CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: ATI-50002-AGA-201

An Open-Label Safety, Tolerability, and Efficacy Study in Male and Female Subjects with Androgenetic Alopecia Treated with ATI-50002 Topical Solution

Original Protocol: V1.0 05 January 2018

Amendment 1: V2.0 16 January 2018

Amendment 2: V3.0 01 February 2018

Amendment 3: V4.0 16 October 2018

Amendment 4: V5.0 24 January 2019

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PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: ATI-50002-AGA-201

Version 5.0: 24 January 2019

Protocol Title: An Open-Label Safety, Tolerability, and Efficacy Study in Male and Female Subjects with Androgenetic Alopecia Treated with ATI-50002 Topical Solution

Sponsor Signature:

1-24-19

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

Date

INVESTIGATOR'S AGREEMENT

Protocol Number: ATI-50002-AGA-201

Protocol Title: An Open-Label Safety, Tolerability, and Efficacy Study in Male and Female Subjects with Androgenetic Alopecia Treated with ATI-50002 Topical Solution

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

1. SYNOPSIS

Name of Sponsor/Company:
Aclaris Therapeutics, Inc.

Name of Investigational Product:
ATI-50002 Topical Solution 0.46%

Title of Study:
An Open-Label Safety, Tolerability, and Efficacy Study in Male and Female Subjects with Androgenetic Alopecia Treated with ATI-50002 Topical Solution

Study center(s): Approximately 3 investigational centers will participate in the study.

Phase of development:
Phase 2a

Objectives:

Primary:

- To assess safety, tolerability and efficacy of ATI-50002 Topical Solution, 0.46% in male and female subjects with androgenetic alopecia (AGA)
- **Secondary:**
- To assess the development of new hair growth/scalp coverage as assessed by the investigator and the subject using a seven-point rating scale and global scalp photographs.
- To assess the change from baseline in cumulative target area hair width
- To assess the change from baseline in androgenetic alopecia stage according to the Norwood-Hamilton scale in males and the Sinclair Scale in females.

Study Design:

This is an open-label phase 2 study designed to evaluate the safety and efficacy of ATI-50002 Topical Solution, 0.46% in male and female subjects with androgenetic alopecia. Subjects will be required to apply ATI-50002 study medication to their scalp twice a day for a total of 26 weeks. Upon completion of the first 26 weeks of treatment, subjects will have the option to consent to continue on study medication for an additional 26 weeks of treatment. All subjects will be required to complete a safety follow up visit4 weeks after last application of study medication.

A total of 24 subjects (approximately 12 males and 12 females) ages 18-50 years with a clinical diagnosis of AGA will be enrolled in the study. Male subjects must have a Norwood classification of Type III vertex, IV or V and woman must have a Sinclair Grade of 2, 3 or 4.

Number of patients (planned):
Approximately 12 male subjects and 12 female subjects will be enrolled to the study.

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

1. Able to comprehend and willing to sign an Informed Consent Form (ICF).

2. Male subjects and non-pregnant, non-nursing female subjects18 to 50 years of age with a clinical diagnosis of AGA.
3. Male subjects with a Norwood-Hamilton classified as III vertex, IV or V and woman subjects with a Sinclair Grade 2, 3 or 4.
4. Subjects willing to agree to have small 1.9 cm diameter circle of hair clipped to ~ 1 mm in length on their balding scalp.
5. Subjects willing to agree to have a permanent dot tattoo applied to their scalp to mark the center of the identified target area
6. Subjects must agree to maintain the same hair style and hair care regimen during the study.
7. Subjects must agree to not use a medicated shampoo or conditioner containing biotin, saw palmetto or tea tree oil (melaleuca oil) throughout the course of protocol treatment and refrain from hair weaving, hair extensions, texturizers, relaxers, occlusive wigs and non-study hair growth products during the study and for a period of 30 days prior to Visit 2.
8. Subjects must have an absolute neutrophil count (ANC) >1,000/mm^3, and a platelet count >50,000/mL.
9. Male subjects with a serum prostate-specific antigen (PSA) level of < 2.0 ng/mL.
10. Subjects receiving oral or topical hormones must be on a stable dose for 6 months prior to V2.
11. Subjects must be willing to refrain from washing hair, using hair products, and participating in strenuous exercise that would cause profuse sweating for 6 hours after each treatment application with ATI-50002.
12. Woman of child bearing potential (WOCBP) 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.
13. Sexually active male subjects must agree to use a barrier form of birth control from the first application until 30 days post last application of ATI-50002.

Exclusion Criteria:

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

1. Females who are nursing, pregnant, or planning to become pregnant for the duration of the study and up to 30 days after the last application of study medication.
2. Clinical diagnosis of alopecia areata or other non-AGA forms of alopecia.
3. Scalp hair loss on the treatment area, due to disease, injury or medical therapy.
4. Active skin disease on the scalp (such as psoriasis or seborrheic dermatitis) or a history of skin disease on the scalp that in the opinion of the investigator would interfere with the study assessments of efficacy or safety.
5. Evidence of hypogonadism defined as serum testosterone < 250ng/dl and/or LH>20mU/ml in males.
6. Active unstable thyroid disease, including subjects on therapy for either hyperthyroidism or hypothyroidism unless their dose of thyroid medication has been stable for 3 months prior to Visit 2 and serum TSH is normal.
7. Subjects with non-pigmented hair.

8. Subjects unable to comply with the following required washout periods:
    - Scalp promoting hair growth products (e.g.minoxidil, finasteride, dutasteride, saw palmetto) for 6 months prior to Visit 2.
    - Anti-androgenetic therapies (e.g. spironolactone, ketoconazole, flutamide, cyproterone acetate) for 6 months prior to Visit 2.
    - Hair transplantation or hair weaving within 6 months of Visit 2
    - Anabolic steroids for 6 weeks prior to Visit 2.
    - Oral or topical JAK inhibitors 3 months prior to Visit 2
    - Platelet rich plasma treatment within 6 months of Visit 2
    - Hair Laser, light or energy treatments to the target hair area within 3 months of Visit 2
    - Systemic steroids for more than 14 consecutive days in the 2 months prior to Visit 2
    - Chemotherapy, cytotoxic agents within 12 months of Visit 2
    - No prior radiation to the scalp

9. History of, current or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than subjects with: a history of adequately treated and well healed and completely cleared non-melanoma skin cancers (basal or squamous cell carcinoma) treated successfully with no evidence of disease.
10. History of human immunodeficiency virus (HIV), hepatitis B or C.
11. Current herpes zoster infection.
12. Evidence of active, latent or inadequately treated Mycobacterium tuberculosis infection, or history of incompletely treated or untreated tuberculosis. Subjects who have successfully completed therapy for latent tuberculosis may participate.

13. History of serious local infection (*e.g.*, cellulitis, abscess) or systemic infection including but not limited to a history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to Visit 1. Subjects on an antibiotic for a non-serious, acute local infection must complete the course prior to enrollment into the study.

14. Participation in an investigational drug, device, or biologic trial in which administration of an investigational drug, device, or biologic occurred within 30 days or 5 half-lives (whichever is longer) of Visit 2. Subjects who have participated in a study of an investigational drug, device or biologic agent for androgenetic alopecia within 1 year of screening will be eligible to participate only with individual permission from the Medical Monitor.

