CLINICAL STUDY PROTOCOL
Protocol Number: ATI-50002-VITI-201
Amendment 3

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

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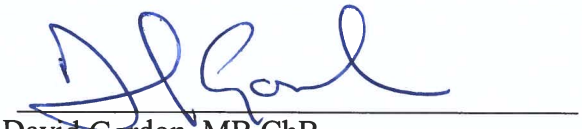
PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: ATI-50002-VITI-201

Version 4.0 February 8, 2019

Protocol Title: 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.

Sponsor Signatures:



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

2/7/19
Date

INVESTIGATOR SIGNATURE PAGE

Protocol Number: ATI-50002-VITI-201

Protocol Title: 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

Version 3.0 October 12, 2018

I have reviewed the above-titled protocol and agree that it contains all the information necessary to conduct the study as required. 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, a written report describing the serious adverse event will be provided to the Sponsor as soon as possible, but no later than five days following the initial notification.

Investigator Signature:

_____ _____

Investigator signature Date

_____

Investigator printed name

AMENDMENT HISTORY

Protocol Amendment 1 (version 2.0 Dated 19JUN2018) provided the following changes to the original protocol (version 1.0, dated 30NOV2017):

- Clarified the area of the face excluded from the TBSA calculation is the *area from the eyebrows to and including* the upper eyelids; *the area from the bony rim of the orbit to and including* the lower eyelids; mucosal lip areas; beard [if applicable] and the forehead and chin areas covered by the stereotactic positioning device for photography,
- Updated the number of sites from 3 to 5,
- Changed the age range from ≥ 18 to 65 to ≥ 18, to allow enrollment of subjects who do not have evidence of significant poliosis, and based on the medical judgement of the investigator are capable of repigmentation,
- Added a contraception requirement for male subjects with a partner who is a WOCBP,
- Clarified that subjects with *significant* spontaneous repigmentation are excluded to allow the inclusion of subjects who have had very minor repigmentation, such as a small macule,
- Revised exclusion criterion for ANC and platelets to below the ACM Laboratory lower limit of normal; ANC from < 1,000/mm^3 to < 1,800/μL and platelet count from < 50,000/mL to < 130,000/μL,
- Clarified that a heart rate of ≤ 45 beats/minutes based on the screening ECG should only exclude subjects from randomization, if in the opinion of the investigator the low heart rate is clinically significant.
- Clarified that subjects with any screening values that meet the study interruption criteria must have repeat lab testing performed with results meeting the minimum criteria for resumption,
- Added a specific exclusion criterion for subjects who are positive for HIV, Hepatitis B or C, previously covered under Exclusion Criterion 9: Subjects with a current viral infection,
- Added to Permitted Concomitant Medications, Therapies and Over the Counter Products (OTC) Section: Male subjects who shave at screening and baseline should maintain the same shaving regimen during the study.
- Added to the Prohibited Medications, concomitant use of:
    - Camouflaging agents with a temporary dyeing effect such as dihydroxyacetone, or self-tanners or,
    - Immune boosting herbal supplements such as astragalus
- Deleted 80% total body VASI from Section 6.4.1
- Revised: Timeframe each bottle of study medication should be used from 14 days to 30 days based on updated stability information,
- Added APPENDIX 6, Area of Interest Diagram in order to clarify the areas of the face with vitiligo that can be included in the TBSA calculation.
- Replaced Vitiligo Area Severity Index (VASI) Vitiligo Area *Scoring* Index (VASI) throughout the protocol.

Administrative Letter #1 Dated 29JAN2018 updated Aclaris Therapeutics, Inc. office location. Administrative Letter #2 Dated 05OCT2018 changed the number of subjects enrolled from 24 to 33. The changes from both Administrative Letters were incorporated into Protocol Amendment 2, Version 3.0 Dated 12OCT 2018.

Protocol Amendment 2 (version 3.0 Dated 12OCT2018) extended the treatment period for an additional 24 weeks of active treatment with a 4-week post-treatment follow-up visit to allow for the timeframe for repigmentation which may require 6 to 12 months of treatment. Protocol Amendment 2 provides the following primary changes to Protocol Amendment 1 (version 2.0 Dated 19JUN2018):

- Added Visit 12 (Week 32), Visit 13 (Week 40), Visit 14 (Week 48), and Visit 15 (Week 52).
- Revised the Primary Efficacy Assessment timepoint to Visit 14, Week 48.

- Added CPK as an additional safety assessment.
- Added the neck as an acceptable treatment area.

Clarified that statistical analyses will be performed after all subjects complete Visit 10 and Visit 15 and that the primary efficacy assessment will be at Visit 14, Week 48.

AMENDMENT RATIONALE

Protocol Amendment 3.0 dated 08FEB2019 allows for the concomitant use of narrowband-UVB according to the Standard of Care protocol for the treatment of vitiligo to see if there is a synergistic effect on repigmentation.

ATI-50002 Topical Solution was not a skin sensitizer in a mouse local lymph node assay. ATI-50002 was shown to have the potential to react to light. In a 3T3 cell assay, ATI 50002 in the absence and presence of UVA did not cause toxicity and, therefore, there was no phototoxic potential identified for ATI-50002.

Protocol Changes			
Protocol Version	**Date**	**Section**	**Revisions**
4.0	08FEB2019	5.6 5.6.1	Added: NB-UVB treatments may be administered according to the Standard of Care protocol for the treatment of vitiligo after the subject has completed Visit 9. NB-UVB treatments should be recorded in the source documents and on the Concomitant Therapies Log of the eCRF.

1. SYNOPSIS

Protocol Number: ATI-50002-VITI-201	**Protocol Title:** 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
Sponsor: Aclaris Therapeutics Inc.	**Phase of Development:** Phase 2
Study Medication Description: ATI-50002 Topical Solution, 0.46%	
Study Objective: The main objective of this study is to assess the safety, tolerability and efficacy of ATI-50002 Topical Solution, 0.46% in subjects with non-segmental facial vitiligo.	
Study Design: This is a multicenter, open-label study designed to evaluate the safety, tolerability and efficacy of ATI-50002 Topical Solution 0.46% in subjects with non-segmental facial vitiligo. Subjects will be required to have a clinical diagnosis of non-segmental facial vitiligo effecting at least 0.25% of total body surface area (TBSA) (excluding: the area from the eyebrows to and including the upper eyelids; the area from the bony rim of the orbit to and including the lower eyelids; mucosal lip areas; beard [if applicable], and forehead and chin areas covered by the stereotactic positioning device for photography) with at least one area of the face with normal pigmentation. Thirty-three eligible subjects will apply ATI-50002 Topical Solution, 0.46%, BID for up to 48 weeks to the vitiliginous areas of the face and neck and a ½" area around these areas. During the screening period, subjects will be assessed for eligibility to receive study medication. Eligible subjects will apply study medication to the vitiliginous areas of the face and neck and a ½" margin around these areas (excluding upper and lower eyelids [defined as the area from the bony rim of the orbit to and including the eyelids], and mucosal lip area) twice-a-day for up to 48 weeks. If applicable, the subject may treat up to the vermillion border of the mucosal lip and the skin underneath the beard. Assessment of response to treatment will be performed using Canfield 2-D photographic digital image analysis, Facial VASI, Vitiligo Noticeability Scale (VNS), VitiQoL and Subject Vitiligo Satisfaction Scale. These will occur as specified in the Schedule of Assessments. Subjects will be seen at up to 15 study visits, including up to 48 weeks of active treatment followed by a 4-week post-treatment follow-up visit. Subjects who consented for the original study treatment period for up to 28 weeks, and do not consent for the additional visits (Visit 12-15) will complete the study at Visit 11 (Week 28.) Safety and tolerability will be evaluated throughout the study by assessment of electro-cardiograms (ECG), clinical laboratory tests, adverse events including local site reactions, and vital signs.	
Number of Subjects (planned): Approximately 33 subjects will be enrolled.	
Number of Study Sites: This study will be conducted at approximately 5 U.S. clinical sites.	

Inclusion Criteria:

In order to be eligible for the study, a subject must fulfill all of the following criteria:

1. Subject is a male or female ≥ 18 years of age.
2. Subject has a clinical diagnosis of new onset or actively progressing non-segmental facial vitiligo or worsening of existing facial lesions within the past 6 months. Actively progressing vitiligo is defined as: subject history of a new vitiliginous lesion or objective signs of disease activity (such as: confetti-like depigmentation, trichrome lesions, and the Koebner phenomenon) as assessed by the investigator. Subjects may have non-facial vitiliginous lesions that are unchanged for more than 6 months provided they meet the requirement for active facial lesions.
3. Subject has non-segmental facial vitiligo effecting at least 0.25% total body surface area (TBSA) (excluding: the area from the eyebrows to and including the upper eyelids; the area from the bony rim of the orbit to and including the lower eyelids; mucosal lip areas; beard [if applicable]; and forehead and chin areas covered by the stereotactic positioning device for photography) with at least one area of the face with normal pigmentation. The face is defined as the area from the border of the hairline, not including areas with hair such as the eyebrow and if applicable the beard to the jawline.
4. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at the baseline visit and must agree to use an approved method of highly effective birth control for the duration of the study and for 30 days after last study medication application.
5. If female, subject who is non-pregnant and non-lactating and not planning a pregnancy during the duration of the study.
6. Subject is in good general health and free of any known disease state or physical condition which, in the opinion of the investigator, would interfere with the study assessments or put the subject at undue risk by study participation.
7. Subject is willing and able to follow all study instructions and to attend all study visits.
8. Subject agrees to refrain from any other treatments for vitiligo from the screening visit through the final follow-up visit. Over the counter (OTC) preparations deemed acceptable by the investigator and camouflage makeups are permitted.
9. Subject is able to comprehend and willing to sign an Informed Consent Form (ICF).
10. Sexually active male subjects with a partner who is a WOCBP, must agree to use a barrier method of contraception from the first application of study medication to at least 30 days after the last dose of study medication.

Exclusion Criteria:

Any subject who meets one or more of the following criteria will not be included in this study:

1. Subject with evidence of poliosis (white hairs) in > 50% of their facial vitiligo lesions.
2. Subject with total facial depigmentation.
3. Subject with significant spontaneous ongoing facial repigmentation (documented based on the subject's reporting in the last 3 months).
4. Subject who has segmental vitiligo.

5. Subject who has failed phototherapy. Failed phototherapy is defined as failure to achieve satisfactory repigmentation following adequately delivered phototherapy as determined by the investigator.
6. Subject currently has, or has a history of, skin disease (e.g., psoriasis, seborrheic dermatitis, etc.) that, in the opinion of the investigator, would interfere with the study medication application or study assessments.
7. Subject has, or has a history of, severe, progressive or uncontrolled autoimmune, metabolic, renal, hepatic, gastrointestinal, pulmonary, cardiovascular, genitourinary (i.e., renal disease), hematological disease, neurologic or cerebral disorders, infectious disease or coagulation disorders that, in the opinion of the investigator, would interfere with the study assessments or put the subject at undue risk by study participation.
8. Subject currently has, a history of, current, or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than a history of adequately treated, 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. Subject currently has evidence of active or latent bacterial (including tuberculosis) or viral infections at the time of enrollment, or a history of incompletely treated or untreated tuberculosis. Subjects who have initiated therapy for latent tuberculosis for at least 2 weeks and agree to continue their therapy through completion may participate.
10. Subject has a history of serious local infection (*e.g.*, cellulitis, abscess) or systemic infection, or history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to the baseline visit. Subjects on an antibiotic for a nonserious, acute local infection must complete the course prior to enrollment into the study.
11. Subject has herpes zoster or cytomegalovirus (CMV) that resolved within 8 weeks prior to Visit 1.
12. Subject has a history of frequent outbreaks of oral Herpes Simplex Virus defined as more than 4 episodes per year.
13. Subjects previously treated with depigmenting agents.
14. Clinically significant laboratory abnormalities at screening that in the opinion of the investigator, would make the subject a poor candidate for the study. Subjects with any other Screening laboratory values meeting the Study Medication Interruption Criteria found in Table 1 must have repeat lab testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2).
15. Subject who has an absolute neutrophil count <1,800/µL, or platelet count < 130,000/µL.
16. Subject unable to comply with the required washout periods:
    1. Use of any biologic, investigational therapy or procedure for vitiligo within 12 weeks or 5 half-lives (whichever is longer) of screening (Visit 1).
    2. Use of laser or light-based vitiligo treatments, including tanning beds, within 8 weeks of screening (Visit 1).
    3. Use of immunomodulating oral or systemic medications (*e.g.,* corticosteroids, methotrexate, cyclosporine) or topical treatments that may affect vitiligo (*e.g.,* corticosteroids, tacrolimus/ pimecrolimus, retinoids) within 4 weeks of screening (Visit 1).

