CLINICAL STUDY PROTOCOL

Open-Label Study of ATI-502 Topical Solution for the Treatment of Alopecia Areata (AA), Alopecia Universalis (AU) and Alopecia Totalis (AT)

Compound:	ATI-502
US IND Number:	134,064
Protocol Number:	ATI-502-AA-203
Phase:	2

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PROTOCOL APPROVAL SIGNATURE PAGE

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11/13/18

David Gordon, MB, ChB
Chief Medical Officer
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Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ATI-502. I have read the ATI-502-AA-203 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

SYNOPSIS

Name of Sponsor/Company: Aclaris Therapeutics, Inc.	
Name of Investigational Product: ATI-502 Topical Solution	
Name of Active Ingredient: ATI-502	
Title of Study: Open-Label Study of ATI-502 Topical Solution for the Treatment of Alopecia Areata (AA), Alopecia Universalis (AU) and Alopecia Totalis (AT)	
Study center(s): Approximately 25 US study centers	
Studied period (years): Estimated date first patient enrolled: December 2018 Estimated date last patient completed: January 2020	**Phase of development:** 2

Objectives:

- To assess the safety, tolerability, and efficacy of ATI-502 Topical Solution in subjects with AA, AU or AT following 24 weeks of treatment with ATI-501 Oral Suspension or Placebo Suspension.
- To assess the ability of ATI-502 Topical Solution to maintain or improve hair regrowth in subjects previously treated with ATI-501 Oral Suspension or Placebo Suspension.

Methodology:

This Phase 2, multicenter, open-label study will evaluate the safety, tolerability, efficacy, and durability of efficacy of ATI-502 Topical Solution, 0.46% for the treatment of alopecia areata (AA), alopecia universalis (AU) and alopecia totalis (AT) in adult subjects who completed 24 weeks of treatment with ATI-501 Oral Suspension or Placebo Suspension.

Subjects who complete 24 weeks of active treatment with ATI-501 Oral Suspension or Placebo Suspension in study ATI-501-AUAT-201 will be assessed for eligibility to enter the study. At Visit 9 in study ATI-501-AUAT-201, subjects who did not experience any adverse events (AEs), serious adverse events (SAEs), or tolerability issues that met study discontinuation criteria in study ATI-501-AUAT-201 and who in the opinion of the investigator are capable of regrowing or maintaining scalp hair and meet the entry criteria are eligible to enroll in this open-label study.

Enrolled subjects will apply ATI-502 Topical Solution, 0.46% BID to the entire scalp and if applicable, the eyebrow(s) and return for safety and efficacy assessments as detailed in the Schedule of Assessments (Table 3). Assessment of response to treatment will be performed at Week 4, Week 8, Week 16, 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 Week 24, and physical examination findings.

Number of patients (planned): approximately 80

Diagnosis and main criteria for inclusion: A clinical diagnosis of AA, AU or AT and completion of the active treatment phase of ATI-501-AUAT-201.

Inclusion Criteria:

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

1. Subject must be able to comprehend and willing to sign the Informed Consent Form (ICF).
2. Male or non-pregnant, non-nursing female ≥ 18 years old at the time of informed consent.
3. Subject has completed 24 weeks of treatment and the assessments for Visit 9 in study ATI-501-AUAT-201.
4. Subject has not experienced any AEs, SAEs or tolerability issues that met study discontinuation criteria in ATI-501-AUAT-201.
5. Subject is capable of regrowing scalp hair or maintaining prior scalp hair regrowth from ATI-501-AUAT-201 in the opinion of the investigator.
6. If a woman of childbearing potential (WOCBP), must have a negative urine pregnancy test at Visit 1 and agree to: use a highly effective method of birth control for the duration of the study; not be planning a pregnancy during the study duration and use contraception for 30 days after last application of study medication. (Refer to Section 8.4).
7. 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.
8. Be willing to maintain the same general hair style throughout the study period. Subjects who shave their scalp must be willing to refrain from shaving their scalp for at least one week or longer prior to each study visit, as determined by the investigator based on visible scalp hair growth. Hair trimming outside the treatment areas to maintain the current hair style is permitted.
9. Be willing and able to follow all study instructions and to attend all study visits.
10. Sexually active male subjects must agree to use a barrier method of contraception from the first application of study medication to at least 30 days after the last application of study medication.

Exclusion Criteria:

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

1. Any study medication discontinuation criteria are met during participation in study ATI-501-AUAT-201.
2. Females who are nursing, pregnant, or planning to become pregnant for the duration of the study and up to 30 days after the last application of study medication.
3. 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.
4. Sensitivity to any of the ingredients in the study medications.
5. Unwillingness to refrain from weaves, hair extensions, or shaving of the scalp for at least one week or longer prior to each study visit, as determined by the investigator based on visible scalp hair growth the duration of the study.

Investigational product, dosage and mode of administration:

ATI-502 Topical Solution, 0.46%

Duration of treatment:

Subjects will apply ATI-502 Topical Solution, 0.46%, BID to the entire scalp and if applicable, eyebrows for 24 weeks followed by a 4-week post-treatment follow up period.

Reference therapy, dosage and mode of administration:

None

Criteria for evaluation:

The efficacy endpoints will compare the assessment (specified below) from the Baseline visit from both ATI-501-AUAT-201 and ATI-502-AA-203 to the applicable post-baseline visits.

Primary Efficacy Endpoint:

The primary efficacy endpoint will be the mean relative percent change from the original baseline visit in study ATI-501-AUAT-201 in the Severity of Alopecia Tool (SALT) score to Visit 6 (Week 24 on study ATI-502-AA-203). This represents the percentage of hair regrowth. It will be calculated as the mean of the changes from baseline SALT score to the SALT score at Visit 6 (Week 24 on study ATI-502-AA-203), divided by baseline SALT score and expressed as a percentage.

