODEX score will use the same methodology as specified for the primary efficacy analysis. Other parameters will be analyzed as detailed in the SAP.

9.5. Safety Analyses

Safety analyses will include descriptive statistics calculated on the safety parameters using the safety population. The proportion of subjects with treatment-emergent adverse events will be

tabulated and presented by treatment and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class. Vital signs and clinically significant abnormal laboratory results will also be tabulated and presented by treatment group.

Data from all randomized subjects will be presented and summarized. Safety summaries by study treatment group will include listings by study medication of adverse events incidences within each MedDRA System Organ Class, and changes from pre-dose values in vital signs. Adverse event summaries will be presented by study medication showing the proportion of subjects experiencing adverse events, both overall and by MedDRA System Organ Class.

9.6. Pharmacokinetic Analyses

The concentration of ATI-502 in the blood will be summarized (mean [SD], minimum, median maximum) pre-dose (Visit 2) and approximately 12-hr post dosing at Visits 4, 6 and 9.

10. TRAINING, DATA HANDLING AND RECORD KEEPING

10.1. Training

For each investigational center, there will be an initiation visit prior to enrolling any study subjects. It is strongly recommended that all investigators, other evaluators, study nurses, study coordinators or other applicable personnel attend this visit. During this visit, participants will be trained to the protocol, study specific procedures, and the eCRFs. Those unable to attend the initiation visit must receive on-site training from an appropriately trained individual prior to participating in any of the procedures and evaluations in this study.

Clinical Research Associates (CRAs) and other applicable personnel will be trained prior to study initiation to familiarize CRAs with the disease, the Standard Operating Procedures (SOPs), the protocol and other study specific items. Team organization, communication and operational issues will also be discussed.

Aclaris Therapeutics, Inc. will provide an investigational center file to each center.

10.2. Data Collection

The Investigator must maintain required records for all study subjects. Data for this study will be recorded in the subject's source document and on the eCRFs. All data on these eCRFs should be recorded completely and promptly. A copy of the completed eCRFs for each subject will be retained by the investigational center.

Records of the subject’s participation in this study will be held confidential except as disclosure is required by law. The study doctor, the sponsor, persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration and the Institutional Review Board will be able to inspect and copy confidential study-related records that identify subjects by name. Therefore, absolute subject confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject’s identity will not be revealed.

10.3. Data Management

Data-management activities of this study will be subcontracted. Edit checks and review processes will be performed by the sub-contractor until all data clarifications are resolved. The data will be exported to be stored in SAS datasets (or equivalent) by the sub-contractor. After all data clarifications are resolved and subject’s evaluability is determined, the database will be locked.

10.4. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Aclaris Therapeutics, Inc. will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Aclaris Therapeutics, Inc. or its

representatives. This will be documented in a Clinical Study Agreement between Aclaris Therapeutics, Inc. and the investigator.

During the study, a monitor from Aclaris Therapeutics, Inc. or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Aclaris Therapeutics, Inc.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Aclaris Therapeutics, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

10.5. Source Documentation

Investigators must keep accurate separate records (other than the eCRFs) of all subjects' visits that include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in this clinical study and have provided written informed consent. Any AEs must be completely documented. Source documentation includes results of any diagnostic tests conducted during the study.

10.6. Inspection of Records

Aclaris or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study medication stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

10.7. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Aclaris or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

11. QUALITY CONTROL AND QUALITY ASSURANCE

The study is conducted under the sponsorship of Aclaris Therapeutics, Inc. in compliance with the applicable regulatory requirements as well as applicable ICH guidelines, Declaration of Helsinki, and in respect of the Aclaris Therapeutics, Inc. and/or sub-contractor SOPs for study conduct and monitoring.

Audits may be carried out by Aclaris Therapeutics, Inc. or Aclaris Therapeutics, Inc.'s representatives, and inspections may be performed by regulatory authorities or IRB/ECs before, during or after the study. The investigator will provide the auditing/inspecting group direct access to all study records (e.g., eCRFs, subject medical records, study medication dispensing records) and the investigational center study facilities. The investigator and study staff will be available and will assist the auditing/inspecting groups as appropriate.