4. Use of any prior concomitant therapy not listed above that may interfere with the objective of the study as per the discretion of the investigator, including drugs that cause photosensitivity or skin pigmentation (*e.g.,* antibiotics such as tetracyclines, sulfa etc.) within 8 weeks of screening (Visit 1).
5. Subjects who have previously received oral or topical JAK inhibitors.

17. Subject who has participated in any investigational drug or device trial, regardless of indication in which administration of an investigational drug or device occurred within 30 days or 5 half-lives (whichever is longer) of screening (Visit 1). Note that investigational treatment for vitiligo (in any body area) requires a longer washout – see Exclusion criterion #16.1 above.
18. Subjects with a clinically significant abnormal thyroid-stimulating hormone or free T4 at screening. Subjects under treatment with stable thyroid replacement who have a free T4 and TSH within the normal range may participate.
19. Subject has history of sensitivity to any of the ingredients in the study medications.
20. Subject has a history of, or current alcohol or drug abuse within 2 years of study enrollment
21. Screening ECG findings of:
    1. QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose)
    2. Clinically significant heart rate ≤ 45 or Heart Rate ≥ 100 beats/minutes
    3. Rhythm disturbance other than sinus arrhythmia or ectopic supraventricular rhythm (ectopic atrial rhythm)
    4. Conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
    5. Acute or chronic signs of ischemia.
    6. Left Bundle Branch Block
    7. Prior myocardial infarction
22. Positive for HIV, Hepatitis B or C. Subject with serologic evidence of Hepatitis B vaccination (HepB surface Ab without the presence of Hep B sAg) will be allowed to participate.

Duration of Treatment

The planned study durations are:

- Enrollment period: 12 weeks (84 days)
- Study participation duration (Visit 1 through Visit 11 is a maximum of 229 days).
- Duration of study participation from Visit 1 thought Visit 15 is a maximum of 372 days.

Criteria for Evaluation:

Efficacy:

The percentage of facial depigmentation will be quantified in the Area of Interest (AOI) through analysis of digital images (Section 8.1.1 Canfield 2D Digital Facial Image Analysis).

The investigator will evaluate facial repigmentation using the Facial Assessment of the Vitiligo AreaScoring Index (F-VASI).

Subject will assess facial repigmentation using the Vitiligo Noticeability Scale (VNS). Treatment success will be defined as follows: VNS score of 1 or 2 = treatment not successful, VNS score of 3 = treatment partially successful, or VNS score of 4 or 5 = treatment successful.
Safety:
The investigator will assess clinical laboratory safety tests, vital signs, ECGs, concomitant therapies, urine pregnancy test results, and adverse events (AEs) throughout the study.

Other:
The investigator will assess the extent of vitiligo using the VASI (total body). VASI will be assessed for descriptive purposes only to track disease progression in untreated areas.

Subjects will assess their satisfaction with the results of the study using the Subject Vitiligo Satisfaction scale.

Subjects will assess the impact of vitiligo on their quality of life using the VitiQoL.

Study Medication Administration
At Visit 2, after confirmation of eligibility, an investigational staff member will instruct the subject on the proper study medication application technique and observe the first study medication application. The subject will then start the treatment period (up to 48 weeks) and will apply a thin film of study medication twice-a-day to the areas of the face and neck with vitiligo and at least a ½" margin around the lesions (excluding the area from the bony rim of the orbit to the upper and lower eyelids and mucosal lip areas). If applicable, the subject may apply study medication up to the vermillion border of the lip and to the skin underneath the beard.

Statistical Methods:
Summary descriptive statistics (N, mean, median, SD) by visit will be provided for all safety and efficacy parameters. Primary and secondary efficacy parameters are described below:
The initial analyses will be performed after all subjects complete Visit 10.

Primary Efficacy Parameter
Mean change from baseline in facial depigmentation in the AOI will be quantified using Canfield-2-D photographic image analysis from baseline (Visit 2) compared to (Visit 14).

Secondary Efficacy Parameters:
Mean change from baseline in facial depigmentation will be calculated as the mean change in Facial assessment of the Vitiligo Area and Scoring Index (F-VASI) from baseline (Visit 2) compared to Week 24 (Visit 10) and if applicable, Week 48 (Visit 14). F-VASI is a modification of the validated quantitative assessment scale for vitiligo which evaluates the percentage of vitiligo involvement of the face only.

Mean change from baseline in facial depigmentation in the AOI based on Canfield 2-D Photographic analysis from baseline (Visit 2) compared to Weeks 4, 8, 12, 16, 20, 24, 32, 40, and post-treatment Week 52 (Visits 5-11, and 12, 13, 15).

Mean change from baseline in the Facial assessment of the Vitiligo Area Scoring Index (F-VASI) from baseline (Visit 2) compared to Weeks 4, 8, 12, 16, 20 24, 32, 40, and post-treatment Week 52 (Visits 5-9, 11, 12-13, 15).

Mean change from baseline in the VitiQoL from baseline (Visit 2) compared to Week 12, 16, 20, 24, and 48 (Visits 7-10, 14).

Treatment success based on the subject's assessment of vitiligo on the Vitiligo Noticeability Scale at Week 4, 8, 12, 16, 20, 24, 32, 40, 48 and post-treatment Week 52 (Visits 5-15).

Mean change from baseline in total VASI from baseline (Visit 2) to Week 4, 8, 12, 16, 20 24 and 48 (Visits 5-15) will be assessed for descriptive purposes only to track disease progression in untreated areas.

Safety analyses will include descriptive statistics calculated on the safety parameters using the safety population. The proportion of subjects with treatment-emergent adverse events will be tabulated and presented by treatment and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class. Vital signs and clinically relevant abnormal laboratory results will also be tabulated and presented. Change from baseline (Visit 2) in the Local Tolerability Assessments (LTA) to end of treatment (Visit 10) will be summarized.

Data from all enrolled and treated 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-application 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.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AOI	Area of Interest
AST	Aspartate Aminotransferase
BID, b.i.d.	Twice-daily
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
°C	Degrees Centigrade
CD	Cluster of Differentiation
CMV	Cytomegalovirus
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Clinically Significant
e.g.	for example (Latin; *exempla gratia*)
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
°F	Degrees Fahrenheit
F-VASI	Facial VASI
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
IC_{50}, IC_{90}	Inhibitory concentration
ICF	Informed Consent Form
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
LDH	Lactate dehydrogenase
LTA	Local Tolerability Assessment

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
µM	Micromolar
mL	Milliliter
Mm	Millimeter
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NCS	Not Clinically Significant
nM	Nanomolar
NMSC	Nonmelanoma Skin Cancer
NSV	Non-segmental Vitiligo
OTC	Over-The-Counter
PP	Per-protocol
PRO	Patient-Reported Outcome
PUVA	Psoralen and Ultraviolet A
SAE	Serious Adverse Event
SI	Subject identifier
SN	Subject Number
SOP	Standard Operation Procedure
SVSS	Subject Vitiligo Satisfaction Scale
STAT	Signal Transducer and Activator of Transcription
TEAE	Treatment Emergent Adverse Event
US	United States
UVA	Ultraviolet A
UVB	Ultraviolet B
VASI	Vitiligo Area Scoring Index
VitiQoL	Vitiligo-Specific Quality-of-Life Instrument
VNS	Vitiligo Noticeability Scale
WOCBP	Women of childbearing potential

2. INTRODUCTION

Aclaris Therapeutics, Inc. is developing ATI-50002 Topical Solution for the treatment of non-segmental vitiligo of the face. ATI-50002 is a potent highly selective inhibitor of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3).

2.1. Summary

Overview of Vitiligo

Vitiligo is an autoimmune dermatologic condition characterized by patchy depigmentation of the skin due to loss of cutaneous melanocytes. The affected skin lacks epidermal melanocytes, whereas hair follicles within the lesional skin are often spared, likely due to the immune privilege of the hair follicle. Vitiligo affects 1-2% of the world's population, occurring in all races and both genders (Fitzpatrick T, Mosher D, 2017) (NIAMS 2017). People with vitiligo may be at increased risk of social or psychological distress, sunburn, eye problems, such as inflammation of the iris (iritis), and hearing loss. There is a genetic predisposition to vitiligo. The average age of vitiligo onset is about 20 years, with onset most commonly observed between the ages of 10 and 30 (Fitzpatrick T, Mosher D, 2017).

There are several clinical classifications of vitiligo. Segmental vitiligo presents as one or more macules in a unilateral distribution. All other types of vitiligo are classified as non-segmental vitiligo (NSV), which is most common.

NSV occurs most often on the face, followed by the trunk. Depigmented patches typically evolve over time, vary in size from a few to several centimeters in diameter, are flat areas of normal-feeling skin, and may have a hyperpigmented edge (Ezzedine K, et al. 2012). The edges typically are well-defined but irregular. Body hair typically remains pigmented although hair depigmentation may occur with disease progression. Scalp involvement and other hair bearing areas may appear with patches of white or gray hairs.

Focal vitiligo is characterized by depigmentation in one area, or macule. Other forms of non-segmental vitiligo often produce symmetric patches, sometimes covering large areas. Mucosal vitiligo affects only mucosal membranes. Generalized vitiligo may be acrofacial, in which depigmentation occurs on the distal fingers and periorificial areas, or vulgaris, which is characterized by widely distributed, scattered patches. Universal vitiligo manifests as complete or nearly complete depigmentation, and frequently is associated with multiple endocrinopathy syndrome.

Recent observations have pointed to a role for cellular immunity in the pathogenesis of vitiligo (Wang et al. 2011). Pathogenesis incorporates both intrinsic defects within melanocytes that activates the cellular stress response as well as autoimmune mechanisms that target these cells (Rashighi M, Harris JE, 2017). Despite some advances in explaining the origins of the disorder, current therapies, such as topical corticosteroids, topical immunomodulators and psoralen phototherapy may have serious side effects and limited therapeutic utility. Vitiligo is a disfiguring disease for which current therapies have proven unsatisfactory.

Immunopathology and Pathophysiology of Vitiligo

Over the past two decades, basic and translational research studies have identified several pathogenic pathways that promote vitiligo (Rashighi M, Harris JE, 2017) (Frisoli ML, Harris JE, 2017). These immune pathways prominently involve interferon-γ (IFN-γ) dependent chemokines and $CD8^+$ T-cells. Signaling by Janus kinases (JAKs) is pivotal to these pathogenic pathways (Villarino et al, 2015). As such, inhibition of IFN-γ using JAK inhibitors is a leading candidate for a clinical treatment strategy. Of the JAK sub-types, JAK1 and JAK3 are associated with vitiliginous pathology.