Secondary Efficacy Endpoints:

- Proportion of subjects achieving a SALT50, SALT 75 (defined as a $\geq 50\%$, $\geq 75\%$ improvement from baseline in SALT) by visit.
- Durability of response: Proportion of subjects achieving a SALT 50 or SALT 75 at Week 24 (study ATI-501-AUAT-201) and maintaining response at post-baseline visits in ATI-502-AA-203.
- Mean Relative Percent Change from Baseline (from the current study ATI-502-AA-203) in Severity of Alopecia Tool (SALT) by visit.
- Mean Relative Percent Change from Baseline in Alopecia Density and Extent Score (ALODEX) score by visit.
- Mean Change from Baseline in SALT and ALODEX score by visit.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Patient-reported outcome [PRO]) by visit.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Clinician-reported outcome [ClinRO]) by visit.
- Change from Baseline in the Physician Global Impression of Severity (PhGIS) by visit.
- Change from Baseline in Alopecia Facial Hair Appearance Assessment (AFHA) (Clinician and Subject) by visit.
- Change from Baseline in the Subject Global Impression of Severity (SGIS) by visit.

- Change from Baseline in the subject reported Alopecia Impact Assessment (AIA) by visit.
- Subject Global Impression of Treatment Satisfaction (SGITS) by visit.
- Change from Baseline in the Subject Global Satisfaction with Hair Quality (SGSHQ) by visit.
- Global Impression of Change (Clinician and Subject) at Week 24 of ATI-502-AA-203.

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 or ear body temperature), and electrocardiograms.

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.

Statistical Methods:

Sample Size/ Power Calculations

The planned sample size 80 enrolled is based on an estimated completion rate from study ATI-501-AUAT-201.

Statistical Methods

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

Summary descriptive statistics (N, mean, median, SD) by visit will be provided for all safety and efficacy parameters. The Intent to Treat population will be used for all efficacy assessments and the Safety population will be used for all safety assessments. No data imputation will be used.

No inferential analyses are planned. For all efficacy evaluations described below, summary statistics will be provided for all treated subjects pooled, and also for each of two sub-groups of subjects based on the treatment they previously received in study ATI-501-AUAT-201.

Primary Efficacy Analyses

For the primary endpoint, the primary efficacy variable will be the mean relative percent change from the original baseline visit in study ATI-501-AUAT-201 in the SALT score to Visit 6 (Week 24). This represents the percentage of hair regrowth. It will be calculated as the mean of the changes from baseline SALT score to the SALT score at Visit 6 (Week 24), divided by baseline SALT score and expressed as a percentage.

Secondary Efficacy Analyses
The secondary efficacy endpoints will be calculated using both the current study baseline scores and the baseline scores from study ATI-501-AUAT-201. These endpoints will be evaluated at each visit and will include: the mean relative percent change from baseline in the ALODEX score (percent regrowth); the mean change from baseline in SALT and the mean change from baseline in ALODEX, the proportion of subjects achieving a ≥ 50% and ≥ 75% hair regrowth compared with baseline; change from baseline in the ASAA (Clinician and Subject), PhGIS, AFHA, SGIS, AIA, and treatment satisfaction questionnaires. The mean relative percent change in ALODEX score analysis will use the same methodology as specified for the primary efficacy analysis. Other parameters will be summarized as detailed in the statistical analysis plan.

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

Data from enrolled subjects will be presented and summarized. Safety summaries 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 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
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
ICH	International Conference on Harmonization

Abbreviation or Specialist Term	Explanation
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
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-502 for the topical treatment of alopecia areata, alopecia universalis, and alopecia totalis. ATI-502 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). As ATI-502 is a potent inhibitor at JAK 1 and JAK 3, it is strongly suggested that ATI-502 may be effective in the treatment of 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 topical administration of ATI-502 support the topical administration of ATI-502 (ATI-502 Investigator Brochure).

1.4. Clinical Study Experience with ATI-502 Topical Solution

Seven Phase 2 clinical studies are ongoing with ATI-502 Topical Solution 0.46%, 0.12% or placebo solution. ATI-50002-AA-201 is a randomized, double-blind vehicle-controlled study in subjects with stable patchy alopecia areata. ATI-50002-AA-202 is a randomized double-blind, vehicle-controlled study in subjects with alopecia universalis or alopecia totalis. ATI-50002-AUATB-201 is an open-label pilot study of the safety, tolerability and efficacy of ATI-50002 topical solution administered twice-daily in adult subjects with eyebrow loss due to alopecia areata, alopecia universalis or alopecia totalis. ATI-50002-AAB-201 is an open-label pilot study of the safety, tolerability and efficacy of ATI-50002 topical solution administered twice-daily in adult subjects with eyebrow loss due to alopecia areata, alopecia universalis or alopecia totalis. ATI-50002-VITI-201 is an open-label pilot study of the safety, tolerability and efficacy of ATI-50002 Topical Solution Administered Twice-Daily in adult subjects with non-segmental facial vitiligo. ATI-50002-AGA-201 is an open-label safety, tolerability, and efficacy study in male and female subjects with androgenetic alopecia treated with ATI-50002 Topical Solution. ATI-502-AD-201 is a phase 2a safety study of ATI-502 Topical Solution in subjects with moderate to severe atopic dermatitis.

As of July 2018, 141 subjects have applied ATI-502 Topical Solution 0.46%, 0.12% or Placebo solution bid for up to 6 months or longer. Two unrelated serious adverse events were reported in one subject each: laceration and depression. The studies are ongoing, adverse events reported to date have been primarily transient and mild in severity. Local application site reactions occurring in one subject in the individual studies have included administration site pain, application site pruritus, application site erythema, application site swelling, erythema, pain of skin, pityriasis rosea, rash, acne, alopecia, and in two subjects; pruritus.

1.5. Study Rationale

Several published case reports have demonstrated the potential for JAK1/3 inhibitors to induce hair growth in patients with AA (Kim 2017, Craiglow 2014 and 2017, Gupta 2016, Scheinberg 2016). These AA case reports have shown promising results with oral tofacitinib and ruxolitinib treatment. However, so far, JAK inhibitors have not been shown to provide long-term efficacy after ending oral treatment. Hair shedding and substantial hair loss have been reported soon after cessation of treatment with oral JAK inhibitors (Mackay-Wiggan 2016).

Among patients with AA, patients with higher disease burdens are unlikely to have satisfactory outcomes with current therapies. Aclaris Therapeutics, Inc. is developing ATI-502 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 the safety and efficacy of ATI-502 Topical Solution in the treatment of subjects with AA, AU or AT. In addition, the study will assess whether topical treatment with ATI-502 Topical Solution will maintain hair regrowth in subjects who completed 24 weeks of treatment with ATI-501 Oral Suspension or Placebo Suspension in study ATI-501-AUAT-201.