15. Sensitivity to any of the ingredients in the study medication.
16. Screening ECG findings of:
    - QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose)
    - Resting heart rate < 45 or > 100 beats/minutes (inclusive)
    - Rhythm disturbance other than sinus arrhythmia or ectopic supraventricular rhythm (ectopic atrial rhythm)
    - Conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
    - Acute or chronic signs of ischemia

- Left Bundle Branch Block
- Prior myocardial infarction

Investigational product, dosage and mode of administration:

Open label ATI-50002 Topical Solution 0.46% will be applied to the balding area of male and female subjects with androgenetic alopecia. Up to 4mls of ATI-50002 Topical Solution 0.46% will be applied to the scalps of eligible study subjects twice a day using a 1ml disposable dropper.

Duration of treatment:

All subjects will apply ATI-50002 Topical Solution 0.46% twice a day for 26 weeks. Subjects will have the option to consent to remain on study for an additional 26 weeks. All subjects will be required to have a safety follow up visit 4 weeks after their last application of study medication.

Study Endpoints:

Efficacy:

The primary efficacy endpoint is the change from baseline in non-vellus target area hair count (TAHC)using a microphotographic technique.

The secondary efficacy endpoints are defined as:

- development of new hair growth/scalp coverage as assessed by the investigator and the subject using a seven-point rating scale and subject global scalp photographs.
- Change from baseline in cumulative target area hair width (TAHW)
- Change from baseline in AGA stage according to the Norwood Hamilton scale in males and the Sinclair Scale in females

Safety:

Subjects will be assessed for local skin reactions and adverse events throughout the duration of the trial. In addition, vital signs, ECGs and clinical laboratory assessments will be performed on all subjects at the protocol defined time-points.

Statistical methods:

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

Primary Efficacy Endpoints:

Mean change from baseline in non-vellus target area hair count (TAHC)will be quantified using a microphotographic technique and calculated along with the median, standard deviation, standard error, and 95% confidence limits around each mean change to allow tests of the null hypothesis that the population mean changes are zero.

Secondary Efficacy Endpoints:

Mean change from baseline in cumulative target area hair width (TAHW) will be quantified using a microphotographic technique and calculated along with the median, standard deviation, standard error, and 95% confidence limits around each mean change to allow tests of the null hypothesis that the population mean changes are zero.

The seven-point rating scale to measure the investigator and subject assessment of the development of new hair growth/scalp coverage will be analyzed with summary statistics (N, mean, median, SD) for each visit where the assessment is made. Similar summary statistics will be used to analyze change from baseline in AGA stage separately for males (Horwood Hamilton Scale) and for females (Sinclair Scale) at each applicable visit.

Safety Assessments:

Data from all enrolled and treated subjects will be presented and summarized. Safety analyses will include descriptive statistics calculated on the safety parameters using the safety population. The proportion of subjects with treatment-emergent adverse events will be tabulated and presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class. Vital signs and clinically significant abnormal laboratory results will also be tabulated and presented. Clinical laboratory and ECG results will be tabulated, highlighting abnormal results. Local skin reaction results will be tabulated and summarized by visit.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AA	Alopecia areata
AE	Adverse event
AGA	Androgenetic alopecia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AT	Alopecia totalis
AU	Alopecia universalis
AV	Atrioventricular
BCC	Basil cell carcinoma
BUN	Blood urea nitrogen
CPK	Creatine Phosphokinase
DHT	Dihydrotestosterone
DMSO	Dimethylsulfoxide
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HF	Hair follicle
HFSC	Hair follicle stem cell
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IRB	Institutional Review Board
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK3	Janus kinase 3
LDH	Lactate dehydrogenase

Abbreviation or Specialist Term	Explanation
LDL	Low-density lipoproteins
LH	Lutenizing hormone
OAE	Other significant adverse event
OSM	Oncostatin M
OSMR	Oncostatin M receptor
PI	Principal Investigator
SAE	Serious adverse event
SCC	Squamous cell carcinoma
TIBC	Total iron binding capacity
TAHC	Target Area Hair Count
TAHW	Target Area Hair Width
TyK2	Tyrosine kinase 2
WOCBP	Woman of child bearing potential
WBC	White blood cell

4. AMENDMENT HISTORY

4.1. Amendment Rationale

Version 2.0 amendment 1 dated 16 January 2018, clarified the size of the area of the subject's scalp that would be required to be clipped at each protocol defined timepoint. The original protocol identified the area on the subject's as a 1cm^2 target area. The accurate clipping size to perform the TAHC and TAHD is a 1.9 cm diameter circle clipped to ~ 1mm in length. The subject inclusion criteria were also amended to require that subjects refrain from strenuous exercise that would cause profuse sweating for a period of 6 hours after application of study medication. This requirement was added to ensure that the study medication was absorbed prior to performing any strenuous exercise. The subject exclusion criteria were amended to allow subjects to enroll to the study if they have previously received treatment with a topical JAK inhibitor. The use of systemic steroids for more than 14-day s in the 2 months prior to Visit 2 was added to the prohibited medication section and the use of anabolic steroids prior to Visit 2 was changed from 3 months to 6 weeks. Section 11.3.6 was added to the protocol to provide definitions for protocol violations and protocol deviations.

Version 3.0 amendment 2 dated 01 February 2018, added in the secondary objective to assess the change from baseline in target area hair width. This objective should have been included in the original protocol. The protocol was also amended to allow pre-menopausal women to enroll to the study.

Version 4.0 amendment 3 dated 16 October 2018, allows subjects enrolled to the study to receive an additional 6 months of study medication. Creatine Phosphokinase (CPK) was also added to the chemistry panel as an additional safety assessment. The amount of study medication dispensed at each visit was also amended. The previous versions of the protocol required that 3 bottles of study medication be dispensed at each visit due to the short stability of the product once the bottles were opened. New stability data has become available to allow the product to be used for 60 days after the bottle is opened. This allows for less study medication to be dispensed between study visits.

Version 5.0 amendment 4 dated 22 January 2019, has been amended to allow the investigator to perform the Investigator Global Assessment by comparing the current subject photos to the to the baseline (Visit 2) photos. The protocol was also amended to allow the subject to perform the Subject Self-Assessment by comparing the current subject photos to the to the baseline (Visit 2) photographs. This revision will enable both the investigator and subject to assess changes in hair growth over the duration of the study.

4.2. Protocol Changes

Protocol Version	Date	Section	Revisions
Version 1.0	5 January 2018	NA	Original Protocol
Version 2.0 Amendment 1:	16 January 2018	Synopsis	Inclusion and Exclusion criteria updated to reflect all changes in main body of protocol
		Section 6.1; Section 7.1; section 10.1	Clarify the diameter size of the area on the subject's scalp that is required to be clipped for the TAHC and TAHD assessments.
		Section 7.1; Appendix 1 Subject Instructions	Added language to Inclusion number 11 to require that subjects refrain from participating in strenuous exercise that would cause profuse sweating for a period of 6 hours after study medication application.
		Section 7.2	Removed exclusion criteria of the use of topical JAK inhibitors and removed exclusion number 8 due to a duplication of the exclusion criteria.
		Section 8.7	Changed the restricted use of anabolic steroids from 3 months to 6 weeks prior to Visit 2 and added the restriction of using systemic steroids for more than 14 consecutive days in the 2 months prior to Visit 2.
		Section 11.3.6	Added section to provide definition for protocol violations and deviations.
Version 3.0 Amendment 2:	01 February 2018	Front Cover	Front Cover of protocol updated with new address for Aclaris Therapeutics
		Synopsis	Synopsis was updated to reflect all changes in the main body of the protocol.
		Section 5.2	Added secondary objective to assess the change from baseline in cumulative target area hair width
		Section 6.5	Added urine pregnancy and serum pregnancy testing fo woman and added Target Area Hair Width.
		Section 7.1	Revised the inclusion criteria for woman to allow pre-menopausal women to enroll to the study and to add in the required birth control procedures for woman being treated on the study.