ATI-50002 is a JAK1/3 inhibitor with enzyme IC_{50} activities of 2nM and 36nM against JAK1 and JAK3, respectively (Data on file). At a cellular/physiologic level, ATI-50002 inhibits interferon-γ-induced pSTAT1 activation with an IC_{50} of 38nM (Data on file). The anticipated IC_{90} concentration is approximately 0.4μM. To expect ATI-50002 to inhibit JAK1/3-mediated signaling, a significant excess of the inhibitor must be present in the target tissue. Based upon tissue penetration studies (Franz chamber with human skin) using the 0.46% ATI-50002 formulation, extrapolated ATI-50002 concentrations were found to be in the range of 10-20μM (Data on file). A 10μM concentration should deliver drug to epidermis and dermis at levels anticipated to achieve inhibition of JAK1/3 signaling and inhibit T-cell-mediated melanocyte depletion.

Vitiligo Treatments

Existing treatments include topical and systemic immunosuppressants, phototherapy, and surgical techniques, which together may serve to arrest disease progressions, stabilize depigmented lesions and encourage repigmentation. Depigmentation creams are used in cases where repigmentation therapies are ineffective or greater than 50% BSA is involved. Current treatments for vitiligo are only moderately effective and are both financially and practically burdensome (Frisoli ML, Harris JE, 2017). Topical immunosuppressants, which suppress immune responses in the superficial skin where the immune infiltrate is located are most useful in treating disease that is localized, comprising less than 5% of the body surface area (BSA) (Frisoli ML, Harris JE, 2017). Phototherapy is effective for more widespread disease, or disease that is active and expanding with the appearance of new lesions. Excimer laser is also effective when treating localized disease that is unresponsive to topical therapies, or when a more rapid response is desired. Highly active, vitiligo can be stabilized through oral pulse steroid therapy, which is continued until another therapy (is therapeutic (Frisoli ML, Harris JE, 2017).

Vitiligo responds slowly to treatment, with early signs of repigmentation visible within 2-3 months of initiating treatment, and significant improvement taking up to 6 months to observe (Frisoli ML, Harris JE, 2017). Biomarkers may serve as excellent early indicators of treatment responses. These include both serum biomarkers as well as biomarkers that can be directly measured within lesional skin.

3. STUDY RATIONALE

3.1. Study Rationale

Preclinical and preliminary clinical information suggests that blockade of the IFN-γ pathway may treat vitiligo. Inhibitors of the JAK/STAT pathway, particularly JAK1 and JAK3, are known to downregulate the effects of IFN-γ (through the inhibition at JAK1). Two case reports have demonstrated the potential for compounds that are JAK inhibitors (ruxolitinib and tofacitinib) to repigment areas of vitiligo in patients (Craiglow BG, King BA, 2015) (Harris JE, Rashighi M, Nguyen N, et al, 2016). In a recent study in a small cohort of patients, treatment with topical ruxolitinib for 20 weeks produced significant improvement in facial vitiligo (Rothstein BA et al., 2017). As ATI-50002 is a potent inhibitor at JAK1 and JAK3, it is strongly suggested that ATI-50002 may be effective in the treatment of vitiligo.

This study will evaluate the safety, tolerability and efficacy of ATI-50002 Topical Solution, 0.46% applied twice-daily for up to 48 weeks in subjects with non-segmental facial vitiligo.

4. STUDY OBJECTIVES

4.1. Primary Objective

The primary objective of this study is to assess the safety, tolerability and efficacy of ATI-50002 Topical Solution, 0.46% in subjects with non-segmental facial vitiligo.

4.2. Secondary Objectives

Secondary objectives include:

- Assessment of the subject's satisfaction with repigmentation following treatment using the Subject Vitiligo Satisfaction scale (SVSS).
- Assessment of the impact of vitiligo of the subject's quality of life using the Vitiligo-Specific Quality-of-Life Instrument (VitiQoL).

5. SELECTION AND DISPOSITION OF STUDY POPULATION

5.1. Number of Subjects and Study Sites

A total of 33 subjects will be enrolled at approximately 5 US sites.

5.2. Study Population Characteristics

Male and female subjects, ≥ 18 years old, with a clinical diagnosis of new onset or actively progressing non-segmental facial vitiligo or worsening of existing facial vitiligo within the past 6 months.

5.3. Inclusion Criteria

In order to be eligible for the study, a subject must fulfill all of the following criteria:

1. Subject is a male or female ≥ 18 years of age.
2. Subject has a clinical diagnosis of new onset or actively progressing non-segmental facial vitiligo or worsening of existing facial lesions within the past 6 months. Actively progressing vitiligo is defined as: subject history of a new vitiliginous lesion or objective signs of disease activity (such as: confetti-like depigmentation, trichrome lesions, and the Koebner phenomenon) as assessed by the investigator. Subjects may have non-facial vitiliginous lesions that are unchanged for more than 6 months provided they meet the requirement for active facial lesions.
3. Subject has non-segmental facial vitiligo effecting at least 0.25% total body surface area (TBSA) (excluding: the area from the eyebrows to and including the upper eyelids, the area from the bony rim of the orbit to and including the lower eyelids; mucosal lip areas; beard [if applicable]; and forehead and chin areas covered by the stereotactic positioning device for photography) with at least one area of the face with normal pigmentation. The face is defined as the area from the border of the hairline, not including hair bearing skin (eyebrows and beard, if applicable) to the jawline.
4. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at the baseline visit and must agree to use an approved method of highly effective birth control for the duration of the study and for 30 days after last study medication application.
5. If female, subject who is non-pregnant and non-lactating and not planning a pregnancy during the duration of the study.
6. Subject is in good general health and free of any known disease state or physical condition which, in the opinion of the investigator, would interfere with the study assessments or put the subject at undue risk by study participation.
7. Subject is willing and able to follow all study instructions and to attend all study visits.
8. Subject agrees to refrain from any other treatments for vitiligo from the screening visit through the final follow-up visit. Over the counter (OTC) preparations deemed acceptable by the investigator and camouflage makeups are permitted.
9. Subject is able to comprehend and willing to sign an Informed Consent Form (ICF).
10. Sexually active male subjects with a partner who is a WOCBP, must agree to use a barrier method of contraception from the first application of study medication to at least 30 days after the last dose of study medication.

5.4. Exclusion Criteria

Any subject who meets one or more of the following criteria will not be included in this study:

1. Subject with evidence of poliosis (white hairs) in > 50% of their facial vitiligo lesions.
2. Subject with total facial depigmentation.
3. Subject with significant spontaneous ongoing repigmentation (documented based on the subject's reporting in the last 3 months).
4. Subject who has segmental vitiligo.
5. Subject who has failed phototherapy. Failed phototherapy is defined as failure to achieve satisfactory repigmentation following adequately delivered phototherapy as determined by the investigator.

6. Subject currently has, or has a history of, skin disease (*e.g.*, psoriasis, seborrheic dermatitis, etc.) that, in the opinion of the investigator, would interfere with the study medication application or study assessments.
7. Subject has, or has a history of, severe, progressive or uncontrolled autoimmune, metabolic, renal, hepatic, gastrointestinal, pulmonary, cardiovascular, genitourinary (i.e., renal disease), hematological disease, neurologic or cerebral disorders, infectious disease or coagulation disorders that, in the opinion of the investigator, would interfere with the study assessments or put the subject at undue risk by study participation.
8. Subject currently has a history of, current, or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than a history of adequately treated, 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. Subject currently has evidence of active or latent bacterial (including tuberculosis) or viral infections at the time of enrollment, or a history of incompletely treated or untreated tuberculosis. Subjects who have initiated therapy for latent tuberculosis for at least 2 weeks and agree to continue their therapy through completion may participate.
10. Subject has a history of serious local infection (*e.g.*, cellulitis, abscess) or systemic infection, or history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to the baseline visit. Subjects on an antibiotic for a nonserious, acute local infection must complete the course prior to enrollment into the study.
11. Subject has herpes zoster or cytomegalovirus (CMV) that resolved within 8 weeks prior to Visit 1.
12. Subject has a history of frequent outbreaks of oral Herpes Simplex Virus defined as more than 4 episodes per year.
13. Subjects previously treated with depigmenting agents.
14. Clinically significant laboratory abnormalities at screening that in the opinion of the investigator, would make the subject a poor candidate for the study. Subjects with any other Screening laboratory values meeting the Study Medication Interruption Criteria found in Table 1 must have repeat lab testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2).
15. Subject who has an absolute neutrophil count <1,800/µL, or platelet count < 130,000/µL.
16. Subject unable to comply with the required washout periods:
    1. Use of any biologic, investigational therapy or procedure for vitiligo within 12 weeks or 5 half-lives (whichever is longer) of screening (Visit 1).
    2. Use of laser or light-based vitiligo treatments, including tanning beds, within 8 weeks of screening (Visit 1).
    3. Use of immunomodulating oral or systemic medications (*e.g.*, corticosteroids, methotrexate, cyclosporine) or topical treatments that may affect vitiligo (*e.g.*, corticosteroids, tacrolimus/ pimecrolimus, retinoids) within 4 weeks of screening (Visit 1).
    4. Use of any prior concomitant therapy not listed above that may interfere with the objective of the study as per the discretion of the investigator, including drugs that cause photosensitivity or skin pigmentation (*e.g.*, antibiotics such as tetracyclines, sulfa, tranexamic acid, etc.) within 8 weeks of screening (Visit 1).

5. Subjects who have previously received oral or topical JAK inhibitors.

17. Subject who has participated in any investigational drug or device trial, regardless of indication in which administration of an investigational drug or device occurred within 30 days or 5 half-lives (whichever is longer) of screening (Visit 1). Note that investigational treatment for vitiligo (in any body area) requires a longer washout – see Exclusion criterion #16.1 above.
18. Subjects with a clinically significant abnormal thyroid-stimulating hormone or free T4 at screening. Subjects under treatment with stable thyroid replacement who have a free T4 and TSH within the normal range may participate.
19. Subject has history of sensitivity to any of the ingredients in the study medications.
20. Subject has a history of, or current alcohol or drug abuse within 2 years of study enrollment
21. Screening ECG findings of:
    1. QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose)
    2. Clinically significant heart rate ≤ 45 or Heart Rate ≥ 100 beats/minutes
    3. Rhythm disturbance other than sinus arrhythmia or ectopic supraventricular rhythm (ectopic atrial rhythm)
    4. Conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
    5. Acute or chronic signs of ischemia.
    6. Left Bundle Branch Block
    7. Prior myocardial infarction
22. Positive for HIV, Hepatitis B or C. Subject with serologic evidence of Hepatitis B vaccination (HepB surface Ab without the presence of Hep B sAg) will be allowed to participate.

5.5. Previous and Concomitant Medications and Therapies

At Screening (Visit 1), the Investigator or designee will question the subject to ensure they have not used any excluded therapies (Section 5.6.1). Concomitant therapies are any new or existing therapies received from Screening (Visit 1) until Week 52 (Visit 15). Concomitant therapies include drug (*e.g.*, prescription and over the counter [OTC]), and non-drug (*e.g.*, chiropractic, physical therapy, energy-based) treatments.

5.6. Permitted Concomitant Medications, Therapies and Over the Counter Products (OTC)

All topical products used on the face and neck should be reviewed by the investigator or designee and are permitted, if in the opinion of the investigator or designee will not affect the safety or efficacy of the subject during the study. Subjects will be allowed to take medications not restricted by the protocol as long as they have been on a stable dose prior to study entry. Vitamins, minerals, and dietary supplements are permitted during the 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 therapies such as topical corticosteroids are permitted as long as they are not applied on or near the face and treated areas of the neck. Inhaled or intranasal corticosteroids are allowed in

the study. Male subjects who shave at screening and baseline should maintain the same shaving regimen during the study.