1.6. Study ATI-501-AUAT-201

Study ATI-501-AUAT-201 is an ongoing Phase 2, multicenter, randomized study designed to evaluate the safety, tolerability and efficacy of ATI-501 for the treatment of AA, AU, or AT in adult subjects. During the screening period, subjects were assessed for eligibility into the study. Eligible subjects were male and non-pregnant, non-nursing females ≥ 18 years of age, who were in good general health and free of any known disease or physical condition which might impair evaluation of the subject. Subjects were excluded from enrollment if they had a history of or current systemic or cutaneous malignancy (except for adequately treated and well healed, and completely cleared non-melanoma skin cancers), had evidence of active or latent bacterial or viral infections (including herpes zoster or disseminated herpes zoster or disseminated herpes simplex), a history of a serious local infection within 3 months prior to baseline or were positive for active tuberculosis, HIV, Hepatitis B or C infection. Subjects with serologic evidence of Hepatitis B vaccination were allowed to participate.

Enrolled subjects were required to have a clinical diagnosis of stable AA, AU, or AT with 30% to 100% total scalp hair loss (based on SALT score at baseline) for a duration of at least 6 months up to and including 12 years. Subjects who met the entry criteria were randomized to take ATI-501 Oral Suspension, 400 mg, 600 mg, 800 mg or placebo suspension twice-daily for 24 weeks. Assessment of response to treatment is being performed at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and post-treatment Week 28.

Subjects who complete ATI-501-AUAT-201 study visits up to and including Week 24 (Visit 9) are eligible to enter this study. At Visit 9 (in study ATI-501-AUAT-201), subjects who agree to participate in study ATI-502-AA-203, must sign consent prior to first application of topical study medication. The assessments completed at Visit 9 (study ATI-501-AUAT-201) will be entered into the source documentation for Visit 1 in study ATI-502-AA-203. Subjects who meet the ATI-502-AA-203 entry criteria will apply ATI-502 Topical Solution, 0.46% BID for 24 weeks followed by a 4-week post-treatment follow up visit.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective is to assess the safety, tolerability, and efficacy of ATI-502 Topical Solution in subjects with AA, AU or AT following 24 weeks of treatment with ATI-501 Oral Suspension or Placebo Suspension in Study ATI-501-AUAT-201.

An additional objective is to assess the ability of ATI-502 Topical Solution to maintain or improve hair regrowth in subjects with AA, AU or AT following 24 weeks of treatment with ATI-501 Oral Suspension or Placebo Suspension Study ATI-501-AUAT-201.

2.2. Efficacy Endpoints

The efficacy endpoints will evaluate the assessment (specified in Section 2.2.1 and Section 2.2.2) from the Baseline visit from both ATI-501-AUAT-201 and ATI-502-AA-203 compared to the applicable post-baseline visits.

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be the mean relative percent change from the original baseline visit in study ATI-501-AUAT-201 in the SALT score at Visit 6 (Week 24 on study ATI-502-AA-203). This represents the percentage of hair regrowth. It will be calculated as the mean of the changes from baseline SALT score to the SALT score at Visit 6 (Week 24 on study ATI-502-AA-203), divided by baseline SALT score and expressed as a percentage.

2.2.2. Secondary Efficacy Endpoints:

- Proportion of subjects achieving a SALT 50, SALT 75 (defined as a ≥ 50%, ≥ 75% improvement from baseline in SALT) by visit.
- Durability of response: Proportion of subjects achieving a SALT 50 or SALT 75 at Week 24 (study ATI-501-AUAT-201) and maintaining response at post-baseline visits in ATI-502-AA-203.
- Mean Relative Percent Change from Baseline (from the current study ATI-502-AA-203) in Severity of Alopecia Tool (SALT) by visit.
- Mean Relative Percent Change from Baseline in Alopecia Density and Extent Score (ALODEX) score by visit.
- Mean Change from Baseline in SALT and ALODEX score by visit.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Patient-reported outcome [PRO]) by visit.
- Change from Baseline in the Alopecia Scalp Appearance Assessment (ASAA) (Clinician-reported outcome [ClinRO]) by visit.
- Change from Baseline in the Physician Global Impression of Severity (PhGIS) by visit.
- Change from Baseline in Alopecia Facial Hair Appearance Assessment (AFHA) (Clinician and Subject) by visit.
- Change from Baseline in the Subject Global Impression of Severity (SGIS) by visit.
- Change from Baseline in the subject reported Alopecia Impact Assessment (AIA) by visit.

- Subject Global Impression of Treatment Satisfaction (SGITS) by visit.
- Change from Baseline in the Subject Global Satisfaction with Hair Quality (SGSHQ) by visit.
- Global Impression of Change (Clinician and Subject) at Week 24 of ATI-502-AA-203.

2.3. 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 or ear body temperature), physical exam, and electrocardiograms.

2.4. 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.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This Phase 2, multicenter, open-label study will evaluate the safety, efficacy, and durability of efficacy of ATI-502 Topical Solution, 0.46% for the treatment of alopecia areata (AA), alopecia universalis (AU) and alopecia totalis (AT) in adult subjects who completed 24 weeks of treatment with ATI-501 Oral Suspension or Placebo Suspension.

Subjects who complete 24 weeks of active treatment with ATI-501 Oral Suspension or Placebo Suspension in study ATI-501-AUAT-201 will be assessed for eligibility to enter the study. At Visit 9 in study ATI-501-AUAT-201, subjects who did not experience any adverse events (AEs), serious adverse events (SAEs), or tolerability issues that met study discontinuation criteria in study ATI-501-AUAT-201 and who in the opinion of the investigator are capable of regrowing scalp hair or maintaining prior regrowth experienced in ATI-501-AUAT-201 and meet the other entry criteria are eligible to enroll in this open-label study.

Enrolled subjects will apply ATI-502 Topical Solution, 0.46% BID to the entire scalp and if applicable, the eyebrow(s) and return for safety and efficacy assessments as detailed in the Schedule of Assessments (Table 3). Assessment of response to treatment and durability of response will be performed at Week 4, Week 8, Week 16, 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 Week 24, and physical examination findings.