Protocol Version	Date	Section	Revisions
		Section 7.2	Added an exclusion criteria to exclude female subjects who plan to get pregnant 30 days after last application of study medication.
Version 4.0 Amendment 3	16 October 2018	Synopsis; Section 7.1, Section 7.5; Table 3	Updated the study design section to state that subjects will be allowed to remain on study for an additional 6 months. New Table of assessments added for those subjects that consent to remain on study beyond the initial 26 weeks of treatment.
		Section 7.5; Section 12.1.7	Addition of Creatine Phosphokinase (CPK) to the chemistry panel as an additional safety assessment.
		Section 8.5 and Section 9.2	Removed the requirement of having to dispense 3 bottles of study medication at each visit due to the longer stability data of the opened bottles.
Version 5 Amendment 4	24 January 2019	Front Cover	Removed Stuart Shanler, MD as the medical monitor and replaced David Gordon MB, ChB.
		Section 11.3	Added language to have the investigator perform the Investigator Global Assessment by comparing the current subject photos back to the baseline visit (Visit 2). Added language to have the subject perform the Subject Self-Assessment by comparing the current subject photo back to the baseline visit (Visit 2).

5. INTRODUCTION

Aclaris Therapeutics, Inc. is developing ATI-50002 Topical Solution as topical treatment for alopecia areata (AA), alopecia totalis (AT), alopecia universalis (AU), androgenetic alopecia (AGA), and vitiligo. ATI-50002, the pharmacologically active metabolite of the orally administered ATI-50001, is a potent and highly selective inhibitor of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3)-dependent cytokine signaling, with minimal activity on JAK2- and Tyrosine kinase-2 (Tyk2)-dependent signaling.

5.1. Overview of Androgenetic Alopecia

Androgenetic alopecia is a hair loss disorder that affects both men and woman. It is an extremely common disorder with relatively few treatment options. There are only two FDA approved treatment options for men [Rogaine® (minoxidil) and Propecia® (finasteride)] and one FDA approved treatment for women (Rogaine®). The disorder affects roughly 50% of men and perhaps as many women and the frequency increases with age in both men and women (Olsen E, et al., 2005) . The pattern of hair loss is gradual in both men and women but the way in which the hair is lost differs. Onset in men may begin any time after the onset of puberty and occurs in varying degrees in the bitemporal, frontal, mid scalp and vertex regions of the head (Olsen E, et al., 2005). Woman with androgenetic alopecia experience diffuse thinning of the hair.

Androgenetic alopecia can be an emotionally debilitating disease for both men and woman.

5.2. Rationale for Using ATI-50002 to Treat AGA

Recent studies in the laboratory of Dr. Angela Christiano (Columbia University; submitted) found that inhibition of JAK-STAT signaling initiates the hair cycle in normal mice and promotes hair growth in humans. Particularly, in normal telogen phase, JAK signaling is elevated and is involved in maintaining quiescence of hair follicle stem cells. Administering a JAK inhibitor results in initiating entry into anagen causing hair growth by inhibiting JAK-STAT signaling so that the hair follicle is no longer quiescent.

Dr. Christiano's laboratory further identified upstream factors that signal via the JAK-STAT pathway to promote hair growth. Oncostatin M (OSM) is one such upstream factor. OSM receptor (OSMR) is expressed on hair follicle stem cells, and all JAKs (JAK1, JAK2, JAK3, Tyk2) are activated by OSM. Signaling from the JAKs is transduced by STATs, primarily via STAT5, in hair follicle keratinocytes.

Unique anti-inflammatory macrophages, that are resident in the dermis near hair follicles, were identified as the source of OSM that promotes hair growth in the follicle. These unique macrophages have been termed "trichophages" due to their having three distinct differences from typical M2-type macrophages. Trichophages produce OSM during early and mid-telogen, which signals via JAK-STAT5 in hair follicle stem cells (HFSC) to inhibit proliferation and maintain hair follicle quiescence, particularly during second telogen. These trichophages predominate during early and mid-telogen, and lose their OSM producing ability as telogen progresses, which allows the hair follicles (HFs) to enter the next anagen stage.

Based on the above findings, as well as prior findings that administering recombinant OSM potently inhibits anagen (Yu, M.et al, 2008) Dr. Christiano anticipated that administering a

JAK/STAT inhibitor should inhibit OSM signaling, initiate anagen and associated hair growth. Christiano's laboratory has demonstrated this activity in a mouse mode of AGA.

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 IC_{50} of 38nM (data on file). The anticipated IC_{90} concentration for pSTAT1 activation is approximately 0.4μM. To expect ATI-50002 to inhibit JAK1/3-mediated pSTAT signaling, a significant excess of the inhibitor must be present in the target tissue. The ability of the 0.46% ATI-50002 formulation to deliver ATI-50002 into the dermis was studied using a human skin permeation model. (Franz chamber with human skin). Resulting ATI-50002 concentrations were found to be in the range of 10-20μM in the dermis and epidermis. A 10μM concentration represents a > 10X excess to the estimated IC_{90} for pSTAT inhibition. The 0.46% ATI-50002 formulation is, therefore, anticipated to deliver sufficient drug to the epidermis and the dermis to inhibit JAK1/3 signaling and diminish immune-mediated inflammation.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective is to assess the safety, tolerability and efficacy of ATI-50002 Topical Solution, 0.46% in male and female subjects with AGA.

6.2. Secondary Objectives

The secondary objectives will assess the following:

- development of new hair growth/scalp coverage as assessed by the investigator and the subject using a seven-point rating scale and global scalp photographs.
- to assess the change from baseline in cumulative target area hair width (TAHW)
- assess the change in AGA stage according to the Norwood Hamilton scale in males and the Sinclair Scale in females.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label phase 2 study designed to evaluate the safety and efficacy of ATI-50002 Topical Solution, 0.46% in male and female subjects with androgenetic alopecia. Subjects will be required to apply ATI-50002 study medication to their scalp twice a day for a total of 26 weeks. Subjects will have the option to consent to remain on study for an additional 26 weeks after Visit 10 is completed. All subjects will be required to complete a safety follow up visit 4 weeks after their last application of study medication.

A total of 24 subjects (12 males and 12 females) ages 18-50 years of age with a clinical diagnosis of AGA will be enrolled in the study. Male subjects must have a Norwood Hamilton classification of Type III vertex, IV or V and woman must have a Sinclair Grade of 2, 3 or 4.

Subjects will be required to have a small 1.9 cm diameter circle clipped to ~ 1 mm in length on their balding scalp. Subjects must also agree to have a dot tattoo applied in the center of the clipped area during Visit 2.

Subjects will be required to complete the following treatment visits:

Visit 1: Screening (Day -14-0)

Visit 2: Day 1

Visit 3: Day 21

Visit 4: Day 28

Visit 5: Day 56

Visit 6: Day 84

Visit 7: Day 112

Visit 8: Day 140

Visit 9: Day 168

Visit 10: Day 182

Subjects that consent to remain on study for an additional 6 months of treatment will have the following study visits:

Visit 11: Week 30

Visit 12: Week 35

Visit 13: Week 39

Visit 14: Week 44

Visit 15: Week 48

Visit 16: Week 52

All subjects will be required to have a Follow up Safety Visit 4 weeks post last application of study medication.

