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

Subjects who complete study visits through Visit 9 will have the option to roll over into an open-label study ATI-502-AA-203. Subjects who withdraw consent or meet study medication discontinuation criteria (Section 3.4.1.2) on study ATI-501-AUAT-201 will not be eligible for roll-over to study ATI-502-AA-203. Subjects who complete the assessments for Visit 9 and then meet study ATI-502-AA-203 entry criteria and provide written consent will skip post-treatment Visit 10. Subjects who are not eligible for ATI-502-AA-203 or who decline to participate should return for the final Visit 10 assessments.

Select Sites:

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

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

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

Inclusion Criteria:

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

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

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

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

2.5. Other Assessments

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

2.6. Pharmacokinetic Endpoints

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

2.7. Safety Endpoints

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

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

During the screening period, subjects will be assessed for eligibility into the study. Subjects will receive ATI-501 Oral Suspension, 400 mg, 600 mg, or 800 mg or Placebo Oral Suspension twice-daily for up to 24 weeks. Assessment of response to treatment will be performed at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and post-treatment Week 28. Safety and tolerability will be evaluated at each study visit by assessment of adverse events, clinical laboratory tests, and vital signs, and at select visits, ECGs.

Subjects who complete study visits through Visit 9 will have the option to roll over into an open-label study ATI-502-AA-203. Subjects who withdraw consent or meet study medication discontinuation criteria (Section 3.4.1.2) on study ATI-501-AUAT-201 will not be eligible for roll-over to study ATI-502-AA-203. Subjects who complete the assessments for Visit 9 and then meet study ATI-502-AA-203 entry criteria and provide written consent will skip post-treatment Visit 10. Subjects who are not eligible for ATI-502-AA-203 or who decline to participate should return for the final Visit 10 assessments.

3.2. Number of Subjects

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

3.3. Treatment Assignment

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

3.4. Dose Adjustment Criteria

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

3.4.1. Safety Criteria for Adjustment or Stopping Doses

3.4.1.1. Study Medication Interruption

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

Table 2: Study Medication Interruption Criteria

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

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

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

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

3.4.1.2. Study Medication Discontinuation

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

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

Table 5: Subject Assessments

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

*Only assessed at final study treatment visit

7.2.1. Alopecia Scalp Appearance Assessment (ASAA)

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

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

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

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

The AFHA: SR is in Appendix 4.

Table 6: Investigator Assessments

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

*Only assessed at final study treatment visit

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

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

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

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

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

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

7.4. Photographic Assessment

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

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

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

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

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

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

8.1.6. Pregnancy Testing

Subjects who are WOCBP should have a UPT performed early in the screening procedures (following informed consent) which shows negative results in order to avoid the continuation of what would then be unnecessary screening testing. Subjects who are WOCBP must also have a negative serum pregnancy test result from Screening (Visit 1) to continue in the study, and a negative UPT at Baseline (Visit 2) prior to randomization. In addition, the investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at the visits detailed in Schedule of Assessments (Table 3). The UPT kits provided by the Central lab have a minimum sensitivity of 25-mIU ß-HCG/milliliter (mL) of urine. If the result of any post-

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

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

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

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

8.2.1.3. Unexpected adverse event

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

8.3. Reporting Adverse Events

8.3.1. Adverse event reporting period

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

8.3.2. Severity

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

Mild – Awareness of signs or symptom, but easily tolerated

Moderate – Discomfort, enough to cause interference with usual activity

Severe – Incapacitating with inability to perform usual activity

8.3.3. Relationship to study medication

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

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

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

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

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

8.3.4. Procedures for reporting adverse events

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

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

8.3.5. Procedure for reporting a serious adverse event

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

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

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

8.4. PREGNANCY

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

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

8.4.2. Highly Effective Methods of Birth Control

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

Highly effective methods include:

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

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

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

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

Exclusion Criteria:

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

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

1. INTRODUCTION

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

1.1. Overview of Alopecia Areata

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

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

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

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

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

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

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

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

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

3.5. Criteria for Study Termination

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

7.2.3. Subject Global Impression of Severity (SGIS)

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

7.2.4. Alopecia Impact Assessment (AIA): Subject Rating

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

7.2.5. Subject Global Impression of Change (SGIC)

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

7.2.6. Subject Global Impression of Treatment Satisfaction (SGITS)

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

7.2.7. Subject Global Satisfaction with Hair Quality (SGSHQ)

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

7.2.8. Dermatology Life Quality Index (DLQI)

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

7.3. Investigator Efficacy Assessments

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

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

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

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

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

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

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

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

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

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

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

8.1.1. Demographic/Medical History/ Alopecia Areata History

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

8.1.2. Vital Signs

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

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

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

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

8.1.3. Physical Examination

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

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

8.1.7. Pharmacokinetic Assessments

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

8.2. Adverse and Serious Adverse Events

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

8.2.1. Definition of Adverse Events

8.2.1.1. Adverse Event (AE)

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

The investigator should, when certain, report a diagnosis rather than the signs, symptoms or clinically significant abnormal laboratory values associated with the AE. Otherwise, signs, symptoms or abnormal laboratory values may be used to describe the AE.

Every new episode or clinically significant worsening of a chronic condition (e.g., headaches, seasonal allergies, depression, or hypertension) should be reported as a separate AE, even if the condition is reported in the subject's medical history. Hair growth in unexpected areas, such as facial hair in women, should be reported as an adverse event.

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

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

8.2.1.2. Serious Adverse Event (SAE)

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

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

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.