NB-UVB treatments may be administered according to the Standard of Care protocol for the treatment of vitiligo after the subject has completed Visit 9. NB-UVB treatments should be recorded in the source documents and on the Concomitant Therapies Log of the eCRF.

Prior permitted concomitant medications taken within 30 days of beginning treatment with ATI-50002 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 11) will be documented in the subject's source document and eCRF.

5.6.1. Prohibited and/ or Restricted Medications

Use of any medication, herbal supplements or other over-the-counter product known to: have an immunomodulatory effect (e.g. astragalus); or known to affect pigmentation including topical products on the face that could potentially lighten the skin (e.g., hydroquinones, azaleic acid, Kojic acid, mequinol, retinoids, niacinamide, arbutin) or known to temporarily dye the skin on the face and treated areas of the neck (such as dihydroxyacetone or hennas) are prohibited throughout the study. Subjects treated with depigmenting agents such as monobenzyl ether or hydroquinone are excluded from the study.

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

1. Use of any biologic, investigational therapy or procedure for vitiligo within 12 weeks or 5 half-lives (whichever is longer) of screening (Visit 1).
2. Use of laser or light-based vitiligo treatments, including tanning beds, within 8 weeks of screening (Visit 1). Subjects with regular outdoor light exposure not for the intent of tanning may participate. NB-UVB treatments may be administered according to the Standard of Care protocol for the treatment of vitiligo after the subject has completed Visit 9. NB-UVB treatments should be recorded in the source documents and on the Concomitant Therapies Log of the eCRF.
3. Use of immunomodulating oral or systemic medications (*e.g.*, corticosteroids, methotrexate, cyclosporine) or topical treatments that may affect vitiligo (*e.g.*, corticosteroids, tacrolimus/ pimecrolimus, retinoids) within 4 weeks of screening (Visit 1).
4. Use of any prior concomitant therapy not listed above that may interfere with the objective of the study as per the discretion of the investigator, including drugs that cause photosensitivity or skin pigmentation (*e.g.*, antibiotics such as tetracyclines, sulfas, tranexamic acid) within 8 weeks of screening (Visit 1).
5. Subjects who have previously received oral or topical JAK inhibitors.

5.7. Subject Identifier (SI)

The Investigator will assign a unique five-digit subject identifier (SI) to each subject at Screening (Visit 1).

The SI format will be NN-NNN, using leading zeros as appropriate, where:

- The first 2 digits are the investigational center site number assigned by Aclaris.
- The final 3 digits are the subject number (SN), assigned in ascending numerical order by the Investigator or designee, without omitting or repeating any number, starting with 001.

For example, the SI for the twenty-third subject that signs an informed consent form at site number 01 would be 01-023. The subject will be identified using the SI in all study documentation for the duration of the study.

5.8. Replacement Subjects

Subjects who are receive study medication at Visit 2 and do not complete the study will not be replaced.

5.9. 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 9.2.4 for study medication discontinuation criteria).

In case of premature discontinuation of study participation, all efforts will be made to perform all Visit 10 (Week 24) assessments or if continuing for the additional 24 weeks, Visit 15 (Week 52). 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.

5.10. Study Termination

This study may be terminated prematurely in whole or in part due to a change in the benefit/risk profile for ATI-50002 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 enrollment is sufficiently slow to prevent the completion of the study in an acceptable timeframe, or if ATI-50002 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.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This Phase 2, multicenter, open label study is designed to evaluate the safety, tolerability and efficacy of ATI-50002 Topical Solution in subjects with facial non-segmental vitiligo. Subjects will be required to have a clinical diagnosis of new onset or actively progressing non-segmental facial vitiligo involving at least 0.25% TBSA (excluding upper and lower eyelids, mucosal lip areas, beard [if applicable]; and forehead and chin areas covered by the stereotactic positioning device for photography) with at least one area of the face with normal pigmentation. The face is defined as the area from the border of the hairline, not including hair bearing skin to the jawline. Thirty-three subjects will receive ATI-50002 Topical Solution, 0.46%, BID for up to 48 weeks.

During the screening period, subjects will be assessed for eligibility to receive study medication. Eligible subjects will apply study medication to the vitiliginous areas of the face and neck including ½" margin around these areas (excluding the upper and lower eyelids and mucosal areas of the lips) twice-a-day for up to 48 weeks. Assessment of response to treatment will be performed using the Canfield 2-D Photographic image analysis, Facial VASI, Vitiligo Noticeability Scale, VitiQoL, and Subject Vitiligo Satisfaction Scale. These assessments will occur as specified in the Schedule of Assessments. Subjects will be seen at up to 15 study visits, including up to 48 weeks of active treatment followed by 4 weeks of post treatment follow-up.

Safety and tolerability will be evaluated throughout the study by assessment of electro-cardiograms (ECG), clinical laboratory tests, adverse events including local site reactions and vital signs.

6.2. STUDY PROCEDURES

The investigator, a designated and appropriately trained staff member, independent evaluator(s), or the subject, will perform the study assessments according to the schedule of assessments (Section 6.3). 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.

6.3. Schedule of Assessments

	Screening	Baseline	Treatment								Post-Treatment
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Week		0	1	2	4	8	12	16	20	24	28
Treatment Day	-28 to 0	1	8	15	29	57	85	113	141	169	197
Treatment Window(days)	N/A	N/A	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 14
Informed consent[1]	X										
Inclusion/exclusion criteria	X	X									
Physical exam[2]	X										X
Demographics & medical history	X										
Vitiligo History	X										
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X
Clinical CBC, Chemistry, Virology, Serum Pregnancy, Urinalysis[4]	X[4]	X	X		X	X	X	X	X	X	X
Urine pregnancy test[5]		X			X	X	X	X	X	X	X
ECG	X	X	X		X	X	X	X	X	X	X
Facial BSA	X	X									
Facial Vitiligo AreaScoring Index (F-VASI)[6]		X Pre-dose			X	X	X	X	X	X	X
Total body VASI	X	X Pre-dose					X			X	
Canfield 2D Photography[7]		X			X	X	X	X	X	X	X
Vitiligo Noticeability Scale (VNS)					X	X	X	X	X	X	X
Subject Vitiligo Satisfaction Scale[8] (SVSS)							X	X	X	X	X
VitiQoL		X					X	X	X	X	X
Local Tolerability Assessment (LTA) **Investigator**		X Pre and post dose	X	X	X	X	X	X	X	X	X
Local Tolerability Assessment (LTA) **Subject**		X Pre and post dose	X	X	X	X	X	X	X	X	X
Subject Eligibility Confirmation		X									
Subject instructions[9]		X	X	X	X	X	X	X	X		
Dispense study medication [10]		X	X	X	X	X	X	X	X		
Collect, medication, assess compliance [10]			X	X	X	X	X	X	X	X	
In office study medication application[11]		X									
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X

	Screening	Baseline	Treatment								Post-Treatment
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Week		0	1	2	4	8	12	16	20	24	28
Treatment Day	-28 to 0	1	8	15	29	57	85	113	141	169	197
Treatment Window(days)	N/A	N/A	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 14
For Subjects Continuing to Visit 12-15:											
Revised ICF for Visits [12-15]										X[12]	X[12, 14]
Subject instructions[9]										X	X[14]
Dispense study medication[10]										X[13]	X[13,14]

[1]A written, signed ICF must be obtained from each subject prior to performing any study related procedure (*i.e.*, prior to performing vital signs, standardized photography, clinical laboratory sampling or urine pregnancy tests).

[2] A physical exam includes: general appearance, examination of head, eyes, ears, nose and throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, lymphatic and skin assessment.

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

[4] Clinical laboratory sampling include: CBC, Chemistry with lipids, and Urinalysis. Quantiferon Gold, HIV, Hepatitis B and C, TSH, T3, Free T4 and Serum Pregnancy should be done at screening visit only. Subjects with any Screening laboratory values meeting the Study Medication Interruption Criteria found in Table 1 must have repeat lab testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2).

[5] UPT must be performed in WOCBP prior application of study medication at Baseline (Visit 2) and must be negative for the subject to continue in the study. UPTs in WOCBP must also be obtained at Visit 5, 6, 7, 8, 9, 10, and 11. WOCBP must have a negative serum pregnancy test at Screening (Visit 1) and a negative UPT at baseline (Visit 2) prior to application of study medication.

[6] F-VASI must be determined at Baseline (Visit 2) and Visits 5-11. During the baseline visit, F-VASI should be determined prior to application of study medication.

[7] Canfield photography will be performed at Prior to dosing at Baseline (Visit 2) and at Visits 5, 6, 7, 8, 9, 10 and 11.

[8] Subjects will complete the Subject Vitiligo Satisfaction Scale at Visits, 7, 8, 9, and 10 and at post-treatment Visit 11.

[9] The study staff must instruct the subject to apply study medication according to the instructions in APPENDIX 1.

[10] The study staff must weigh the study medication bottle(s) with cap prior to dispensing to the subject and after the study medication bottles are returned to the investigational site. Staff should review the usage based on the weight of the bottle and counsel the subject as necessary.

[11] At Baseline (Visit 2), the first application of study medication should be performed by the subject under the supervision of the study staff and the subject should be observed for 20 minutes after the initial application.

[12]A written, signed ICF with the additional visits (Visits 12 -15) must be obtained from each subject prior to performing any Visit 12 study related procedure.

[13] For subjects who consent to continue for additional study visits, Visit 12-15, study medication should be dispensed.

[14] If a subject completes Visit 10 prior to implementation of Amendment 3, they may return for Visit 11 to sign consent, receive additional study medication and have the other tests performed as detailed in the Schedule of Assessments.

Procedures	**Open-Label Treatment**			**Post-Treatment**
	Visit 12	**Visit 13**	**Visit 14**	**Visit 15**
Week	**32**	**40**	**48**	**52**
Treatment Day	**225**	**281**	**337**	**365**
Treatment Window(days)	**± 7**	**± 7**	**± 7**	**± 7**
Physical exam[2]				X
Vital signs[3]	X	X	X	X
Clinical CBC, Chemistry, Urinalysis[4]	X	X	X	X
Urine pregnancy test[5]	X	X	X	X
ECG				X
Facial Vitiligo Area Scoring Index (F-VASI)[6]	X	X	X	X
Total body VASI			X	
Canfield 2D Photography[7]	X	X	X	X
Vitiligo Noticeability Scale (VNS)	X	X	X	X
Subject Vitiligo Satisfaction Scale[8] (SVSS)	X	X	X	
VitiQoL			X	
Subject instructions[9]	X	X	X	
Dispense study medication [10]	X	X		
Collect, medication, assess compliance [10]	X	X	X	
Concomitant therapies	X	X	X	X
Adverse events	X	X	X	X

6.4. Study Visits Description and Procedures

A written, signed informed consent form (ICF) must be obtained from each subject prior to performing any study related procedure (*i.e.*, physical examination, clinical laboratory sampling, urine pregnancy test, ECG, or photography).

6.4.1. Visit 1/ Screening (Day -28 to 0)

At this visit, the investigator or designee will:

1. Review and explain the nature of the study to the subject, obtain the subject's signature on the appropriate approved ICF and provide a signed and dated copy to the subject.
2. Assign a SI to the subject.
3. Confirm the subject meets all inclusion criteria and no exclusion criteria.
4. Collect demographic and medical history information (including vitiligo history).
5. Collect concomitant therapies information.
6. Perform a physical examination.
7. Measure vital signs.
8. Conduct an ECG.
9. Collect blood samples for clinical laboratory tests including serum pregnancy test.
10. Quantify the facial vitiligo BSA involvement. The subject must have non-segmental facial vitiligo involving at least 0.25% TBSA (excluding the upper and lower eyelids, mucosal lip areas, and forehead and chin areas covered by the stereotactic positioning device) with at least one facial area with normal pigmentation.
11. Perform the Vitiligo Area & Scoring Index (VASI).
12. Review the study instructions with the subject.
13. Schedule Visit 2 as appropriate.