All protocol defined treatment assessments are outlined in Table 2 .

7.2. Number of Subjects

A total of 24 evaluable subjects will be enrolled to the study (12 male and 12 female) at approximately 3 investigational centers.

7.3. Treatment Assignment

This is an open label study. All subjects will apply ATI-50002 Topical Solution 0.46% twice a day for 26 weeks followed by a 4 week follow up period.

7.4. Criteria for Study Termination

This study may be terminated prematurely in whole or in part due to a change in the benefit/risk profile for ATI-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.

7.5. Schedule of Assessments

Table 2: Schedule of Assessments-Initial 26 weeks of Treatment

	Screening	Baseline	Treatment								Follow up Safety/Early Termination Visit[15]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	
			Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 26	4 weeks post last application of ATI-50002
Treatment Day	**-14 to 0**	**1**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	
Visit Windows	**N/A**	**N/A**	**+/- 3 days**	**+/-4 days**	**+7 days**	**+/-7 days**	**+7 days**	**+/-7 days**	**+/-7 days**	**+7 days**	**+7 days**
Informed Consent[1]	X										
Inclusion/Exclusion Criteria	X	X									
Demographics and Medical History	X										
Physical Exam[2]	X										X
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X
Fitzpatrick Skin Type	X										
Prior Hair Treatment Assessment[4]	X										

	Screening	**Baseline**	**Treatment**								**Follow up Safety/Early Termination Visit[15]**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	
			Week 3	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**4 weeks post last application of ATI-50002**
Treatment Day	**-14 to 0**	**1**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	
Visit Windows	**N/A**	**N/A**	**+/- 3 days**	**+/-4 days**	**+7 days**	**+/-7 days**	**+7 days**	**+/-7 days**	**+/-7 days**	**+7 days**	**+7 days**
Clinical Chemistry and CBC[5]	X				X		X		X	X	X
Quantiferon Gold[6]	X										
Total Iron Binding Capacity (TBIC), Serum Iron, Serum Ferritin	X										
Dihydrotestosterone (DHT), Testosterone, Estrogen, DHEA	X				X		X		X	X	X
Urine Pregnancy Test		X		X	X	X	X	X	X	X	X
Serum Pregnancy	X										
Serum PSA	X										
Thyroid Panel	X										
ECG	X			X						X	X

	Screening	**Baseline**	**Treatment**								**Follow up Safety/Early Termination Visit[15]**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	
			Week 3	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**4 weeks post last application of ATI-50002**
Treatment Day	**-14 to 0**	**1**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	
Visit Windows	**N/A**	**N/A**	**+/- 3 days**	**+/-4 days**	**+7 days**	**+/-7 days**	**+7 days**	**+/-7 days**	**+/-7 days**	**+7 days**	**+7 days**
Norwood-Hamilton classification(males); Sinclair Scale (females)Assessment	X	X					X			X	X
Target Area Hair Identification and Tattoo application[7]		X									
Global Scalp Photograph [8]	X	X[8]			X[9]		X[9]			X[9]	X
Macro Scalp Photographs[10]		X			X		X			X	
Target Area Hair Count (TAHC) and Target Area Hair Width (TAHW)[11]		X			X		X			X	
Demonstration of study drug application[12]		X		X	X	X	X	X	X	X[14]	
Dispensing of study medication[13]		X		X	X	X	X	X	X	X[14]	

	Screening	Baseline	Treatment								Follow up Safety/Early Termination Visit[15]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	
			Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 26	4 weeks post last application of ATI-50002
Treatment Day	**-14 to 0**	**1**	**21**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	
Visit Windows	**N/A**	**N/A**	**+/- 3 days**	**+/-4 days**	**+7 days**	**+/-7 days**	**+7 days**	**+/-7 days**	**+/-7 days**	**+7 days**	**+7 days**
Investigator Assessment of Hair Growth					X		X			X	
Subject Self - Assessment of Hair Growth					X		X			X	
Local Skin Reaction Assessment		X	X	X	X	X	X	X	X	X	X
Adverse Events[14]		X									
Concomitant Therapies		X									

[1]A written, signed ICF must be obtained from each subject prior to performing any study related procedure
[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]Vital signs include: oral or ear temperature, blood pressure, heart rate, respiration rate (height and weight at baseline only).

[4] Prior therapies or treatments a subject received to treat his/her AGA must be documented for each subject.
[5] Serum chemistry panel to include: albumin, alk phos, ALT, AST, BUN, bicarbonate, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, total protein, uric acid, total cholesterol, LDL, HDL triglycerides, CPK, and complete blood count including differential.
[6] All subjects must have a blood sample drawn to test for the tuberculosis virus. The blood sample will be sent to a central laboratory for analysis and results must be received prior to enrolling the subject.

[7] The investigational study staff will be required to identify target area of the scalp that is located in an actively balding area. Directions for proper hair clipping are outlined in Section 9.2 . Sites will be required to apply a permanent dot tattoo to the subject's scalp to identify the target hair area.
[8]Global scalp photographs are to be performed at the screening visit. If the photos are not of the appropriate quality, the site staff will perform a re-shoot at Visit 2.
[9] Canfield staff will review all global photographs within 2 days of the photographs being submitted. If a re-take is required, Canfield will notify the site and the re-take photographs will need to be performed within 7 days of the visit.
[10] Canfield staff will review all macro photographs within 2 days of the photographs being submitted. If a re-take is required, Canfield will notify the site and the re-take photographs will need to be performed within 7 days of the visit.
[11]Sites will take the macro photographs and transmit these to Canfield in order for the Canfield scientists to perform the Target Area Hair Counts and the Target Area Hair Widths. The TAHC and TAHW will be entered into the Canfield database.
[12]Sites will be required to review with each subject the proper application of the study medication and remind the subjects that they are only to wash their hair with the same shampoo/conditioner and maintain the same hair style throughout the study.
[13]Subjects will be dispensed bottles of study medication at each monthly visit. Study medication will be weighed prior to dispensing the medication to the subject and upon return of both used and unused bottles.
[14] Subjects that are not remaining on protocol therapy for an additional 6 months of treatment will not have study medication dispensed at Visit 10.
All non-serious AEs will be collected from the time of first study medication application until the final study visit. Serious AEs will be collected from the time of consent through the final study visit.
[15] Subjects that consent to remain on study for an additional 6 months of treatment will continue on study with Visit 11 (week 30) and then will have a final follow up Visit 4 weeks after the last application of study medication in the 6-month extension part of the study. Those subjects that do not consent to continuing on study medication for an additional 6 months will be required to have a final safety follow up visit conducted at week 30. For those subjects that discontinue the study early, they must return to the clinic 4 weeks following the last study medication application for a final safety visit.