12. ETHICS

12.1. Ethics Review

This protocol, informed consent form, any information provided to subjects, subject-recruiting advertisements, and any amendments to these items will receive IRB/EC approval prior to use.

The IRB/EC must receive a copy of the Investigator's Brochure, all protocol amendments, safety reports and other study related information as required by regulation or the IRB/EC procedures.

12.2. Ethical Conduct of the Study

The rights, safety and well-being of the subjects are the most important considerations in this study and take priority over the interests of society and science.

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, the current ICH E6 GCP guideline, local regulatory requirements and, at US investigational centers, in compliance with the HIPAA. The study will be conducted in compliance with the IRB/EC approved version of the protocol and any applicable amendments.

12.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures. The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

12.4. Study Conduct and Protocol Amendments

With the exception of eliminating an immediate hazard to a subject, the investigator should not deviate from the protocol or implement any changes without prior written approval from the Aclaris Therapeutics, Inc.'s representative or designee and prior review and documented approval from the IRB/EC.

Changes that involve only logistical or administrative changes are allowed. The investigator should document and explain any deviation from the protocol. A protocol deviation is a non-adherence to protocol-specific study procedures or schedules that does not increase the risk to a study subject and does not affect the scientific integrity of the study.

A protocol violation is defined as any divergence from the protocol-specific study procedures or schedules that may results in an increased risk to a study subject or that affect the scientific integrity of the study. All protocol violations must be reviewed by the Medical Monitor and reported to the IRB by the Investigator, as directed by the IRB-specific procedures.

12.5. Regulatory Documents

The investigator must maintain a study file containing current and complete regulatory documentation in compliance with the current ICH E6 GCP guideline. This file will be reviewed as part of the routine monitoring for this study.

12.6. Contractual Requirements

A contractual agreement will be signed between Aclaris Therapeutics, Inc. and each investigator. This document will contain supplemental information, including financial terms, confidentiality, study schedule, third party responsibility, and publication rights.

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APPENDIX 1. ALOPECIA AREATA HISTORY

The following AA history will be obtained:

1. Onset date of alopecia

2. Onset date of current episode of AA, AU or AT

3. Does the subject have AA, AU or AT?

4. Does the subject have an ophiasis pattern of hair loss?
    a. Ophiasis only
    b. Ophiasis and AA

5. Did the subject use previous therapies for AA, AU or AT?

    a. If Yes, indicate which therapies
        1. Topical immunotherapy
        2. Corticosteroids
        3. Systemic Steroids
        4. DMARDS
        5. Biologics or immunosuppressants
        6. Plaquenil
        7. PDT
        8. Janus kinase inhibitors
        9. Phototherapy
        10. Laser therapy
        11. Narrow-band UVB
        12. Other

APPENDIX 2. FITZPATRICK'S SKIN TYPE CHART

Fitzpatrick Skin Type	
Description (Sunburn & Tanning History According to Skin Type)	**Skin Type**
Always Burns; never tans (pale white skin)	I
Burns easily; tans minimally (white skin)	II
Burns moderately; tans uniformly (light brown skin)	III
Burns minimally; always tans (moderate brown skin)	IV
Rarely burns; tans profusely (dark brown skin)	V
Never burns; deeply pigmented (dark black skin)	VI

APPENDIX 3. ALOPECIA SCALP APPEARANCE ASSESSMENT FOR PATCHY AA: SUBJECT RATING (ASAA-AAP:SR)

Instructions for item 1: Please mark an "X" in the box (☐) that best describes the appearance of the **target patch** right now. Please select the one response that best represents your answer.

☐ Full hair, scalp of the target patch completely covered with hair

☐ Most hair, scalp of the target patch mostly covered with hair

☐ Some hair, scalp of the target patch somewhat covered with hair

☐ A little hair, scalp of the target patch mostly exposed

☐ No hair, scalp of the target patch completely exposed

Instructions for item 2: Please mark an "X" in the box (☐) that best describes the appearance of your **whole scalp** right now. Please select the one response that best represents your answer.