3.2. Number of Subjects

Approximately 80 subjects will be enrolled at approximately 25 US sites.

3.3. Treatment Assignment

Subjects will apply ATI-502 Topical Solution, 0.46% 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 apply 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-502 Topical Solution should be temporarily interrupted in the event of severe adverse events considered related to ATI-502, 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 (from baseline value on ATI-501-AUAT-201)	≥ 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 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

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 (Visit 1) values.

3.4.1.2. Study Medication Discontinuation

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

- 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.

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-502 Topical Solution 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 ATI-502 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

Assessments		Visit 9[1] from Study ATI-501-AUAT-201	Visit 1[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (ET)	Post-Treatment Visit 7
Week		NA	0	2	4	8	16	24	28
Treatment Day		NA	1	15	29	57	113	169	197
Treatment Window(days)		N/A	N/A	± 3	± 3	± 3	± 3	± 3	± 7
Informed consent[2]			X						
Inclusion/exclusion criteria			X						
Physical exam[3]		✓	(X)^					X	
Demographics and Medical History Update			X						
Alopecia Areata History (Transcribe)			X						
Vital signs[4]		✓	(X)^		X	X	X	X	X
Clinical CBC, Chemistry, Urinalysis		✓			X	X	X	X	X
Urine pregnancy test[5]		✓	(X)^		X	X	X	X	X
ECG		✓							
Subject[6]	Alopecia Scalp Appearance Assessment (ASAA-AAP: SR or ASAA-AT/AU: SR)	✓	(X)^			X		X	X
	Alopecia Facial Hair Appearance Assessment (AFHA: SR)	✓	(X)^			X		X	X
	Subject Global Impression of Severity (SGIS-AAP or SGIS-AT/AU)	✓	(X)^			X		X	
	Alopecia Impact Assessment (AIA): Subject Rating	✓	(X)^			X		X	
	Subject Global Impression of Change (SGIC)[7]	✓						X	
	Subject Global Impression Treatment Satisfaction (SGITS-AAP or SGITS-AT/AU)[8]	✓	(X)^			X		X	
	Subject Global Satisfaction with Hair Quality (SGSHQ-AAP or SGSHQ-AT/AU)	✓	(X)^			X		X	
Investigator[6]	Alopecia Scalp Appearance Assessment (ASAA: -AAP:CR of ASAA-AT/AU:CR)	✓	(X)^			X		X	X
	Alopecia Facial Hair Appearance Assessment (AFHA: CR)	✓	(X)^			X		X	X
	Non-Scalp Hair Loss Assessment (NSHA)	✓	(X)^			X		X	
	Physician Global Impression of Severity (PhGIS-AAP or PHGIS-AT/AU)	✓	(X)^			X		X	
	Physician Global Impression of Change (PhGIC)	✓	(X)^					X	
	Hair Quality Assessment (Patchy AA Subjects Only)[9]	✓	(X)^			X		X	X

Assessments	Visit 9[1] from Study ATI-501-AUAT-201	Visit 1[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (ET)	Post-Treatment Visit 7
SALT Score (prior to ALODEX)[10]	✓	(X)^		X	X	X	X	X
ALODEX Score (after SALT)[11]	✓	(X)^		X	X	X	X	X
Vellus and Indeterminate Hair Assessment	✓	(X)^		X	X	X	X	X
Photography (complete scalp)	✓	(X)^		X	X	X	X	
Subject instructions[12]		X	X	X	X	X		
In office study medication application		X						
Dispense study medication[13]		X	X	X	X	X		
Collect study medication and assess compliance[14]			X	X	X	X	X	
Concomitant therapies	✓	(X)^	X	X	X	X	X	X
Adverse events	✓	(X)^	X	X	X	X	X	X

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

[1]Visit 1 will occur on the same day as Visit 9 of study ATI-501-AUAT-201. Visit 9 procedures for study ATI-501-AUAT-201 must be completed prior to initiation of any study related activity for ATI-502-AA-203. Eligible subjects must sign consent prior to first application of topical study medication. The assessments performed for Visit 9 in study ATI-501-AUAT-201 will be entered into the source document and eCRF for Visit 1 in study ATI-502-AA-203. ATI-502-AA-203 enrollment may not be open at the time of a subject's ATI-501-AUAT-201 Visit 9. If this scenario occurs, the subject may be brought back to the clinic prior to their ATI-501-AUAT-201 Visit 10. At this visit, the subject will then be given topical treatment. Assessments marked as (X)^ represent repeat assessments that would need to be performed if the subject cannot enroll directly at Visit 9 (or within 14 calendar days of Visit 9) from study ATI-501-AUAT-201.

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

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

[4]Vital signs include oral or ear temperature, blood pressure, heart rate, respiration rate.

[5] For WOCBP, the UPT performed at Visit 9 in study ATI-501-AUAT-201 must be negative prior to study medication application. UPT in WOCBP must also be obtained at Visits 3, 4, 5, 6, and 7 and must be negative for the subject to continue in the study.

[6] The subject should perform assessments prior to the Investigator assessments. The investigator may assist the subject in locating a Target Patch.

[7]The subject should refer to the Baseline (Visit 2 from ATI-501-AUAT-201 and Visit 1 from ATI-502-AA-203) photographs when assessing the change over time.

[8]The study staff should remind the subject that this question is in relation to the satisfaction with the result of the hair regrowth.

[9]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 1), the assessment should be determined prior to the first dose of study medication.

[10]SALT score must be determined prior to ALODEX using device provided.

[11]ALODEX score determined after SALT score using device provided.

[12]The study staff must instruct the subject to apply study medication according to the instructions in Appendix 13 and Appendix 14.

Assessments	Visit 9[1] from Study ATI-501-AUAT-201	Visit 1[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (ET)	Post-Treatment Visit 7
[13]Each study medication bottle contains approximately 100 ml of ATI-502- Topical Solution. The study staff should dispense a number of bottles to each subject based on the quantity applied at the first visit.								
[14]Staff should review the usage based on the number of used and unused bottles, weight of the bottle and counsel the subject as necessary.								