Table 3: Schedule of Assessments – 6-month Extension Study

							Follow up Safety/Early Termination Visit[10]
	Visit 11	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**
Treatment week	**Week 30**	**Week 35**	**Week 39**	**Week 44**	**Week 48**	**Week 52**	**Week 56**
Visit Windows	**+7 days**	**+7 days**	**+7 days**	**+7 days**	**+/-7 days**	**+7 days**	**+7 days**
Physical Exam[1]							X
Vital Signs[2]	X	X	X	X	X	X	X
Clinical Chemistry and CBC[3]			X	X		X	X

Dihydrotestosterone (DHT), Testosterone, Estrogen, DHEA			X			X	X
Urine Pregnancy Test	X		X	X	X	X	X
ECG			X				X
Norwood-Hamilton classification(males); Sinclair Scale (females)Assessment						X	X
Global Scalp Photograph			X[4]			X[4]	X
Macro Scalp Photographs[5]						X[5]	
Target Area Hair Count (TAHC) and Target Area Hair Width (TAHW)[6]						X	
Demonstration of study drug application[7]	X	X	X	X	X	X	
Dispensing of study medication[8]	X	X	X	X	X	X	
Investigator Assessment of Hair Growth			X			X	X
Subject Self - Assessment of Hair Growth			X			X	X

Local Skin Reaction Assessment	X	X	X	X	X	X	X
Adverse Events[9]	X						
Concomitant Therapies	X						

[1] A physical exam includes: general appearance, examination of head, eyes, ears, nose and throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, lymphatic and skin assessment.
[2] Vital signs include: oral or ear temperature, blood pressure, heart rate, respiration rate.
[3] Serum chemistry panel to include: albumin, alk phos, ALT, AST, BUN, bicarbonate, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, total protein, uric acid, total cholesterol, LDL, HDL triglycerides, CPK, and complete blood count including differential.
[4] Canfield staff will review all global photographs within 2 days of the photographs being submitted. If a re-take is required, Canfield will notify the site and the re-take photographs will need to be performed within 7 days of the visit.
[5] Canfield staff will review all macro photographs within 2 days of the photographs being submitted. If a re-take is required, Canfield will notify the site and the re-take photographs will need to be performed within 7 days of the visit
[6]Sites will take the macro photographs and transmit these to Canfield in order for the Canfield scientists to perform the Target Area Hair Counts and the Target Area Hair Widths. The TAHC and TAHW will be entered into the Canfield database.
[7]Sites will be required to review with each subject the proper application of the study medication and remind the subjects that they are only to wash their hair with the same shampoo/conditioner and maintain the same hair style throughout the study.
[8]Subjects will be dispensed bottles of study medication at each monthly visit. Study medication will be weighed prior to dispensing the medication to the subject and upon return of both used and unused bottles.
[9] All non-serious AEs will be collected from the time of first study medication application until the final study visit. Serious AEs will be collected from the time of consent through the final study visit.
[10]A final safety follow up visit will be conducted at week 56 (Visit 17). For those subjects that discontinue the study early, they must return to the clinic 4 weeks following the last study medication application for a final safety visit.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Able to comprehend and willing to sign an Informed Consent Form (ICF).
2. Male subjects and non-pregnant, non-nursing female subjects 18 to 50 years of age with a clinical diagnosis of AGA.
3. Male subjects with a Norwood-Hamilton classified as III vertex, IV or V and woman subjects with a Sinclair Grade 2, 3 or 4.
4. Subjects willing to agree to have small 1.9 cm diameter circle of hair clipped to ~ 1 mm in length on their balding scalp.
5. Subjects willing to agree to have a permanent dot tattoo applied to their scalp to mark the center of the identified target area.
6. Subjects must agree to maintain the same hair style and hair care regimen during the study.
7. Subjects must agree to not use a medicated shampoo or conditioner containing biotin, saw palmetto or tea tree oil (melaleuca oil) throughout the course of protocol treatment and refrain from hair weaving, hair extensions, texturizers, relaxers, occlusive wigs and non-study hair growth products during the study and for a period of 30 days prior to Visit 2.
8. Subjects must have an absolute neutrophil count (ANC) >1,000/mm^3, and a platelet count >50,000/mL.
9. Male subjects with a serum prostate-specific antigen (PSA) level of < 2.0 ng/mL.
10. Subjects receiving oral or topical hormones must be on a stable dose for 6 months prior to Visit 2.
11. Subjects must be willing to refrain from washing hair, using hair products, and participating in strenuous exercise that would cause profuse sweating for 6 hours after each treatment application with ATI-50002.
12. Woman of child bearing potential (WOCBP) 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.
13. Sexually active male subjects must agree to use a barrier form of birth control from the first application until 30 days post last application of ATI-50002.

8.2. Subject Exclusion Criteria

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

1. Females who are nursing, pregnant, or planning to become pregnant for the duration of the study and up to 30 days after the last application of study medication
2. Clinical diagnosis of alopecia areata or other non-AGA forms of alopecia.
3. Scalp hair loss on the treatment area, due to disease, injury or medical therapy.

4. Active skin disease on the scalp (such as psoriasis or seborrheic dermatitis) or a history of skin disease on the scalp that in the opinion of the investigator would interfere with the study assessments of efficacy or safety.
5. Evidence of hypogonadism defined as serum testosterone < 250ng/dl and/or LH>20mU/ml in males.
6. Active unstable thyroid disease, including subjects on therapy for either hyperthyroidism or hypothyroidism unless their dose of thyroid medication has been stable for 3 months prior to V2 and serum TSH is normal.
7. Subjects with non-pigmented hair.
8. Subjects unable to comply with the following required washout periods:
    - Scalp promoting hair growth products (e.g. minoxidil, finasteride, dutasteride, saw palmetto) for 6 months prior to Visit 2.
    - Anti-androgenetic therapies (e.g. spironolactone, ketoconazole, flutamide, cyproterone acetate) for 6 months prior to Visit 2.
    - Hair transplantation or hair weaving within 6 months of Visit 2
    - Anabolic steroids for 6 weeks prior to Visit 2.
    - Oral or topical JAK inhibitors 3 months prior to Visit 2
    - Platelet rich plasma treatment within 6 months of Visit 2
    - Hair Laser, light or energy treatments to the target hair area within 3 months of Visit 2.
    - Systemic steroids for more than 14 consecutive days in the 2 months prior to Visit 2.
    - Chemotherapy or cytotoxic agents within 12 months of Visit 2.
    - No prior radiation to the scalp.

9. History of, current or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than subjects with: a history of adequately treated and well healed and completely cleared non-melanoma skin cancers (basal or squamous cell carcinoma) treated successfully with no evidence of disease.
10. History of human immunodeficiency virus (HIV), hepatitis B or C.
11. Current herpes zoster infection.
12. Evidence of active, latent or inadequately treated Mycobacterium tuberculosis infection, or history of incompletely treated or untreated tuberculosis. Subjects who have successfully completed therapy for latent tuberculosis may participate.

13. History of serious local infection (*e.g.*, cellulitis, abscess) or systemic infection including but not limited to a history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to Visit 1. Subjects on an antibiotic for a non-serious, acute local infection must complete the course prior to enrollment into the study.

14. Participation in an investigational drug, device, or biologic trial in which administration of an investigational drug, device, or biologic within 30 days or 5 half-lives (whichever is longer) of Visit 2. Subjects who have participated in a study of an investigational drug, device or biologic agent for androgenetic alopecia within 1 year of screening will be eligible to participate only with individual permission from the Medical Monitor.

15. Sensitivity to any of the ingredients in the study medications.
16. Screening ECG findings of:
    - QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose)

    - Heart rate < 45 or > 100 beats/minutes (inclusive)

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

8.3. Subject Withdrawal Criteria

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

Subjects will be permanently discontinued from the study 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%).
- 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:
    - 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

A subject that experiences any of the above events must be discontinued from study medication treatment, the site staff must inform the Aclaris medical monitor of the event, and the site staff must perform protocol-required procedures for trial discontinuation and follow-up.