☐ Full hair, whole scalp completely covered with hair

☐ Most hair, whole scalp mostly covered with hair

☐ Some hair, whole scalp somewhat covered with hair

☐ A little hair, whole scalp mostly exposed

☐ No hair, whole scalp completely exposed

APPENDIX 4. ALOPECIA FACIAL HAIR APPEARANCE ASSESSMENT: SUBJECT RATING (AFHA:SR)

Instructions for item 1a: Please mark an "X" in the box (☐) that best describes the appearance of your **left** eyebrow hair right now. Please select the one response that best represents your answer.

☐ Full eyebrow hair
☐ Most eyebrow hair
☐ Some eyebrow hair
☐ A little eyebrow hair
☐ No eyebrow hair

Instructions for item 1b: Please mark an "X" in the box (☐) that best describes the appearance of your **right** eyebrow hair right now. Please select the one response that best represents your answer.

☐ Full eyebrow hair
☐ Most eyebrow hair
☐ Some eyebrow hair
☐ A little eyebrow hair
☐ No eyebrow hair

Instructions for item 2a: Please mark an "X" in the box (☐) that best describes the appearance of your **left** eyelashes right now. Please select the one response that best represents your answer.

☐ Full eyelashes
☐ Most eyelashes
☐ Some eyelashes
☐ A little eyelashes
☐ No eyelashes

Instructions for item 2b: Please mark an "X" in the box (☐) that best describes the appearance of your **right** eyelashes right now. Please select the one response that best represents your answer.

- ☐ Full eyelashes
- ☐ Most eyelashes
- ☐ Some eyelashes
- ☐ A little eyelashes
- ☐ No eyelashes

Instructions for item 3: Please mark an "X" in the box (☐) that best describes the appearance of your beard hair right now. Beard hair can include hair on the chin, cheeks, neck, and above the upper lip. Please select the one response that best represents your answer.

- ☐ Full beard hair
- ☐ Most beard hair
- ☐ Some beard hair
- ☐ A little beard hair
- ☐ No beard hair
- ☐ N/A – Female

APPENDIX 5. SUBJECT GLOBAL IMPRESSION OF SEVERITY FOR PATCHY AA (SGIS-AAP)

Please mark an "X" in the box (☒) that best describes the severity of your patchy alopecia areata right now.

Overall, how severe is your patchy alopecia areata right now?

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

☐ Extremely Severe

APPENDIX 6. ALOPECIA IMPACT ASSESSMENT

Alopecia Impact Assessment (AIA)

Instructions: The following questions are about your alopecia. For each question, please select the box (☒) below the number that best describes your experience with alopecia during the past seven days. There are no right or wrong answers.

1. During the past seven days, how bothersome was it to cover your hair loss (e.g., wearing a wig, using makeup to fill in eyebrows, wearing hats)?	Not at all bothersome											Extremely bothersome	
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
2. During the past seven days, how worried were you about your appearance due to your hair loss?	Not at all worried											Extremely worried	
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
3. During the past seven days, how sad did you feel due to your hair loss?	Not at all sad											Extremely sad	
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
4. During the past seven days, how much did your hair loss impact your confidence?	Not at all impacted											Extremely impacted	
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
5. During the past seven days, how self-conscious did you feel due to your hair loss (e.g., feeling uncomfortable with hair/hair loss in public)?	Not at all self-conscious											Extremely self-conscious	
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
6. During the past seven days, how embarrassed did you feel due to your hair loss (e.g., feeling awkward about, or ashamed of, hair loss)?	Not at all embarrassed											Extremely embarrassed	
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