6.4.2. Visit 2 (Day 1) / Baseline

This visit must occur within 28 days after Visit 1.

Subsequent study visit dates must be scheduled based on the date of Visit 2.

This visit may not occur before the investigator reviews the Visit 1 clinical laboratory test results for all the measured analytes. For the subject to continue in the study all clinical laboratory test results must be within the range of normal for the laboratory or, if there are any abnormal results, they must be defined as not clinically significant (NCS) by the investigator. Subjects with any Screening laboratory values meeting the Study Medication Interruption Criteria found in Table 1 must have repeat lab testing performed with results meeting the minimum criteria for resumption in order to initiate treatment at Baseline (Visit 2). For WOCBP, the serum pregnancy test from Visit 1 must be negative for a subject to continue in the study.

The investigator must review the evaluator's interpretation of each subject's Visit 1 ECG prior to Baseline/Visit 2 and comment on the clinical significance of any result that is defined by the evaluator as abnormal. The subject must not continue in the study and apply study medication, if the Visit 1 ECG meets any of the Criteria in Exclusion Criterion 21.

At this visit, the investigator or designee will perform the following procedures PRIOR TO APPLICATION OF STUDY MEDICATION:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report changes on the appropriate form.
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form.
3. Confirm the subject continues to comply with all study requirements, is eligible to continue in the study and has followed all study instructions.
4. Confirm the subject meets all inclusion criteria and no exclusion criteria.
5. Confirm Facial vitiligo TBSA is at least 0.25% with at least one area of normal pigmentation on the face.
6. Measure vital signs.
7. Perform a urine pregnancy test for WOCBP; results must be negative for the subject to apply the first dose of study medication.
8. Quantify the facial vitiligo BSA involvement. The subject must have non-segmental facial vitiligo involving at least 0.25% TBSA (excluding: the area from the eyebrows to and including the upper eyelids, the area from the bony rim of the orbit to and including the lower eyelids; mucosal lip areas; and forehead and chin areas covered by the stereotactic positioning device) with at least one facial area with normal pigmentation.
9. Perform the Facial Vitiligo Area Scoring Index (F-VASI).
10. Perform the total body VASI.
11. Confirm subject is eligible to apply the first dose of study medication.
12. Have the subject perform a pre-application Local Tolerability Assessment (LTA).
13. The Investigator or designee will perform a pre-application LTA.
14. Collect blood samples for clinical laboratory tests.
15. Take standardized photographs.
16. Conduct an ECG.
17. Have the subject complete the VitiQoL.
18. Discharge from the study subjects who are not eligible to apply the first dose of study medication.

For subjects who are eligible to apply the first dose of study medication the investigator or designee will perform the following procedures:

1. Dispense study medication to the subject.
2. An investigational staff member will instruct the subject on the proper study medication application technique and will observe the subject's first study medication application.
3. A staff member will monitor the subject for at least 20 minutes after the first study medication application completion time to detect any adverse events.
4. Have the subject perform a post-application LTA 10 (±4) minutes after the application completion time.
5. The investigator or designee will perform a post-application LTA 20 (±4) minutes after the application completion time.
6. Review the study instructions with the subject.
7. Schedule Visit 3 as appropriate.

6.4.3. Visit 3-9 (Weeks 1, 2, 4, 8, 12, 16 and 20) These visits must occur on the following weeks after Visit 2:

- Visit 3, 1 week (±4 days)
- Visit 4, 2 weeks (±4 days)
- Visit 5, 4 weeks (±4 days)
- Visit 6, 8 weeks (±4 days)
- Visit 7, 12 weeks (±4 days)
- Visit 8, 16 weeks (±4 days)
- Visit 9, 20 weeks (±4 days).

At these visits, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form.
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form.
3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions.
4. Measure vital signs.
5. **AT VISIT 3, 5-9, ONLY** collect blood samples for clinical laboratory tests.
6. **AT VISIT 3, 5-9, ONLY** conduct an ECG.
7. **AT VISIT 3-9,** Have the subject perform an LTA.
8. **AT VISIT 3-9,** The investigator or designee will perform an LTA.
9. **AT VISITS 5-9 ONLY**, perform the F-VASI
10. **AT VISIT 7 ONLY,** perform the total body VASI.
11. **AT VISIT 5-9 ONLY**, have the subject complete the Vitiligo Noticeability Scale (VNS).
12. **AT VISIT 7-9 ONLY**, have the subject complete the VitiQoL.
13. **AT VISITS 5-9**, **ONLY** perform a urine pregnancy test for WOCBP; results must be negative for the subject to continue in the study.
14. **AT VISIT 7-9 ONLY**, have the subject complete the Subject Vitiligo Satisfaction Scale (SVSS).
15. **AT VISITS 5-9 ONLY**, take standardized photographs.
16. Dispense and/or collect study medication as appropriate.
17. Review the study instructions with the subject.
18. Schedule the next visit as appropriate.

6.4.4. Visit 10 (Week 24)

This visit must occur 24 weeks (±4 days) after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form.
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form.
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions.

4. Measure vital signs.
5. Conduct an ECG.
6. Collect blood samples for clinical laboratory tests.
7. Perform a urine pregnancy test for WOCBP.
8. Have the subject perform an LTA.
9. The investigator will perform an LTA.
10. Perform the F-VASI.
11. Perform the total body VASI.
12. Have the subject complete the VNS.
13. Have the subject complete the SVSS.
14. Have the subject complete the VitiQoL.
15. Collect all study medication.
16. Take standardized photographs.
17. Review the study instructions with the subject.
18. For subjects who agree to continue to participate in additional study visits (Visits 12-15):
    a. Obtain consent for additional study visits, Visit 12-15:
    b. Dispense study medication.
    c. Review study instructions with the subject.
19. Schedule Visit 12. For subjects who do not consent to continue with additional study visits (Visit 12-15), schedule the next visit, Visit 11.

6.4.5. Visit 11 (Week 28)

For subjects who agree to continue with additional visits (Visit 12-15) at Visit 10, Visit 11 should be marked as not done, unless Visit 11 is when the subject consents to the additional Visits 12-15.

This visit must occur 28 weeks (±14 days) after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study requirements and has followed all study instructions
4. Conduct a physical examination
5. Measure vital signs
6. Conduct an ECG
7. Collect blood samples for clinical laboratory tests
8. Perform a urine pregnancy test for WOCBP
9. Have the subject perform an LTA
10. The investigator or designee will perform an LTA
11. The investigator or designee will perform the F-VASI
12. Have the subject complete the VNS
13. Have the subject complete the SVSS
14. Have the subject complete the VitiQoL
15. Take standardized photographs

16. Discharge the subject from the study, unless the subject agrees to continue with additional study visits (Visit12-15)**.**
17. For subjects who agree to continue with additional study visits (Visits 12-15).
    a. Obtain consent for additional study visits, Visit 12-15.
    b. Dispense study medication.
    c. Review study instructions with the subject.
18. Schedule Visit 12, 32 weeks from Visit 2.

6.4.6. Visit 12 (Week 32)

This visit must occur 32 weeks (± 7 days) of Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form.
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form.
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions.
4. Measure vital signs.
5. Collect blood samples for clinical laboratory tests.
6. Perform a urine pregnancy test for WOCBP.
7. Perform the F-VASI.
8. Have the subject complete the VNS.
9. Have the subject complete the SVSS.
10. Dispense and collect study medication.
11. Take standardized photographs.
12. Review the study instructions with the subject.
13. Schedule the Visit 13 40 weeks ± 7 days from Visit 2.

6.4.7. Visit 13 (Week 40)

This visit must occur 40 weeks (± 7 days) of Visit 2.
At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form.
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form.
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions.
4. Measure vital signs.
5. Collect blood samples for clinical laboratory tests.
6. Perform a urine pregnancy test for WOCBP.
7. Perform the F-VASI.
8. Have the subject complete the VNS.
9. Have the subject complete the SVSS.

10. Dispense and collect study medication.
11. Take standardized photographs.
12. Review the study instructions with the subject.
13. Schedule the Visit 14 48 weeks ± 7 days from Visit 2.

6.4.8. Visit 14 (Week 48)

This visit must occur 48 weeks (± 7 days) of Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form.
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form.
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions.
4. Measure vital signs.
5. Collect blood samples for clinical laboratory tests.
6. Perform a urine pregnancy test for WOCBP.
7. Perform the F-VASI.
8. Have the subject complete the VNS.
9. Have the subject complete the SVSS.
10. Collect study medication.
11. Have the subject complete the VitiQoL.
12. Take standardized photographs.
13. Review the study instructions with the subject.
14. Schedule the Visit 15 52 weeks ± 7 days from Visit 14.

6.4.9. Visit 15 (Week 52)

This visit must occur 52 weeks (± 7 days) of Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form.
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form.
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions.
4. Measure vital signs.
5. Conduct an ECG.
6. Perform a physical examination.
7. Collect blood samples for clinical laboratory tests.
8. Perform a urine pregnancy test for WOCBP.
9. Perform the F-VASI.

10. Perform the total body VASI.
11. Have the subject complete the VNS.
12. Take standardized photographs.
13. Discharge the subject from the study.

7. STUDY TREATMENT

7.1. Investigational Study Medication

The study medication for this study is ATI-50002 Topical Solution, 0.46%. The study medication is 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.

STUDY MEDICATION INFORMATION	
Study medication name	**ATI-50002**
Dosage Strength	0.46%
Manufacturer	PMRS, Inc., Horsham, PA
Pharmaceutical Form	Topical Solution
Container	Amber Glass Bottle, 30 mL with screw cap (20mL fill)
	Amber Glass Bottle, 120 mL with screw cap (100mL fill)
Storage Conditions	59°F to 77°F (15°C to 25°C)
Dose regimen	
Route	Topical
Frequency	Twice-daily
Duration of administration	Up to 48 weeks
Other supplies	Disposable, single-use applicators will be provided.

7.2. Subject Study Medication Assignment

At Baseline (Visit 2), an investigational center staff member will assign study medication to eligible subjects by selecting an appropriate Subject Kit. The staff member must select Subject Kits in chronological sequence and in an ascending numerical order starting with the lowest available Subject Kit number. No Subject Kit number may be omitted or reused.

The investigational staff member will enter the subject identifier, subject initials, and date dispensed on the Subject Kit label, and record the Subject Kit number in the subject's eCRF.

The site will dispense study medication bottles provided in the individual Subject Kits first and then dispense the individual 120 ml (100 ml fill) bottles to the subject, as needed.

7.3. Application of Study Medication

Subjects will be instructed to apply a thin film of ATI-50002 Topical Solution, up to 2-mL, twice-daily; once in the morning and approximately 8-12 hours later to the vitiliginous areas of the face and neck including a ½" inch margin around these areas (excluding: the area from the bony rim of the orbit to and including the upper and lower eyelids; and mucosal lip areas) following the instructions in APPENDIX 1. 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. The disposable applicators should be disposed of at the subject's home out of the reach of children.

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 the Baseline visit (Visit 2), 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 1.
- Observe the subject's first study medication application to ensure proper coverage and monitor the subject for at least 20 minutes.
- After the first application, the study staff should weigh the study bottle with the cap.
- Dispense the study medication to the subject.
- Provide feedback on the application procedure, if needed.