9. TREATMENT OF SUBJECTS

9.1. Hair Care During Study

Subjects enrolled to the study must agree to use the same shampoo/conditioner through the course of the protocol therapy. This information will be documented in the source notes and captured in the subject's CRF. Shampoo/Conditioner must not contain biotin, saw palmetto or tea tree oil (melaleuca oil). Study medication must be applied to a dry scalp. Subjects should not wash their hair for 6 hours after application of study medication. Subjects are required to maintain the same hair style while on study.

9.2. Target Area Hair Identification

In order to assess the efficacy of the study medication, a 1 cm^2 area of the subject's scalp will be identified and be used to count the number of hair follicles that appear in the area throughout the duration of the study treatment period.

Using the Canfield supplied clear plastic template, a 1 cm^2 area will be identified in an actively balding area. The hair will be pulled through the circular area of the plastic template and then the hair will be clipped short using the supplied electric hair clippers. After the hair is clipped, the template is to be removed and the hairs are to be further trimmed to approximately 1mm in length using 4- inch curved scissors. Once the target area is identified and the hair is clipped then a small tattoo will be applied to mark the target area. Refer to Section 9.4 regarding the procedure for the scalp tattoo. This target area will be used for each TAHC/TAHW assessment throughout the study.

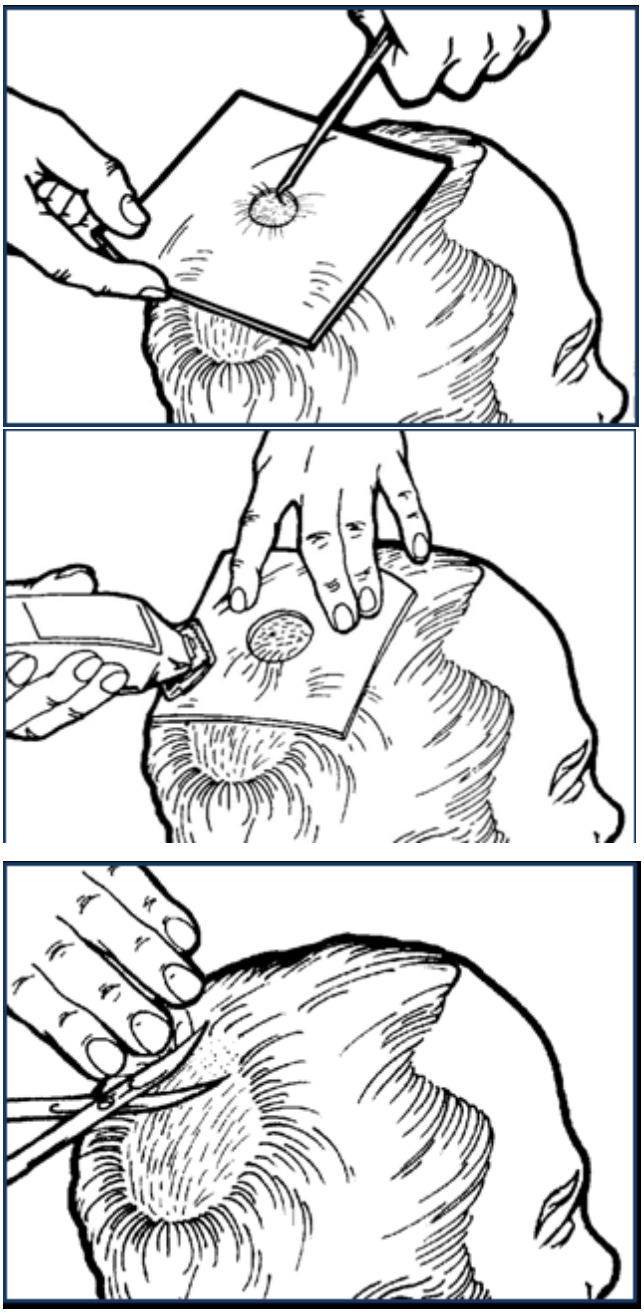


Figure 1: Target Area Identification

9.3. Preparation of Subjects Scalp for Global and Macro Photographs

Investigational sites are to perform the global photographs prior to performing the macro photographs.

For all vertex global scalp photographs (male subjects only), the subject's hair is to be combed outwards from the vertex like the spokes of a wheel. For all frontal global scalp photographs

(male and female subjects), the subject's hair is to be parted in the center and the hair is to be combed away from the center part.

The global photographs will be used by the investigator to perform the Investigative Global Assessment (IGA) and by subject to perform the Subject Self-Assessment (SSA). Refer to Section 11.3 .

9.4. Scalp Tattoo

At Visit 2 all subjects will be required to have a permanent dot tattoo applied to their scalp in an actively balding area. The tattoo will mark the center of the identified target area from which the macro photographs and TAHC and TAHW will be performed.

All sites will be supplied with a tattoo machine and the necessary ink to apply the tattoo. The tattoo machines will be supplied by Canfield and sites will be provided with instructions on how to prepare the machine and the subject's scalp to ensure that the tattoo is applied appropriately.

9.5. Application of Study Medication

Subjects will be instructed to apply a thin film of ATI-50002 Topical Solution 0.46% (up to 4-mL), twice-daily; once in the morning and approximately 12 hours later to the balding area of the clean dry scalp. Refer to Appendix 1 for the complete application instructions. The subject must wash her/his hands thoroughly before and after each study drug application. Investigational site staff will dispense a month's supply of study medication along with disposable droppers to the subject at each study visit. Study medication bottles will be weighed by the site staff at the time of dispensing and when the bottles are returned. Subjects are to return used and unused study medication at each study visit. The disposable droppers should be disposed of at the subject's home.

At each study visit, the study staff will review the study medication instructions and proper application technique. (Appendix 1) with the subject. During Visit 2, the subject will apply the first dose of study medication in the office under the instruction and supervision of the study staff.

During each site visit, the study staff member will:

- Dispense study medication bottles to the subject.
- Instruct the subject on the appropriate application technique following instructions in Appendix 1.
- Weigh the bottles prior to dispensing the study medication
- Observe the subject's first study medication application to ensure proper coverage and monitor the subject for at least 20 minutes (Visit 2 only).

All used study medication bottles will be weighed by the investigational site at each visit.

9.6. Concomitant Medications

Concomitant therapies are any new or existing therapy received from Visit 1 until discharge from the study.

Concomitant therapies include drug (*e.g.*, prescription, over-the-counter [OTC]) and non-drug (*e.g.*, chiropractic, physical therapy, energy-based treatments) therapies. Subjects will refrain from receipt of any therapy in compliance with the inclusion/exclusion criteria. Subjects should refrain from changing the use of any concomitant therapies during the study.

All new or modified concomitant therapies used during the study must be recorded in the subject's eCRF.