7. During the past seven days, how unattractive did you feel due to your hair loss?	Did not feel unattractive at all										Felt extremely unattractive		
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
8. During the past seven days, how much did your hair loss limit your social activities (e.g., spending time with friends, going to a social event)?	Not at all limited										Extremely limited		
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
9. During the past seven days, how much did your hair loss limit your physical activities (e.g., going to the gym, swimming, playing sports)?	Not at all limited										Extremely limited		
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
10. During the past seven days, how bothersome was unwanted or negative attention from others due to your hair loss (e.g., staring, questions)?	Not at all bothersome										Extremely bothersome		
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
11. During the past seven days, how bothersome was your experience of getting sweat in your eyes due to your hair loss?	Not at all bothersome										Extremely bothersome		
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
12. During the past seven days, how bothersome was your experience of getting debris in your eyes due to your hair loss?	Not at all bothersome										Extremely bothersome		
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
13. During the past seven days, how bothersome was your experience getting debris in your nose due to your hair loss?	Not at all bothersome										Extremely bothersome		
		0	1	2	3	4	5	6	7	8	9	10	
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

APPENDIX 7. SUBJECT GLOBAL IMPRESSION OF TREATMENT SATISFACTION FOR AA PATCHY (SGITS-AAP)

Please mark an "X" in the box (☐) that best describes how satisfied you are with the treatment for your patchy alopecia areata.

How satisfied or dissatisfied are you with the treatment you received in this study for your patchy alopecia areata?

☐ **Extremely satisfied**

☐ **Moderately satisfied**

☐ **A little satisfied**

☐ **Neither satisfied or dissatisfied**

☐ **A little dissatisfied**

☐ **Moderately dissatisfied**

☐ **Extremely dissatisfied**

APPENDIX 8. SUBJECT GLOBAL SATISFACTION WITH HAIR QUALITY (SGSHQ-AAP)

Instructions: Please mark an "X" in the box (☐) that best describes your satisfaction with your scalp hair quality (such as its color, texture, and thickness) right now. Please select the one response that best represents your answer.

1. How satisfied or dissatisfied are you with your hair quality in the **target patch** right now?

☐ **Extremely satisfied**

☐ **Moderately satisfied**

☐ **A little satisfied**

☐ **Neither satisfied or dissatisfied**

☐ **A little dissatisfied**

☐ **Moderately dissatisfied**

☐ **Extremely dissatisfied**

2. How satisfied or dissatisfied are you with your hair quality in the **all treated patchy areas** right now?

☐ **Extremely satisfied**

☐ **Moderately satisfied**

☐ **A little satisfied**

☐ **Neither satisfied or dissatisfied**

☐ **A little dissatisfied**

☐ **Moderately dissatisfied**

☐ **Extremely dissatisfied**

APPENDIX 9. DERMATOLOGY LIFE QUALITY INDEX

When completing the questionnaire, think of your hair loss in place of "skin problem" and "skin" in the questions below.

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?

   Very much
   A lot
   A little
   Not at all

2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?
   Very much
   A lot
   A little
   Not at all

3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?
   Very much
   A lot
   A little
   Not at all
   Not relevant

4. Over the last week, how much has your skin influenced the **clothes** you wear?
   Very much
   A lot
   A little
   Not at all
   Not relevant

5. Over the last week, how much has your skin affected any **social** or **leisure** activities?

   Very much
   A lot
   A little
   Not at all
   Not relevant

6. Over the last week, how much has your skin made it difficult for you to do any **sport**?

   Very much
   A lot
   A little
   Not at all
   Not relevant

7. Over the last week, has your skin prevented you from **working** or **studying**?
   Yes, No, or Not relevant
   If "No", over the last week how much has your skin been a problem at **work** or **studying**?
   A lot
   A little
   Not at all

8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?
   Very much
   A lot
   A little
   Not at all
   Not relevant

9. Over the last week, how much has your skin caused any **sexual difficulties**?
   Very much
   A lot
   A little
   Not at all
   Not relevant

10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?
    Very much
    A lot
    A little
    Not at all
    Not relevant

Please check you have answered EVERY question. Thank you.

APPENDIX 10. ALOPECIA SCALP APPEARANCE ASSESSMENT FOR AT AND AU: SUBJECT RATING (ASAA-AT/AU:SR)

Instructions: Please mark an "X" in the box (☒) that best describes the appearance of your **whole scalp** right now. Please select the one response that best represents your answer.