If the subject develops a new patch of vitiligo on the face or neck during the study, the investigator or designee will instruct the subject to treat the new area of facial vitiligo. The investigator must incorporate the new area of facial vitiligo, once it is clinically evident, into the F-VASI assessment. New areas of vitiligo on the face or other body areas that develop during the study are not considered adverse events.

7.4. Study Medication Weights

A study staff member will weigh the study medication bottles with the cap prior to dispensing to the subject and after collection of the study medication bottles during study treatment visits. The weights should be recorded in the source documents. Bottles that are not dispensed to the subject do not need to be weighed.

7.5. Treatment Compliance

The investigator or designee will be responsible for monitoring subject compliance through questioning the subject, documenting missed doses, if any, weighing the bottle before dispensing and after return and visual inspection of the quantity in the study medication bottles (used and unused). Study staff will counsel the subjects, as required to make sure subjects are compliant with study medication applications. The subject will be given a calendar to complete to confirm administration of twice-daily doses.

7.6. Dose Modification

If the subject experiences application site AE(s), study medication may be stopped for up to a total of 3 days or the frequency of study medication application may be reduced from twice-daily to once-daily for up to a total of 6 days. Dose interruptions must be documented in the source document and eCRF. Dose modifications greater than these must be reviewed and approved by the Medical Monitor. Refer to Section 9.2.4 for Study Medication Interruption or Discontinuation due to related SAEs or specific abnormal laboratory values.

7.7. Study Medication Accountability

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 shipment documentation provided. One copy of this document will be returned to Aclaris Therapeutics, Inc. (or designee) and one copy 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 returned to Aclaris Therapeutics, Inc. or designee for disposal.

7.8. Other Study Supplies

Aclaris Therapeutics, Inc. or a third party will provide:

- Supplies and instructions for collecting, labeling, shipping and result reporting for the clinical laboratory tests and urine pregnancy tests
- A scale to weigh the study medication bottles.
- Equipment, supplies, and training for taking standardized photographs
- Equipment, supplies, and training for performing standardized ECGs
- Study medication applicators
- An insulated lunch box to transport study medication

7.9. Blinding

The study is an open-label study.

7.10. Study Medication Packaging, Labeling, Storage and Security

The study medication must be used by the study subjects only. Investigational site staff will explain the application of the study medication to subjects.

Study medication will be provided by Aclaris Therapeutics, Inc. and labeled according to regulations. 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 original glass bottle (in the carton provided) at room temperature, away from heat, moisture, direct light, and to keep it from freezing and out of the reach of children.

The study medication will be supplied in amber glass 30-mL bottles with a 20-mL fill. Disposable applicators will be provided.

One Subject Kit box will contain 24 bottles, in individual boxes and disposable applicators. Each kit will be labeled with a single-panel label. Each box and bottle will be labeled with a single panel label.

Additional supplies will be packaged in amber glass 120 ml (100 mL fill) bottles in individual cartons. Each carton and bottle will be numbered with a unique number and labeled with a single-panel label.

8. STUDY ASSESSMENTS

The investigator, a designated and appropriately trained staff member (*e.g.*, subinvestigator) or the subject will perform the study assessments according to the schedules noted below.

The same individual 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 the study should perform the assessments.

Similar lighting conditions and subject positioning should be used for all evaluations for a given subject. A Wood's lamp should be used to assess the subject's vitiliginous lesions.

8.1. Assessments of Efficacy

8.1.1. Canfield 2D Digital Facial Image Analysis

A qualified investigational staff member will take 18 photographs (5 lighting modalities x 3 views [left, front, right]) of the face at baseline and then monthly during the study. Each imaging session includes a sequence of images including the following lighting/capture modalities:

- Standard 1 (default settings) – General purpose white light photograph, the typical "clinical" photo. Provides balanced cross lighting for good subjective evaluation of most skin features.
- Standard 2 (default settings) – 'Diffuse light'. Provides even, white light across the entire image with a minimum of highlight and shadow. Ideal for many quantitative image analysis applications.
- Cross Polarized (default settings) – Polarized light sources with a Perpendicular polarizer over the camera lens. Filters out surface reflections for superior visualization of sub-surface detail (vascular features, erythema, pigment, etc.)

- UV Fluorescence - NF (default settings) – UV filters (365nm band pass) over powerful strobes captured through an un-attenuated lens. The Fluorescence photo is geared toward enhancing the visibility of pigment features that absorb UV light. Fluorescing Porphyrin details are also visible.
- Parallel Polarized (default settings) – Polarized light sources with a Parallel polarizer over the camera lens. Passes only surface reflections for superior visualization of topographical data (wrinkles, fine lines, pores, etc.)

Equipment, supplies, training and detailed instructions for obtaining and managing photographs will be provided to the investigational center prior to the initiation of subject enrollment.

Canfield Scientific will conduct image analysis. The obtained cross-polarized image will be transformed using Canfield's RBX technique to separate melanin (Brown image) from hemoglobin (Red image). A segmentation algorithm detects hyperpigmentation (pigmented areas with concentration higher than normal skin concentration) and depigmentation (pigmented areas with concentration lower than normal skin concentration) within the areas of interest (AOI) from the RBX Brown images. Area of detected pigmentation and intensity measurements can be reported by the algorithm after segmentation. The measurement will be the ratio of the detected area of pigmentation and the AOI. The primary endpoint will be based on the quantification of depigmentation in the AOI over time.

Area of Interest
The AOI includes approximately 90% of the total facial surface area and is defined as the area from the border of the hairline to the jawline. Hair bearing areas such as the eyebrows and the areas of the forehead and chin covered by the stereotactic positioning device for photographs are not included in the AOI. Refer to APPENDIX 6 for a diagram of the AOI.

8.1.2. Facial Vitiligo Area Scoring Index (F-VASI) and Facial Total Body Surface Area (TBSA)

The F-VASI is an assessment of the subject's facial vitiligo modified from the VASI for the face only. The investigator or designee will assess the face using a Wood's lamp to assist in the identification of the vitiliginous lesions and then calculate the F-VASI score based on the descriptor that best matches the presentation of the subject at each individual visit: Baseline (Visit 2) and Visits 5, 6, 7, 8, 9, 10,11 (if applicable) and if continuing for 24 additional weeks of treatment, Visit 12-15. The investigator should not refer to any other visits assessments when performing the F-VASI.

The percentage of vitiligo involvement for the face is calculated using the palmar method. The palmar method uses the palmar surface area of the investigator's hand as an estimation guide and defines the surface of the hand including fingers to be 1.0% of the total body surface area.

At screening and baseline, the **Facial TBSA** will be calculated and must be at least 0.25% (excluding: the area from the eyebrows to and including the upper eyelids; the area from the bony rim of the orbit to and including the lower eyelids; mucosal lip areas, and the area of the chin and forehead covered by stereotactic photographic device) and include at least one area of normal pigmentation. The face is then clinically evaluated by visual assessment for the pattern

of skin depigmentation using a visual scale. The publication by Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, and Lui H. 2004 will be provided to the investigators to depict the pattern of depigmentation as illustrated in descriptive patient photographs.

Facial VASI = % BSA x residual depigmentation

- **BSA** - used as a guide to estimate % of vitiligo involvement of the face
- **Extent of residual depigmentation** is expressed by the following percentages:
  - 0
  - 10% - only specks of depigmentation are present
  - 25% - the pigmented area exceeds the depigmented area
  - 50% - the depigmented and pigmented areas are equal
  - 75% - the depigmented area exceeds the pigmented area
  - 90% - specks of pigment are present
  - 100% - no pigment is present

8.1.3. Vitiligo Noticeability Scale (VNS)

The VNS is the subject's assessment of the noticeability of facial vitiligo determined at Visits 5, 6, 7, 8, 9, 10, 11 (if applicable) and if continuing for an additional 24 weeks of treatment, Visit 12-15. The subject will complete the following question:

Compared to before treatment, how noticeable is the vitiligo now?

- More noticeable (1)
- As noticeable (2)
- Slightly less noticeable (3)
- A lot less noticeable (4)
- No longer noticeable (5)

Treatment success will be defined as follows: VNS score of 1 or 2 = treatment not successful, VNS score of 3 = treatment partially successful, or VNS score of 4 or 5 = treatment successful.

8.1.4. Vitiligo Area Scoring Index (VASI)

The VASI will be assessed by the investigator or designee to track the total body vitiligo status throughout the study at screening (Visit 1), baseline (Visit 2), Week 12 (Visit 7), Week 24 (Visit 10), and Week 48 (Visit 14). The body is divided into the following 6 separate and mutually exclusive sites: head/neck, hands, upper extremities (excluding hands), trunk, lower extremities (excluding feet), and feet. The investigator or designee will assess each of the 6 body sites using a Wood's lamp to assist in the identification of the vitiliginous lesions.

The percentage of vitiligo involvement for each body region is calculated using the palmar method. The palmar method uses the palmar surface area of the investigator or designee's hand as an estimation guide and defines the surface of the evaluator's hand including fingers to be 1.0% of the total body surface area. Each of the 6 body sites is then clinically evaluated by visual assessment for the pattern of skin depigmentation using a visual scale. The publication by Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, and Lui H. 2004 will be provided to the investigators to depict the pattern of depigmentation as illustrated in descriptive patient photographs.

Total body VASI = Sum of all the values from the body sites (in Hand units) x (Residual depigmentation)

- **Hand unit** - One hand unit is approximately 1% BSA – used as a guide to estimate % of vitiligo involvement in each body area. (Body is divided into 6 areas)
- **Extent of residual depigmentation** is expressed by the following percentages:
  - 0
  - 10% - only specks of depigmentation are present
  - 25% - the pigmented area exceeds the depigmented area
  - 50% - the depigmented and pigmented areas are equal
  - 75% - the depigmented area exceeds the pigmented area
  - 90% - specks of pigment are present
  - 100% - no pigment is present

8.1.5. Subject Vitiligo Satisfaction Scale (SVSS)

The SVSS is the subject's assessment of her/his satisfaction with the status of the overall repigmentation of the treated areas of the face with vitiligo, at a particular point in time (See APPENDIX 5). The subject should NOT refer to any other assessments to assist with these assessments.

At Visits 7-10, and if applicable, Visit 11 and Visits 12-14, the subject will assess the treatment areas of the face with vitiligo using the scale below and report the one integer that best describes her/his satisfaction with the status of the repigmentation of the treated areas of his or her face.

Please report the number that best describes how satisfied you are with the results of the study medication applications on the treated areas of the face.

How satisfied or dissatisfied are you with the appearance of your facial vitiligo as a result of the study medication applications?

Subject's Vitiligo Satisfaction Scale

Grade	Descriptor
1	Extremely satisfied
2	Moderately satisfied
3	A little satisfied
4	Neither satisfied or dissatisfied
5	A little dissatisfied
6	Moderately dissatisfied
7	Extremely dissatisfied

An investigational staff member will educate the subject on the SVSS scale before each evaluation and direct the subject to assess the treated areas of the face. The staff member should not influence the subject's assessment.

The study staff member will report the SVSS grade the subject indicates in the source document. Both the subject and the study staff member must sign/initial the source document to indicate the subject performed the SVSS as instructed.

8.1.6. Vitiligo-Specific Quality of Life Instrument (VitiQoL)

The subject will complete the VitiQoL questionnaire at baseline (Visit 2), Visits 7, 8, 9, 10, Visit 11 (if applicable) and Visit 14 (Week 48) (see Appendix 4). The study staff should instruct the subject to answer the questions based on the impact of vitiligo over the past month. The response to each question will be scored on a 0 (not at all) to 6 (all of the time) continuous bipolar scale.