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Male and female subjects, 18 years of age or older, with a clinical diagnosis of 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. Subject must be able to comprehend and willing to sign the Informed Consent Form (ICF).
2. Male or non-pregnant, non-nursing female ≥ 18 years old at the time of informed consent.
3. Subject has completed 24 weeks of treatment in study ATI-501-AUAT-201.
4. Subject has not experienced any clinically significant AEs, SAEs or tolerability issues that met study discontinuation criteria in ATI-501-AUAT-201.
5. Subject is capable of regrowing scalp hair or maintaining prior scalp hair regrowth from ATI-501-AUAT-201 in the opinion of the investigator.
6. If a woman of childbearing potential (WOCBP), must have a negative urine pregnancy test at Visit 1 and agree to: use a highly effective method of birth control for the duration of the study; not be planning a pregnancy during the study duration and use contraception for 30 days after last application of study medication. (Refer to Section 8.4).
7. 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.
8. Be willing to maintain the same hair style throughout the study period. Subjects who shave their scalp must be willing to refrain from shaving their scalp for at least one week or longer prior to each study visit, as determined by the investigator based on visible scalp hair growth. Hair trimming outside the treatment areas to maintain the current hair style is permitted.
9. Be willing and able to follow all study instructions and to attend all study visits.
10. Sexually active male subjects must agree to use a barrier method of contraception from the first application of study medication to at least 30 days after the last application 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. Any study medication discontinuation criteria are met during participation in study ATI-501-AUAT-201.
2. Females who are nursing, pregnant, or planning to become pregnant for the duration of the study and up to 30 days after the last application of study medication.
3. 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.
4. Sensitivity to any of the ingredients in the study medications.

5. Unwillingness to refrain from weaves, hair extensions, or shaving of the scalp for at least one week or longer prior to each study visit, as determined by the investigator based on visible scalp hair growth the duration of the study.

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 3.4.1.2 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 6) 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 applied by the subject. Subjects will be instructed to apply a thin film of ATI-502 Topical Solution up to 4-mLs, twice-daily; once in the morning and approximately 12 hours later to the entire scalp and eyebrows (if applicable) following the instructions in Appendix 13 and Appendix 14 (if applicable). The subject must wash her/his hands thoroughly before and after each study drug application. At each study visit, subjects should bring the study medication including unused bottles back to the site. The disposable droppers and applicators should be disposed of at the subject's home.

Following review of study medication instructions, subjects will apply the first dose of study medication in the office under the instruction and supervision of the study staff.
During Visit 1, the study staff member will:

- Dispense the appropriate study medication bottle.
- Weigh the bottle with the cap prior to the first study medication application.
- Instruct the subject on the appropriate application technique following instructions in Appendix 13 and Appendix 14 (if applying study medication to the eyebrow area).
- Observe the subject's first study medication application to ensure proper coverage and monitor the subject for at least 20 minutes after application.
- Record the quantity in mLs of study medication the subject applied to cover the entire scalp in the source document, eCRF and on the subject instruction sheet.
- After the first application, the study staff should weigh the study bottle with the cap.
- Provide feedback on the application procedure, if needed.

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 13 and Appendix 14. 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 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 if applicable the eyebrow(s) 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-502 Topical Solution 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 7?) will be documented in the subject's source document and eCRF.

5.3. Grooming

Routine shaving of the scalp and beard is allowed during the study if the subject refrains from shaving for a period sufficient to show hair growth prior to Visits 4 and 6. Subjects who shave their scalp must be willing to refrain from shaving their scalp for at least one week or longer prior to each study visit, as determined by the investigator based on visible scalp hair growth. Hair trimming outside the treatment areas to maintain the current hair style is permitted. Subjects are allowed to grow their hair longer than the length at the baseline visit (Visit 1), 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. Treatment with finasteride for alopecia during the study is prohibited.

The following medications and therapies 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, and Plaquenil.
- JAK inhibitors (oral or topical) other than ATI-502 Topical Solution.
- Intralesional steroids or platelet rich plasma treatment in the scalp.
- Topical treatments on the scalp with anthralin, bimatoprost, corticosteroids, diphencyprone, diphenylcyclopropenone (DPCP), squaric acid dibutylester (SADBE), minoxidil, pimecrolimus, or tacrolimus.
- Phototherapy (narrow band Ultraviolet B [NB UVB] or broadband therapy).

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 to determine if the subject's continuation in the study is allowed.

5.5. 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.

5.6. Blinding

This is an open-label study.

6. STUDY MEDICATION MATERIALS AND MANAGEMENT

6.1. Study Medication

The study medication for this study is ATI-502 Topical Solution, 0.46%. The study medication is formulated as a thin clear solution. The inactive ingredients include: water, transcutol P, propylene glycol, PEG400, dimethyl sulfoxide (DMSO), kolliphor CS 20, benzyl alcohol, poloxamer 188, and povidone K30.

Table 4: Investigational Product

STUDY MEDICATION INFORMATION	
Study medication name	**ATI-502 Topical Solution**
Dosage Strength	0.46%
Manufacturer	PMRS, Horsham, PA
Pharmaceutical Form	Topical Solution
Container	Amber Glass Bottle, 120 mL (100 mL fill) with screw cap
Storage Conditions	59°F to 77°F (15°C to 25°C)
Dose regimen	
Route	Topical to the scalp, and if applicable, eyebrows
Frequency	Twice-daily
Duration of administration	24 weeks
Other supplies	Disposable, single-use droppers, and applicators will be provided.

6.2. Packaging and Labeling

The study medication must be used by the study subjects only. The study medication will be supplied in amber glass 120 mL bottles with each bottle packaged in a carton. Disposable droppers with 1 mL calibration mark and applicators will be provided Each carton and bottle will be labeled with a single panel label.