9.7. Prohibited Medications

The following medications will be prohibited from being used while the subject is on study and for the identified time-frame prior to Visit 2:

- Scalp hair growth promoting products (e.g.minoxidil, finasteride, dutasteride, saw palmetto) for 6 months prior to Visit 2.
- Anti-androgenetic therapies (e.g. spironolactone, flutamide, cyproterone acetate) for 6 months prior to Visit 2.
- Hair transplantation or hair weaving within 6 months of Visit 2.
- Semi-permanent hair products (e.g. texturizers, relaxers) for 30 days prior to Visit 2.
- Anabolic steroids for 6 weeks prior to Visit 2.
- Oral and topical JAK inhibitors for 3 months prior to Visit 2.
- Medicated shampoo or conditioner containing biotin, saw palmetto or tea tree oil (melaleuca oil) for 30 days prior to Visit 2.
- Platelet rich plasma treatment within 6 months of Visit 2.
- Hair Laser, light or energy treatments to the target hair area within 3 months of Visit 2.
- Systemic steroids for more than 14 consecutive days in the 2 months prior to Visit 2
- Chemotherapy, cytotoxic agents or within 12 months of Visit 2.
- Prior radiation to the scalp.

9.8. 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.

9.9. 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 4 .

Table 4: 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 4 , 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 4 .

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.

9.10. Randomization and Blinding

This study is an open label study so therefore subject randomization does not apply for this clinical trial.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The study medication for this study is ATI-50002 Topical Solution 0.46%. It is a clear, colorless to light pink solution. The inactive ingredients include: purified water, transcutol P, propylene glycol, PEG400, dimethyl sulfoxide (DMSO), kolliphor CS 20, benzyl alcohol, poloxamer 188, and povidone K30

Table 5: Investigational Product

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, 120 mL with screw cap
Storage Conditions	59°F to 77°F (15°C to 25°C)
Dose regimen	
Route	Topical
Frequency	Twice-daily
Duration of administration	52 weeks
Other supplies	Disposable, single-use droppers will be provided.

10.2. Study Drug Packaging, Labeling and Storage

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 120 mL bottles. Disposable droppers with 1 mL calibration mark will be provided to the investigational sites for dispensing to enrolled subjects.

Study drug for this study is AT50002 Topical Solution 0.46%. The study medication will be supplied to subjects enrolled to the study on a monthly basis.

10.3. Study Drug Accountability and Disposal

The Principal Investigator or designee is responsible for ensuring accountability for the investigational agent, including reconciliation of medications and maintenance of medication records. Upon receipt of study medication, the clinical site will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided. One copy of this document will be returned to Aclaris Therapeutics, Inc. (or designee) and one copy will be maintained in the study file at the site. 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.

10.4. Additional Clinical Supplies

In addition to the study medication supplies, each site will be supplied with the following clinical supplies to conduct the study:

- Disposable dispensing droppers
- Canon Rebel T6i 18MP D-SLR
- Canfield IntelliFlash
- Stereotactic Head Device
- Dedicated laptop computer
- Canfield Capture Software
- Blue Drape Cloth
- Canfield VEOS SLR (18 MP)
- Canfield LED
- Secure Digital (SD) Memory Card
- Tattoo Machine and Ink
- Hair Clippers
- 4-inch curved scissors

11. ASSESSMENT OF EFFICACY

11.1. Target Area Hair Count (TAHC) and Target Area Hair Width (TAHW)

The primary efficacy endpoint of the study is the change from baseline in non-vellus (TAHC (hairs/cm^2) and one of the secondary efficacy endpoints is the change from baseline in the cumulative TAHW. The subject's identified target area will be assessed for TAHC and TAHW by the Canfield trained and validated image analysis technicians who are blinded to the center/subject/visit/treatment information. Canfield Scientific, Inc. will supply all investigational sites with photography equipment, tattoo equipment, computer based scanners imaging software, and printers required to capture all global and macro photographs.

As described in Section 8.4, all subjects will be required to have a small permanent tattoo applied to their scalp to mark the center of the identified target area. Global and macrophotographs will be taken by the investigational study staff in accordance with the schedule of assessments. Refer to Table 2 and Table 3 .

The Canfield supplied VEOS SLR camera will be used to take the macrophotographs of the subject's scalp. These images will be transmitted to Canfield for analysis using a computer assisted technique to assess the TAHC and TAHW.

Study staff will receive training from Canfield on the use of the photography equipment, scanners and imaging software in order to transmit all imaging data to Canfield.

11.2. Norwood-Hamilton and Sinclair Scales

Treating investigators will be required to rate the subject's level of hair loss at baseline based on the Norwood Hamilton Scale for male subjects and the Sinclair scale for women. In addition, at the protocol defined time-points, the Investigator will be required to use the appropriate scale to assess the change in hair growth in both male and female subjects.

11.3. Investigator Global Assessment and Subject Self-Assessment

Global photographs will be taken of the vertex scalp of male subjects and of the frontal scalp of both male and female subjects. These global scalp photographs will be used by the investigator and the subject to rate the subject's amount of hair growth at each protocol defined time-point.

After the global photographs are taken the investigator and the subject will use the current photos to rate the change in hair growth from the baseline visit (Visit 2). Both the investigator and the subject will record their assessment into the Canfield computer system. The following 7-point rating scale will be used:

Table 6: 7-Point Rating Scale of Subjects Scalp Hair Based on Evaluation of Global Photographs

Grade	Description
-3	Greatly decreased hair growth
-2	Moderately decreased hair growth

Grade	Description
-1	Slightly decreased hair growth
0	No change
+1	Slightly increased hair growth
+2	Moderately increased hair growth
+3	Greatly increased hair growth

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

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

12.1.1. Demographic/Medical History

During the screening visit (Visit 1), 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, total hysterectomy. Information regarding the subject's prior treatments or therapies related to AGA must be documented along with the type of shampoo/conditioner the subject will use during the study.

12.1.2. Vital Signs

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

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height (at Visit 2 only)
- Weight (at Visit 2 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.

12.1.3. 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 Baseline (Visit 2) and end of study Week 30 (Visit 11)

12.1.4. Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed by a qualified staff member at Screening (Visit 1), Visit 4 (Day 28) Visit 10 (Day 182) and Visit 11/Safety Follow up. 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 cardiology laboratory will provide ECG equipment, supplies and site training. In addition, the central cardiology laboratory 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 the evaluator's interpretation of all ECG reports in a timely manner and comment on the clinical relevance of any result that is defined by the evaluator as abnormal.

Any abnormalities that are, in the opinion of the investigator, clinically significant, must be reported as 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.

If a subject's ECG results meets the ECG withdrawal criteria that is outlined in section 7.3, the site staff must discontinue the subject from study medication and perform all protocol required assessments at the early termination/follow up visit.

12.1.5. 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 study entry. 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. In addition, the investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at monthly visits during the study.

12.1.6. Local Skin Reactions

Investigators and subjects will be required to assess the treated scalp area for local skin reactions (LSRs) at visits 2-11. The following signs and symptoms of contact dermatitis will be assessed:

- Stinging/Burning
- Itching
- Dryness
- Erythema
- Scaling

The Investigator and Subject should report the one integer that best describes the severity of each LSR sign or LSR symptom for the treated scalp area using the scale below.

Local Skin Reactions	
Grade	**Descriptor**
0	None
1	Mild
2	Moderate
3	Severe

If a local skin reaction requires treatment or causes an interruption or discontinuation of study medication then the LSR needs to be recorded and assessed as an adverse event.