8.2. Assessment of Safety

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

8.2.1. ECGs

Standard 12-lead ECGs will be performed by a qualified staff member at Screening (Visit 1), Baseline (Visit 2), Day 8 (Visit 3), Visits 5-10, Visit 11 (if applicable) and if continuing for the additional visits, Visit 15. The ECGs must be obtained using a standard 12-lead ECG with a 10mm/mV amplitude, at 25mm/sec and a 5-10-second duration. To ensure a steady heart rate the subject must rest quietly in the supine position for at least 5 minutes prior to performing the ECG.

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

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

Any abnormalities that are, in the opinion of the investigator, clinically significant, must be reported as history if found prior to the start of the first study medication application or as an AE if found after the start of the first study medication application (see Section 9.1.1).

8.2.2. Physical Examination

The investigator or designee will perform a physical examination for all body systems (general appearance, examination of head, eyes, ears, nose and throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, lymphatic and skin assessment) at Screening (Visit 1) and end of study Week 28 (Visit 11) or if continuing for the additional visits, Week 52 (Visit 15).

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

8.2.3. 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 history if found prior to the first study medication application, or as an AE if found after the first study medication application begins.

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.

8.2.4. Clinical Laboratory Assessments

At the visits detailed in the Schedule of Assessments, a qualified staff member will collect non-fasting samples for clinical laboratory analysis. Approximately 18.5 ml of blood will be collected at Visit 1 and approximately 10.5 ml for each sample detailed in the Schedule of Assessments a total of approximately 113 ml per subject for Visit 1-11, approximately 42 ml for Visits 12-15, and up to approximately 155 ml for the entire study. Samples will be sent to a central laboratory for analysis. Refer to the study specific laboratory manual for handling and shipping instructions. The following tests will be conducted:

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

Total protein
Uric acid
Total cholesterol, LDL, HDL,
Triglycerides
CPK
Screening Only
Virology (HepB, HCV, HIV)
Quantiferon Gold
T3/T4, TSH
Serum pregnancy

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 for each subject prior to 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.

8.2.5. Local Tolerability Assessment (LTA)

The LTA is the investigator's assessment of the average overall severity of signs and the subject's assessment of the average overall severity of symptoms associated with an application site reaction on the treated areas of the face. The investigator and subject must NOT refer to any other evaluation to assist with these assessments. This is not a comparison with the assessment at any other time point.

At Visits 2-11, the investigator and the subject will evaluate the LTA signs and the LTA symptoms respectively.

LTA Signs (Investigator or designee assessment):
- Erythema
- Edema
- Scaling/dryness

LTA symptoms (Subject assessment):
- Stinging
- Burning

The investigator will assess the LTA signs as follows:
- At Visit 2:
  - Prior to the first study medication application
  - 20 (±4) minutes after the application completion time.
- At Visits 3-11.

The subject will assess the LTA symptoms as follows:

- At Visit 2:
  - Prior to the first study medication application report the LTA for each symptom over the previous 24 hours
  - 10 (±4) minutes after the application completion time report the average severity since the application completion time.
- At Visits 3-11:
  - Report the average LTA for each symptom over the previous 24 hours.

The investigator, for the signs, should report the one integer that best describes the average overall severity on the treatment areas of the face using the scales below:

Local Tolerability Assessment – Erythema

Grade	Descriptor
0	Clear: No erythema present
1	Mild: Slight erythema
2	Moderate: Definite erythema
3	Severe: Marked, fiery erythema

Local Tolerability Assessment – Edema

Grade	Descriptor
0	Clear: No edema present
1	Mild: Slight edema
2	Moderate: Definite edema
3	Severe: Marked edema

Local Tolerability Assessment – Dryness/Scaling

Grade	Descriptor
0	Clear: No signs of dryness or scaling
1	Mild: Slight roughness (may be more easily felt than seen), barely perceptible scaling
2	Moderate: Moderate roughness, definite scaling
3	Severe: Marked roughness, heavy scaling

The subject, for the symptoms, should report the one integer that best describes the average overall severity on the treatment areas of the face using the scales below:

Local Tolerability Assessment – Itching

Grade	Descriptor
0	Clear: No itching
1	Mild: Slight itching, not bothersome

2	Moderate: Definite itching, slightly bothersome
3	Severe: Intense itching, bothersome and/or uncomfortable

Local Tolerability Assessment – Burning/ Stinging

Grade	Descriptor
0	Clear: No burning or stinging
1	Mild: Slight warmth or tingling, not bothersome
2	Moderate: Definite warmth or tingling, slightly bothersome
3	Severe: Intense feeling of heat or tingling, bothersome and/or uncomfortable

Follow these steps to complete the LTA for each symptom by a subject:

- An investigational center staff member, other than the evaluating investigator, will show the appropriate LTA symptom grading scale to the subject and instruct the subject on the time interval to be considered
- The staff member should not give any opinion on the meaning of the LTA descriptors
- The subject should verbally indicate the appropriate grade for each symptom and the staff member will report the grade in the source document
- Both the subject and the staff member must sign/initial the source document to indicate the subject performed the LTA for symptoms as instructed
- The staff member must not influence the subject's assessment.

8.2.6. Pregnancy tests

Subjects who are WOCBP must have a negative serum pregnancy test result at Screening (Visit 1) to continue in the study, and a negative UPT at Baseline (Visit 2) prior to application of study medication. In addition, the investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at monthly visits during the study. 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.

8.3. Other Assessments

8.3.1. Demographics, Medical History and Vitiligo 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 extensive vitiligo history at screening

9. ADVERSE EVENTS

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

9.1. Definitions

9.1.1. Adverse events (AE)

An AE is any untoward medical occurrence in a subject administered a study medication(s) and which does not necessarily have a causal relationship with the study medication. An AE can therefore be any unfavorable and unintended sign or symptom associated with the use of a study medication (including an abnormal laboratory finding), whether or not related to the study medication.

Thus, any new, clinically significant worsening of an existing sign, symptom or disease, should be considered an AE.

Every new episode or clinically significant worsening of a chronic condition (*e.g.*, headaches, seasonal allergies, depression, or hypertension) should be reported as a separate AE, even if the condition is reported in the subject's medical history.

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

9.1.2. Serious adverse event (SAE)

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is an important medical event.

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.

Inpatient hospitalization is considered to have occurred if the subject is admitted to the hospital on an in-patient basis, even if released the same day. Prolongation of hospitalization is defined as an additional night stay in the hospital. Hospitalization for a diagnostic test (even if related to an AE) or elective hospitalization that was planned before study enrollment (signing the ICF) are not themselves reasons for an event to be defined as a SAE.

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. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization.

9.1.3. Unexpected adverse event

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

9.1.4. Adverse event reporting period

The investigator must start reporting non-serious AEs with the subject's first study medication application and continue reporting until the end of the subject's last study visit. Reporting for SAEs must start when the subject signs the ICF and continue until the end of the subject's last visit.

9.1.5. 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.

9.1.6. 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).

9.2. Reporting Procedures

9.2.1. 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.

9.2.2. 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.
   Immediately (within 24 hours) inform the Medical Monitor of the SAE by telephone:
   Terrence Chew, M.D.
   Office Telephone: 858-720-0647
   SAE facsimile 484-324-2359
   E-mail: tgchew@icloud.com
2. Within 24-hours complete, as fully as possible, an AE eCRF and an SAE form; fax or e-mail the forms and any other relevant information (*e.g.*, concomitant medication eCRF, medical history eCRF, laboratory test results) to the Aclaris Therapeutics, Inc. Medical Monitor.
3. 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 AE reaches a clinically stable outcome with or without sequelae AND the investigator and Aclaris Therapeutics, Inc. Medical Monitor agree that the SAE is satisfactorily resolved.
4. Inform the Aclaris Therapeutics, Inc. Medical Monitor of SAE updates by telephone followed by an SAE form update sent by e-mail.
5. 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).

9.2.3. Safety Monitoring Discontinuation Criteria

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 screen. 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.

9.2.4. Study Medication Interruption and Discontinuation Criteria

9.2.4.1 Study Medication Interruption

Treatment with ATI-50002 Topical Solution should be temporarily interrupted in the event of severe adverse events considered related to ATI-50002, or in the event of one or more of the abnormal laboratory values in Table 1.

Table 1: Study Medication Interruption Criteria

Laboratory Test	Hold Study Medication if:	Resume Study Medication if:
WBC count	$< 2 \times 10^9$/L	$\geq 2.5 \times 10^9$/L
ANC	$< 1 \times 10^9$/L	$\geq 1.5 \times 10^9$/L
Lymphocyte count	$< 0.5 \times 10^9$/L	$\geq 0.75 \times 10^9$/L
Platelet count	$< 75 \times 10^9$/L	$\geq 100 \times 10^9$/L
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

If a subject has one or more of the abnormal laboratory values noted in Table 1, the investigator or designee upon receipt and review of the central laboratory report should instruct the subject to hold study medication applications. 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 1.

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) return to normal or to baseline values.

9.2.4.2 Study Medication Discontinuation

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

- Severe infection requiring parental antimicrobial therapy or hospitalization
- Symptomatic herpes zoster
- Malignancy – except for non-melanoma skin cancer (SCC or BCC) not in or near the treatment area
- Anaphylactic or severe allergic reaction
- WBC Count: $< 1 \times 10^9$/L or second occurrence of $< 2 \times 10^9$/L
- ANC:$< 0.5 \times 10^9$/L or second occurrence of $< 1 \times 10^9$/L
- Lymphocyte count:$< 0.3 \times 10^9$/L or second occurrence of $< 0.5 \times 10^9$/L
- Platelet count: $< 50 \times 10^9$/L or second event of $< 75 \times 10^9$/L - 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.

10. PREGNANCY

10.1. 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 application of study medication.

10.2. 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 application 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)
- obstruction of fallopian tubes via medical device (Essure ™)
- 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 may have been or was pregnant at the time of study medication exposure (including at least 2 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.

11. STATISTICAL ANALYSES

11.1. Sample Size and Power Calculations

Thirty-three subjects will be enrolled. This is a pilot study and the first study with ATI-50002 Topical Solution for the treatment of facial vitiligo. A formal power calculation was not performed. The initial analyses will be performed after all subjects complete Visit 10 (Week 24).

11.2. Statistical Methods

Summary descriptive statistics (N, mean, median, SD) by visit will be provided for all safety and efficacy parameters. Primary and secondary efficacy parameters are described below:

Primary Efficacy Parameter
Mean change from baseline in facial depigmentation in the AOI will be quantified using Canfield-2-D photographic image analysis from baseline (Visit 2) compared to Week 48 (Visit 14).

Secondary Efficacy Parameters:
Mean change from baseline in facial depigmentation will be calculated as the mean change in Facial assessment of the Vitiligo Area Scoring Index (F-VASI) from Visit 2 compared to Week 24 (Visit 10) and if applicable, Week 48 (Visit 14). F-VASI is a modification of the validated quantitative assessment scale for vitiligo which evaluates the percentage of vitiligo involvement of the face only.

Mean change from baseline in facial depigmentation in the AOI based on Canfield 2-D Photographic analysis from Visit 2 compared to Weeks 4, 8, 12, 16, 20, 24, 32, 40, and post-treatment Week 52 (Visits 5-11, and 12, 13, and 15).

Mean change from baseline in the Facial assessment of the Vitiligo Area Scoring Index (F-VASI) from Visit 2 compared to Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48 and post-treatment Week 52 (Visits 5-11, and Visits 12, 13, 14 and 15).

Mean change from baseline in the VitiQoL from Visit 2 compared to Week 12, 16, 20, 24, and 48 (Visits 7-10, 14).

Treatment success based on the subject's assessment of vitiligo on the Vitiligo Noticeability Scale (VNS) at Week 4, 8, 12, 16, 20, 24, 32, 40, and 48.

Mean change from baseline in total VASI from Visit 2 to Visits 7 and Visit 14 (Week 48) will be assessed for descriptive purposes only to track disease progression in untreated areas.