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 carton 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. For the purposes of the ATI-502-AA-203 study, subjects will retain their original disease classification (AA, AT, or AU) from the ATI-501-AUAT-201 study. For subjects classified with AA (30%-95% scalp hair loss at Baseline in study ATI-501-AUAT-201), the investigator may assist the subject in determining the location of the target patch by showing him/her baseline photography of the original target patch from the ATI-501-AUAT-201 study. Investigators should not review the subject's completed 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. 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 at Baseline in study ATI-501-AUAT-201)	Subjects with AU or AT (>95% scalp hair loss at Baseline in study ATI-501-AUAT-201)
1.	Alopecia Scalp Appearance Assessment for Patchy AA: Subject Rating (ASAA-AAP: SR) Appendix 2	Alopecia Scalp Appearance Assessment for AT/AU: Subject Rating (ASAA-AT/AU: SR) Appendix 8
2.	Alopecia Facial Hair Appearance Assessment: Subject Rating (AFHA: SR) Appendix 3	
3.	Subject Global Impression of Severity for Patchy AA (SGIS-AAP) Appendix 4	Subject Global Impression of Severity for AT/AU (SGIS-AT/AU) Appendix 9
4.	Alopecia Impact Assessment (AIA) Appendix 5	
5.	Subject Global Impression of Change (SGIC)* Appendix 12	
6.	Subject Global Impression of Treatment Satisfaction for Patchy AA (SGITS-AAP) Appendix 6	Subject Global Impression of Treatment Satisfaction for AT/AU (SGITS-AT/AU) Appendix 10
7.	Subject Global Satisfaction with Hair Quality (SGSHQ-AAP) Appendix 7	Subject Global Satisfaction with Hair Quality (SGSHQ_AT/AU) Appendix 11

*Only assessed at final study treatment visit

7.1.1. Alopecia Scalp Appearance Assessment (ASAA)

Subjects with patchy AA (30 – 95% scalp hair loss at Baseline in study ATI-501-AUAT-201), 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 the visits detailed in Schedule of Assessments (Table 3). The scalp assessment for subjects (ASAA-AAP: SR) is in Appendix 2.

Subjects with AU and AT (>95% scalp hair loss at Baseline in study ATI-501-AUAT-201) 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 scalp appearance for the subjects (ASAA-AT/AU: SR) is in Appendix 8.

7.1.2. 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 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 3.

7.1.3. Subject Global Impression of Severity (SGIS)

The severity of the subject's AA, AU or AT will be assessed by all subjects at the visits detailed in Schedule of Assessments (Table 3) using the Global Impression of Severity Questionnaire in Appendix 4 for subjects with AA or Appendix 9 for subjects with AT/AU.

7.1.4. Alopecia Impact Assessment (AIA): Subject Rating

The Investigator or study staff will instruct subjects with AA, AT or AU to answer the AIA (Appendix 5) during the study visit at the visits detailed in the Schedule of Assessments (Table 3).

7.1.5. 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 12. Subjects should be given the baseline photo prints from study ATI-501-AUAT-201 to review to complete this assessment.

7.1.6. 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 at Baseline in study ATI-501-AUAT-201) will complete the SGITS-AAP found in Appendix 6. Subjects with AT or

AU (> 95% scalp hair loss at Baseline in study ATI-501-AUAT-201) will complete the SGITS-AT/AU found in Appendix 10.

7.1.7. 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 at Baseline in study ATI-501-AUAT-201) will complete the SGSHQ-AAP found in Appendix 7. Subjects with AT or AU (> 95% scalp hair loss at Baseline in study ATI-501-AUAT-201) will complete the SGSHQ-AT/AU found in Appendix 11.

7.2. 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 at Baseline in study ATI-501-AUAT-201)	Subjects with AU or AT (>95% scalp hair loss at Baseline in study ATI-501-AUAT-201)
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

7.2.1. 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 at Baseline in study ATI-501-AUAT-201) or the ASAA-AT/AU: CR for subjects

with AT or AU (>95% scalp hair loss at Baseline in study ATI-501-AUAT-201) at the visits listed in Table 3, Schedule of Assessments.

For subjects with patchy AA (30% to 95% scalp hair loss at Baseline in study ATI-501-AUAT-201), 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 7.2.1.1).

For subjects with AT or AU (scalp hair loss > 95% at Baseline in study ATI-501-AUAT-201), the appearance of the whole scalp will be assessed by the investigator by completing the ASAA-AT/AU: CR (Section 7.2.1.2).

7.2.1.1. 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

7.2.1.2. 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

7.2.2. 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 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

7.2.3. 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 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

7.2.4. PHYSICIAN GLOBAL IMPRESSION OF SEVERITY (PhGIS)

The severity of the subject's AA, AU or AT will be assessed 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 at Baseline in study ATI-501-AUAT-201) (Section 7.2.4.1) or the PhGIS-AT/AU for subjects with AT or AU (> 95% scalp hair loss at Baseline in study ATI-501-AUAT-201) (Section 7.2.4.2).

7.2.4.1. 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

7.2.4.2. 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

7.2.5. 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 6) using the PhGIC detailed below and referencing the baseline photos from study ATI-501-AUAT-201.

Compared to the subject's hair loss at Baseline [prior to study medication initiation on study ATI-501-AUAT-201], 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.

7.2.6. Hair Quality Assessments

Hair quality will be assessed by the investigator using the hair pull test including the presence of exclamation point hairs at the visits detailed in Schedule of Assessments (Table 3). For subjects with AU or AT (>95% scalp hair loss at Baseline in study ATI-501-AUAT-201), the hair pull test will not be conducted.

7.2.6.1. 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)

7.2.7. 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 the visits detailed in Schedule of Assessments (Table 3). The SALT score must be determined prior to the ALODEX score. Equipment, supplies, training and the detailed Reference Guide will be provided to the investigational site prior to the initiation of subject enrollment.

7.2.8. 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 the visits detailed in Schedule of Assessments (Table 3). The ALODEX score must be determined after the SALT score. Equipment, supplies, training and the detailed Reference Guide will be provided to the investigational site prior to the initiation of subject enrollment.

7.2.9. 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).

7.3. Photographic Assessment

A qualified investigational staff member will take standardized photographs of the scalp at the visits detailed in Schedule of Assessments (Table 3). The photographs are to document loss, maintenance, or increase of 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 the post-baseline study visits. 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

The study site staff will review and if necessary, update the demographic, medical history and alopecia history obtained in study ATI-501-AUAT-201 and record into the source document and eCRF for study ATI-502-AA-203. Any adverse events that were ongoing at completion of Visit 9 in ATI-501-AUAT-201 will be recorded as medical history in the ATI-502-AA-203 eCRF. Adverse Events that started and resolved during the course of study ATI-501-AUAT-201 do not need to be reported as medical history unless the investigator considers the event(s) to be clinically significant in relation to the subject's continuation in study ATI-502-AA-203. 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 subject's alopecia history (Appendix 1) 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

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.