☐ Full hair, whole scalp completely covered with hair

☐ Most hair, whole scalp mostly covered with hair

☐ Some hair, whole scalp somewhat covered with hair

☐ A little hair, whole scalp mostly exposed

☐ No hair, whole scalp completely exposed

APPENDIX 11. SUBJECT GLOBAL IMPRESSION OF SEVERITY FOR AT/AU (SGIS-AT/AU)

Please mark an "X" in the box (☒) that best describes the severity of your alopecia totalis or alopecia universalis right now.

Overall, how severe is your alopecia totalis or alopecia universalis right now?

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

☐ Extremely Severe

APPENDIX 12. SUBJECT GLOBAL IMPRESSION OF TREATMENT SATISFACTION FOR AT/AU (SGITS-AT/AU)

Please mark an "X" in the box (1) that best describes how satisfied you are with the treatment for your alopecia totalis or alopecia universalis.

How satisfied or dissatisfied are you with the treatment you received in this study for your alopecia totalis or alopecia universalis?

- ☐ **Extremely satisfied**
- ☐ **Moderately satisfied**
- ☐ **A little satisfied**
- ☐ **Neither satisfied or dissatisfied**
- ☐ **A little dissatisfied**
- ☐ **Moderately dissatisfied**
- ☐ **Extremely dissatisfied**

APPENDIX 13. SUBJECT GLOBAL SATISFACTION WITH HAIR QUALITY FOR AT/AU (SGSHQ-AT/AU)

Instructions: Please mark an "X" in the box (☐) that best describes your satisfaction with your scalp hair quality (such as its color, texture, and thickness) right now. Please select the one response that best represents your answer.

1. How satisfied or dissatisfied are you with your **scalp** hair quality right now?

☐ **Extremely satisfied**

☐ **Moderately satisfied**

☐ **A little satisfied**

☐ **Neither satisfied or dissatisfied**

☐ **A little dissatisfied**

☐ **Moderately dissatisfied**

☐ **Extremely dissatisfied**

APPENDIX 14. SUBJECT GLOBAL IMPRESSION OF CHANGE (SGIC)

(Please mark an "X" in the box (☐):

1. Compared to your hair loss at the beginning of the study [before starting study medication], your alopecia is?

☐ 1=Very much improved since starting study medication

☐ 2=Much improved

☐ 3=A little improved

☐ 4=No change since starting study medication

☐ 5=A little worse

☐ 6= Much worse

☐ 7=Very much worse since starting study medication

APPENDIX 15. STUDY MEDICATION INSTRUCTION SHEET

General Instructions:

1. Each month during the treatment phase of the study, the site staff will provide you with a one-month supply of study medication (with a few extra doses in case of spillage, loss or a missed appointment).
2. Do not take the study medication on an empty stomach. Food improves how much drug is absorbed and how much drug reaches your blood, which will give the drug the best chance of reaching your scalp.
3. You will drink one bottle of study medication two times a day with a meal (approximately 8 to 12 hours between doses).
4. Make sure the cap is tightly secured and gently shake the study medication before taking a dose.
5. Swallow all the study medication in the bottle.
6. Add water to the study medication bottle and drink the liquid, followed by a large glass of water.
7. Do not change your dose without talking to the study doctor.
8. Avoid excessive natural or artificial ultraviolet radiation (e.g., sunlight, tanning beds) and use sunscreen, if excessive sun exposure cannot be avoided.
9. Remember to bring your compliance sheet, study medication bottles, both used and unused, to each study visit.

Missed Doses

If you miss a dose of this study medication, take the dose as soon as possible. However, if it is almost time for your next dose, skip the missed dose, and go back to your regular dosing schedule. Tell the study staff about any missed doses at your next study visit.

Storage

Store the study medication in the original bottle at room temperature, away from heat, moisture, and direct light. Do not refrigerate or freeze. Keep out of reach of children.