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 relevant abnormal laboratory results will also be tabulated and presented. Change from baseline in the Local Tolerability Assessments (LTA) to end of treatment (Visit 10) will be summarized.

Data from all enrolled and treated subjects will be presented and summarized. Safety summaries by study will include listings of adverse events incidences within each MedDRA System Organ Class, and changes from pre-application 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.

12. TRAINING, MONITORING, DATA MANAGEMENT AND QUALITY ASSURANCE

12.1. Training

For each investigational center, there will be an initiation visit prior to enrolling any study subjects.

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

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

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

12.2. Monitoring

The conduct of the study will be closely monitored by representatives of Aclaris Therapeutics, Inc. to verify adherence to ICH Good Clinical Practice (GCP) guidelines, and applicable SOPs. Reports of these verifications will be archived with the study report. The investigator will allow the Aclaris Therapeutics, Inc. representative's designee and/or any regulatory agency to have direct access to all study records, eCRFs, corresponding subject medical records, study medication-dispensing records and study medication storage area, and any other documents considered source documentation. The investigator also agrees to assist the representative, if required.

12.3. 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.

12.4. 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.

13. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

13.1. Institutional Review Board (IRB)/Ethics Committee (EC)

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.

13.2. 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 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.

13.3. Subject Information and Consent

All subjects who participate in this study must be fully informed about the study in accordance with the GCPs, federal regulations, local regulations and, at US investigational centers, with HIPAA. The ICF will contain all the required elements in compliance with the current ICH E6 GCP guideline and local regulatory requirements. The investigator must have a defined process for obtaining voluntary informed consent from every subject.

The ICF, approved by an IRB/EC, will be fully explained to the subject. Prior to any study related procedures, including washout from therapies, the subject will voluntarily sign and date the ICF. The investigator must maintain each subject's ICF in the investigational center's study file and must provide each subject with a copy of the signed and dated ICF.

13.4. 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 result 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.

13.5. 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.

13.6. 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.

13.7. Data Collection and Archiving

13.7.1. 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.

13.7.2. 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.

13.7.3. Archiving

All pertinent data, samples, photographs, correspondence, original or amended protocol, reports and all other material relating to the study will be maintained securely in Aclaris Therapeutics, Inc. /contract research organization/investigator archives for the legally required duration for archiving.

The investigator should maintain the essential study documents as specified in ICH GCP, and in compliance with all regulatory requirements. The investigator should ensure these documents are protected from accidental destruction or disposal.

If the Investigator needs to re-assign responsibility for maintaining these documents (*e.g.*, due to retirement) it must be transferred to a person willing to accept this responsibility. The investigator must notify Aclaris Therapeutics, Inc., in writing, of the name and address of the new individual.

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APPENDIX 1: Subject Instructions for Study Medication Application to the Face and Neck (If Applicable)

General Instructions:

1. Before application of study medication, your face and neck (if applicable) 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. You will be asked to apply a thin layer of study medication to the white areas of your face and if applicable, your neck including ½ inch around the white areas (excluding your eyelids and red (mucosal) lip areas) with an applicator as instructed by the study doctor or the study staff. Keep applying study medication to the same facial and neck areas throughout the study, even if the color is returning in these areas.
3. 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 discarded. You may use more than one applicator per session as needed to ensure all areas of your face and if applicable, your neck designated by the study staff for treatment have medication applied.
4. 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.
5. You will apply study medication twice a day, approximately 8 to 12 hours apart. Once you apply study medication, do not wash your face of neck (If applicable) for at least 6 hours.
6. Remember to bring your study medication bottles, both used and unused, to each study visit.
7. Avoid exposing your face and neck (if applicable) to excessive natural or artificial ultraviolet radiation (e.g., sunlight, tanning beds) and use sunscreen on the face and neck (if applicable), if excessive sun exposure cannot be avoided.
8. Remove any products applied to the face and neck (if applicable) 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.
9. Open one bottle of study medication at a time. 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 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 face and if applicable, your neck, ensuring all facial and neck 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 if applicable, your neck.
4. Pat your face and if applicable your neck 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. Swipe the applicator across your facial and if applicable, your neck areas, applying a thin layer of study medication over all facial and neck areas and about ½ inch around these areas affected by vitiligo. Your face and if applicable your neck 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 facial and neck areas, use a new applicator and repeat the application process as described in #2 and #3.

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.
4. Do not apply any products (moisturizers, sunscreens, cosmetics, etc.) to your face and if applicable, your neck until the study medication has completely dried, at least 30 minutes after applying study medication.
5. Do not wash your face and if applicable, your neck 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 and box at room temperature, away from heat, moisture, and direct light. Do not refrigerate or freeze. Keep out of reach of children.

APPENDIX 2: Vitiligo History

The following Vitiligo history will be obtained:

Onset of initial diagnosis vitiligo (Month/Year): _____

Initial presentation: _____
(segmental, non-segmental, mixed)

Location: _____

Current clinical type: _____
(segmental, non-segmental, mixed)

Location: _____

Onset of current episode of vitiligo (Month/Year):_____

History of Treatments for Vitiligo:

Treatment (Drug, Device, Other)	**Start Date (DD/MMM/YYYY)**	**Stop Date (DD/MMM/YYYY)**

APPENDIX 3: Fitzpatrick's Skin Type Chart

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

APPENDIX 4: VitiQoL

The aim of these questions is to measure how much your skin has affected you over the past month.

During the past month,	Not at all ↓ . ↓ All of the time
1. Have you been bothered by the appearance of your skin condition?	☐ ☐ ☐ ☐ ☐ ☐ ☐
2. Have you felt frustrated about your skin condition?	☐ ☐ ☐ ☐ ☐ ☐ ☐
3. Has your skin condition made it hard to show affection?	☐ ☐ ☐ ☐ ☐ ☐ ☐
4. Has your skin condition affected your daily activities?	☐ ☐ ☐ ☐ ☐ ☐ ☐
5. When you were talking to someone, have you worried about what they may be thinking about you?	☐ ☐ ☐ ☐ ☐ ☐ ☐
6. Have you been afraid that people would find fault with you?	☐ ☐ ☐ ☐ ☐ ☐ ☐
7. Have you felt embarrassed or self-conscious because of your skin?	☐ ☐ ☐ ☐ ☐ ☐ ☐
8. Has your skin condition influenced the clothes you wear?	☐ ☐ ☐ ☐ ☐ ☐ ☐
9. Has your skin condition affected your social or leisure activities?	☐ ☐ ☐ ☐ ☐ ☐ ☐
10. Has your skin condition affected your emotional well-being?	☐ ☐ ☐ ☐ ☐ ☐ ☐
11. Has your skin condition affected your overall physical health?	☐ ☐ ☐ ☐ ☐ ☐ ☐
12. Has your skin condition affected your grooming practices (i.e. hairstyle, use of cosmetics)?	☐ ☐ ☐ ☐ ☐ ☐ ☐
13. Has your skin condition affected your sun protection efforts during recreation (i.e. limiting exposure time during peak sun hours, seeking shade, wearing hat, long sleeves or pants)?	☐ ☐ ☐ ☐ ☐ ☐ ☐
14. Has your skin condition affected the possibility of making new friends?	☐ ☐ ☐ ☐ ☐ ☐ ☐
15. Have you worried about progression or spread of disease to other new areas of the body?	☐ ☐ ☐ ☐ ☐ ☐ ☐

Please check how severe you currently feel your skin condition is:	No skin Involvement ↓ . ↓ Most severe case
16. Severity of skin condition.	☐ ☐ ☐ ☐ ☐ ☐ ☐

Have you answered every item? Yes ☐ No ☐ Initial _____Date _____

APPENDIX 5: Subject Vitiligo Satisfaction Scale

Please circle the grade below that best describes how satisfied or dissatisfied you are with the results of the study medication applications on the treated areas of the face.

How satisfied or dissatisfied are you with the appearance of your facial vitiligo because of the study medication applications?

Subject's Vitiligo Satisfaction Scale

Grade	Descriptor
1	Extremely satisfied
2	Moderately satisfied
3	A little satisfied
4	Neither satisfied or dissatisfied
5	A little dissatisfied
6	Moderately dissatisfied
7	Extremely dissatisfied

Initial _____Date _____

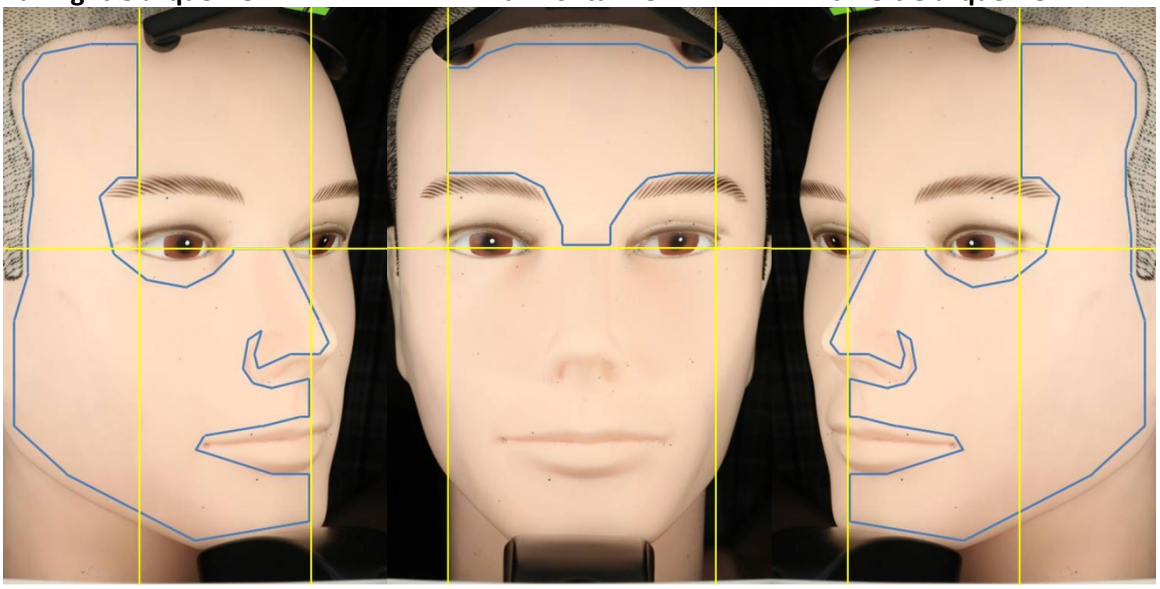
APPENDIX 6: Area of Interest

The area of Interest (AOI) mask template will be applied to all images obtained in the study. The following guidelines will be used to delineate boundaries for the AOI. For the Left and Right Oblique image template, horizontal and vertical guidelines will be placed at the outer canthus as well as a vertical guideline at the commissure and the center of the lip. For boundary points not defined by these guidelines, Canfield may adjust the template points along the brow line, hairline, jawline, lip line, beard, nose tip and/or bridge, and top of the cheek bone.

For the Frontal template, vertical guidelines will be placed at the outer canthi and a horizontal guideline will be placed at the right inner canthus to delineate the edges of the AOI. For the boundaries not defined by these guidelines, Canfield may adjust the template points along the brow line and headrest (see Figure 1).

Figure 1: Area of Interest Diagram

2a. Right Oblique AOI **2b. Frontal AOI** **2c. Left Oblique AOI**



The Facial VASI should be calculated based on the depigmented areas within the mask template above excluding the facial areas covered by a beard, if applicable. Study staff may instruct the subject to treat the areas of depigmentation which are blocked by the stereotactic device (forehead and chin) and the eyebrow area down to the level of the bony rim of the orbit and the beard, if applicable.