8.1.3. Physical Examination

The investigator or designee will perform a physical examination for all body systems at the end of treatment Week 24 (Visit 6). A physical examination may also be performed at Visit 1 if the Visit 1 did not occur at Visit 9 of the ATI-501-AUAT-201 study. 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)

Any abnormalities arising from ECGs collected during the ATI-501-AUAT-201 study that are, in the opinion of the investigator, clinically significant, must be reported as medical history on the ATI-502-AA-203 study.

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
Albumin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Bicarbonate
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase (LDH)
Phosphorus
Potassium
Sodium
Total bilirubin
Total protein
Uric acid
CPK
Total cholesterol, LDL, HDL, Triglycerides

Urine Pregnancy Test for WOCBP (At the visits detailed in Schedule of Assessments (Table 3)).

Complete Blood Count
Hematocrit
Hemoglobin
Platelet count
Red blood cell morphology
Red blood cell count
White blood cell count
White blood cell differential
- % & absolute
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Urinalysis

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 laboratory test results against the study entry criteria and the Study Medication Interruption Criteria Table 2 for each subject. Subjects with 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.

The investigator must report all laboratory results from samples collected on the ATI-502-AA-203 study that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator, CS as an AE. Laboratory results from samples collected at V9 on the ATI-501-AUAT-201 study that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator, CS must be reported as medical history on the ATI-502-AA-203 study eCRF. The investigator must review all laboratory reports in a timely manner.

8.1.6. Pregnancy Testing

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.

8.2. 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 (e.g. laboratory or ECG results from Visit 9 in study ATI-501-AUAT-201) 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.

Any adverse events that were ongoing at the time of completion from study ATI-501-AUAT-201, will be recorded in the medical history at Visit 1.

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 SAE 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 UPT at Visit 9 (study ATI-501-AUAT-201)/Visit 1 (study ATI-502-AA-203) prior to dispensing study medication.

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 80 enrolled subjects.

9.2. Analysis Populations

The Safety analysis population will be comprised of all subjects who received at least one dose of study medication. The Efficacy analysis population will include all subjects who received at least one dose of study medication using observed cases with no imputation for missing data.

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 scalp hair regrowth (Baseline SALT – Follow-up SALT/Baseline SALT) and change in absolute percent scalp hair loss from baseline (Baseline SALT – Follow-up SALT). A responder is a subject who achieves a SALT50 or SALT75 defined as ≥ 50%, ≥ 75% improvement in SALT score from baseline values in the ATI-501-AUAT-201 study. Durability of response will be assessed in subjects who achieved a SALT50 or SALT75 in study ATI-501-AUAT-201. Results will be summarized using descriptive statistics.

9.4.1. Primary Efficacy Analyses

For the primary endpoint, the primary efficacy variable will be the mean relative percent change from the original baseline visit in study ATI-501-AUAT-201in the SALT score at Visit 6 (Week 24 on study ATI-502-AA-203). This represents the percentage of hair regrowth. It will be calculated as the mean of the changes from baseline SALT score to the SALT score at each visit, divided by baseline SALT score and expressed as a percentage.

9.4.2. Secondary Efficacy Analyses

The secondary efficacy endpoints will be calculated using both the current study baseline scores and the baseline scores from study ATI-501-AUAT-201. These endpoints will be evaluated at each visit and will include: the mean relative percent change from baseline in the ALODEX score (percent regrowth); the mean change from baseline in SALT and the mean change from baseline in ALODEX, the proportion of subjects achieving a ≥ 50% hair regrowth compared with baseline; change from baseline in the AAA (Clinician and Subject), PhGIS, AFHA, SGIS, AIA, and treatment satisfaction questionnaires. The mean relative percent change in ALODEX

score analysis will use the same methodology as specified for the primary efficacy analysis. Other parameters will be summarized as detailed in the statistical analysis plan.

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

Data from all enrolled subjects will be presented and summarized. Safety summaries will include listings 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 showing the proportion of subjects experiencing adverse events, both overall and by MedDRA System Organ Class.

10. TRAINING, DATA HANDLING AND RECORD KEEPING

10.1. Training

For each investigational center, participants will be trained to the protocol, study specific procedures, and the eCRFs. Those unable to attend the training 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. or designee 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

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. 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 3. 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 4. 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 5. 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 6. 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 7. 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 8. 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 9. 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 10. SUBJECT GLOBAL IMPRESSION OF TREATMENT SATISFACTION FOR AT/AU (SGITS-AT/AU)

Please mark an "X" in the box (☐) 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 11. 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 12. 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 on study ATI-501-AUAT-201], 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 13. SUBJECT INSTRUCTIONS FOR STUDY MEDICATION APPLICATION TO THE ENTIRE SCALP

Preparation and General Instructions:

1. Gather a clean washcloth and towel, the study medication bottle, disposable dropper and gloves (parent application only). Parents must wear gloves when applying study medication to their child's scalp.
2. Hair and scalp should be clean (free of any hair and scalp styling products), and dry or at least towel-dried before applying study medication. Ensure that your scalp is as dry as possible. A clean scalp will allow the study medication to penetrate down into the scalp to ensure you are getting the best application. The scalp should be washed using your normal cleansing products at least an hour prior to study medication application, at least once a day to prevent accumulation of study medication on your skin.
3. Wash your hands with soap and water before and after using this study medication.
4. You will apply a thin layer of study medication to the entire scalp as instructed by the study doctor or the study staff. Once medication has been applied to all current patchy areas, part hair into approximately 4 sections (from front to back). Take each section one by one and apply up to 1mL to the scalp part and massage the study medication into the scalp from the part to the sides until the entire scalp is covered in a thin film of study medication. Keep applying study medication throughout the study, even if scalp hair is regrowing. If you experience new areas of scalp hair loss (for example, areas of the scalp with active hair shedding and abnormal sensations that in your experience is a sign of scalp hair loss) discuss these new areas with the study Doctor so they can be appropriately documented.
5. **The amount of study medication you will apply during one treatment is a total of __ mL (__ -1mL droppers).**
6. Avoid study medication contact with the eye. If the study medication gets on any part of your body other than your scalp, rinse the area well with water.
7. You will apply study medication twice-a-day, approximately 8 to 12 hours apart. Remember to bring your study medication bottles both used and unused to each study visit.

Study Medication Application:

1. Draw up exactly 1 mL of study medication into the dropper. The medication level should be at the 1mL line.
2. During study medication application, keep your head tilted back to avoid any study medication running into your eyes.
3. Section hair into approximately 4 sections (from front to back). Apply up to 1 mL to the scalp of each parted section from front to back and massage the study medication into the scalp from the part to extending to the sides until the **entire scalp** is covered in a thin film of study medication.
4. Replace the screw top cap and make sure it is closed tightly. Dispose of the used dropper(s).
5. It is important to continue to apply study medication to the entire scalp throughout the study, even if there is hair growth.
6. Wash your hands after using this product to prevent any residue being left on your hands.
7. Allow the study medication to dry for at least 15 minutes before you apply any styling products to the hair. All topical products applied to the hair and scalp must be reviewed and approved by your study doctor before use.
8. If you missed a dose or doses, record on your subject compliance record and tell the study staff at your next visit.
9. Do not wash your hair or scalp for at least 6 hours after applying study medication or participate in strenuous exercise that would cause profuse sweating for at least 6 hours.

Wigs and Hairpieces

1. Wigs and hairpieces may be worn while participating in the study but must be appropriately managed.
2. Wigs or hairpieces should not be worn until the study medication is completely dry on the scalp. Thus, wigs or hairpieces should not be reapplied for at least 15 minutes after the study drug has been applied.
3. Wigs and hairpieces will need to be removed at each study visit to allow the study doctor to evaluate your scalp and hair loss. Any hairpieces that may be difficult to remove will prevent you from participating in the study. Do not have semi-permanent or difficult to remove hairpieces placed during the study. Hair "weaves" that only involve areas of the scalp that continue to have hair may be accepted on a case by case basis.
4. If scalp irritation develops during the study, it may be necessary to temporarily stop wearing of a hairpiece or wig. The study doctor will discuss this with you should scalp irritation develop.

Missed Doses: If you miss a dose of this study medicine, apply it 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 medicine in the original glass bottle, in the carton provided, at room temperature, away from heat, moisture, and direct light. Keep from freezing. Keep study medication and used droppers out of the reach of children.

APPENDIX 14. SUBJECT INSTRUCTIONS FOR STUDY MEDICATION APPLICATION TO THE EYEBROWS

General Instructions:

1. Before application of study medication, your eyebrow area should be clean (free of any makeup, moisturizers, sunscreen, etc.), and dry. This will allow the study medication to penetrate down into the skin to ensure you are getting the best application.
2. The study doctor will instruct you to apply study medication to one or both eyebrows. You will apply the study medication to the entire eyebrow area, both with and without eyebrow hair.
3. You will be asked to apply a thin layer of study medication to the affected eyebrow with an applicator as instructed by the study doctor or the study staff. Keep applying study medication to the affected eyebrow(s) throughout the study, even if hair is re-growing in these areas.
4. You will want the tip of your applicator to be saturated but not too much as to cause dripping. An applicator should only be dipped in the bottle once and then disposed of.
5. Keep the study medication out of your eyes. If the study medication gets in your eyes, rinse the area well with water for up to 15 minutes. Contact the study doctor for further advice on managing the eye exposure.
6. You will apply study medication twice-a-day, approximately 8 to 12 hours apart. Once you apply study medication, do not wash your face and eyebrow area or participate in strenuous exercise that would cause profuse sweating for at least 6 hours.
7. Remember to bring your study medication bottles, both used and unused, to each study visit.
8. Avoid exposing your face to excessive natural or artificial ultraviolet radiation (e.g., sunlight, tanning beds) and use sunscreen on the face including the eyebrows, if excessive sun exposure cannot be avoided.
9. Remove any products applied to the eyebrow area at least 1 hour before study visits. Do not apply study medication less than 6 hours before a study visit. If your visit is in the morning you should wait until after the visit to apply your study medication.
10. Each bottle of study medication should be used for 60 days only, even if there is remaining study medication.

Preparation for Study Medication Application

1. Gather a clean, dry washcloth or towel, the study medication bottle, disposable applicators and a mirror.
2. Wash your hands with soap and water before and after using this study medication.
3. Gently wash your eyebrow areas, ensuring your eyebrow areas are clean. Use your normal cleansing regime as approved by your study doctor. Do not use abrasive cleansers or materials on your face and eyebrow area.
4. Pat your face dry with a clean towel and then let it air dry until it is completely dry to the touch.

Study Medication Application:

1. Unscrew the cap from the bottle. Place the open bottle on a stable, level surface.
2. Dip a disposable applicator into the bottle of study medication for about 2 seconds. Tap the tip of the applicator twice inside the edge of the bottle to remove any excess study medication. The applicator should be saturated, but not dripping.
3. Tilt your head back and place your clean, dry washcloth over one eye. Swipe the applicator across your affected eyebrow ridge above the covered eye, applying a thin layer of study medication over the entire affected eyebrow area. Your eyebrow area should be wet, but not dripping wet. Dispose of the applicator. **Do not dip the same applicator in the study medication bottle more than once.**
4. If you need additional study medication to cover your entire affected eyebrow, use a new applicator and repeat the application process as described in #2 and #3.
5. If you are instructed by the study doctor to treat both eyebrows, apply study medication to your other eyebrow following instructions in #2, #3, and #4.

After Study Medication Application

1. Securely close the study medication bottle and dispose of any used applicators.
2. Wash your hands after using this product.
3. Allow the study medication to completely dry for at least 10 minutes.
4. Do not apply any products (moisturizers, sunscreens, cosmetics, etc.) to your eyebrow area until the study medication has completely dried, at least 30 minutes after applying study medication.
5. Do not wash your face and eyebrow areas or participate in strenuous exercise that would cause profuse sweating for at least 6 hours after applying the study medication.

Missed Doses

If you miss a dose of this study medication, apply it 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 glass bottle at room temperature, away from heat, moisture, and direct light. Do not refrigerate or freeze. Keep out of reach of children.