12.1.7. Laboratory Assessments

12.1.7.1. Clinical Chemistry/Hematology

All subjects are required to have a blood chemistry panel performed at Visit 1 (Screening), Visit 5 (Day 56), Visit 7 (Day 112), Visit 9 (Day 168), Visit 10 (Day 182) and Visit 11 (Day 210) /Safety Follow up Visit. A qualified staff member will collect non-fasting blood samples and ship the samples to a central laboratory for analysis. The following tests will be performed:

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
CPK	
Calcium	White blood cell differential
Chloride	% & absolute
Creatinine	Basophils
Glucose	Eosinophils
Lactate dehydrogenase (LDH)	Lymphocytes
Phosphorus	Monocytes
Potassium	Neutrophils
Sodium	
Total bilirubin	
Total protein	

Uric Acid

Total cholesterol, LDL, HDL

Triglycerides

Total Iron Binding Capacity (TIBC) (Visit 1 only)

Serum iron (Visit 1 only)

Serum Ferritin (Visit 1 only)

Testosterone

Estrogen

DHEA

Dihydrotesterone (DHT)

Serum PSA (males only; Visit 1 only)

Lutenizing Hormone (LH) (Visit 1 only)

Thyroid Panel (Visit 1 only) (including TSH, Total T4, Total T3, Free T4, Free T3, Reverse T3 (rT3), T3U, Free T4 Index, and TPO and AntiTG antibodies)

12.1.7.2. Virus Serology

All subjects will be required to have a QuantiFERON TB blood test performed at screening to assess for exposure to the tuberculosis virus. At Visit 1 (Screening) a blood sample will be drawn and sent to a central laboratory for analysis. Subjects that test positive will not be eligible for enrollment to the study.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

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.

All AEs that occur from the time of first study medication application (V2) until 30 days after last study medication application must be documented in the subject's source documents and in the Aclaris' electronic data capture system.

12.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

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

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

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

SAEs will be reported from the time of informed consent until 30 days past last application of study medication, whether or not they are related to the study. SAEs will be documented on the Aclaris SAE report form and in the eCRF.

12.2.1.3. 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.

12.3. Recording Adverse Events

12.3.1. 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.

12.3.2. Severity

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

Mild – Awareness of signs or symptom, but easily tolerated.

Moderate – Discomfort, enough to cause interference with usual activity.

Severe – Incapacitating with inability to perform usual activity.

12.3.3. Relationship to study medication

The investigator will determine if there is a reasonable causal relationship between the study medication and an AE or not. The investigator will use her/his best medical judgment and consider all relevant factors (*e.g.*, temporal relationship, location of the event, the subject's relevant medical history, concomitant therapies and concurrent conditions) to determine the relationship of the AE to the study medication. The investigator will define the relationship of an AE to the study medication by selecting one of the following categories:

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

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

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

12.3.4. Procedures for reporting adverse events

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

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

Should a pregnancy occur, it must be reported and recorded on Aclaris's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.3.5. Procedure for reporting a serious adverse event

Upon becoming aware of a SAE occurring during the SAE reporting period (time of subject consent until the end of the subject's last visit), whether or not related to the study medications, the investigator must:

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

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).

12.4. Pregnancy

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

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

12.4.2. Highly Effective Methods of Birth Control

The Investigator or sub-investigator 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)
- 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 ≥90 days)
- Injectables (on a stable dose for ≥90 days)
- Patches (on a stable dose for ≥90 days)
- Combined oral contraceptives (on a stable dose for ≥90 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.

12.5. Protocol Deviation and Protocol Violations

A *protocol deviation* is defined as an accidental or unintentional change to, or non-compliance with the research protocol that does not increase risk, or decrease benefit or; does not have a significant effect on the subject's right, safety, or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher or research staff. A protocol deviation does not involve inclusion/exclusion criteria.

A *protocol violation* is defined as an accidental or unintentional change to, or non-compliance with the IRB approved protocol without prior sponsor approval. Protocol violations generally increase risk or decrease benefit, affects the subject's rights, safety, or welfare, or the integrity of the data.

13. STATISTICS

13.1. Statistical Methods

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

13.2. Primary Efficacy Endpoint

Mean change from baseline in non-vellus TAHC will be quantified using a microphotographic technique and calculated along with the median, standard deviation, standard error, and 95% confidence limits around each mean change to allow tests of the null hypothesis that the population mean changes are zero.

13.3. Secondary Efficacy Endpoints

Mean change from baseline in cumulative TAHW will be quantified using a microphotographic technique and calculated along with the median, standard deviation, standard error, and 95% confidence limits around each mean change to allow tests of the null hypothesis that the population mean changes are zero.

The seven-point rating scale to measure the investigator and subject assessment of the development of new hair growth/scalp coverage will be analyzed with summary statistics (N, mean, median, SD) for each visit where the assessment is made. Similar summary statistics will be used to analyze change from baseline in AGA stage separately for males (Horwood Hamilton Scale) and for females (Sinclair Scale) at each applicable visit.

13.4. Safety Assessments

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

14. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

15. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

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

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit the written approval to Aclaris Therapeutics, Inc. before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or EC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Aclaris Therapeutics, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines.

15.2. 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.

15.3. Written Informed Consent

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

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

15.4. 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 inclusion/exclusion criteria or 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 reported to the IRB by the Investigator, as directed by the IRB-specific procedures.

15.5. 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.

15.6. 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.

16. DATA HANDLING AND RECORDKEEPING

16.1. 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.

16.2. Study Monitoring

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

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Aclaris Therapeutics, Inc. or its representatives. This will be documented in a Clinical Study Agreement between Aclaris Therapeutics, Inc. and the investigator.

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

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

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

16.3. 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.

16.4. Inspection of Records

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

16.5. Retention of Records

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

17. REFERENCES

1. Dinh, Q and Sinclair R. "Female pattern hair loss: Current treatment concepts". Clinical Interventions in Aging 2007: 2(2) 189-199.
2. Gupta Mrinal and Mysore Venkataram. " Classifications of Patterened Hair Loss: A Review." Journal Cutaneous Aesthetic Surgery. 2016. Jan-Mar; 9(1): 3-12.
3. Olsen E, et al. "Evaluation and treatment of male and female pattern hair loss." Journal American Academy Dermatology. 2005: 52: 301-311.
4. Yu, M.et al. "Interluki-6 cytokine family member oncostatin M is a hair follicle expressed factor with hair growth inhibitory properties." Exp. Dermatology, 2008. 17 (1): 12-90.

18. APPENDICES

APPENDIX 1. SUBJECT INSTRUCTIONS FOR STUDY MEDICATION APPLICATION TO THE SCALP

Preparation and General Instructions:

1. Gather a clean washcloth and towel, the study medication bottle, and disposable dropper.
2. Scalp should be clean (free of hair styling products), and dry or at least towel-dried before applying study medication. Ensure that your scalp is as dry as possible. A clean scalp will allow the study medication to penetrate down into the scalp to ensure you are getting the best application.
3. Subjects are to wash their hair using a non-medicated shampoo [not containing biotin, saw palmetto or tea tree oil (melaleuca oil)] during the treatment period (26 weeks).
4. Subjects are not to wash their hair or participate in strenuous exercise that would cause profuse sweating for 6 hours after application of study medication.
5. Wash your hands with soap and water before and after using this study medication.
6. You will apply a thin layer of study medication to the identified area of the scalp as instructed by the study doctor or the study staff. Keep applying study medication to the area of hair loss throughout the study, even if scalp hair is re-growing in these areas.
7. **The amount of study medication you will apply during one treatment is a total of up to 4ml (1 ml droppers supplied with study medication).**
8. Avoid study medication contact with the eye. If the study medication gets on any part of your body other than your scalp, rinse the area well with water.
9. You will apply study medication twice-a-day, approximately 12 hours apart.
10. Remember to bring your study medication bottles both used and unused to each study visit.

Study Medication Application:

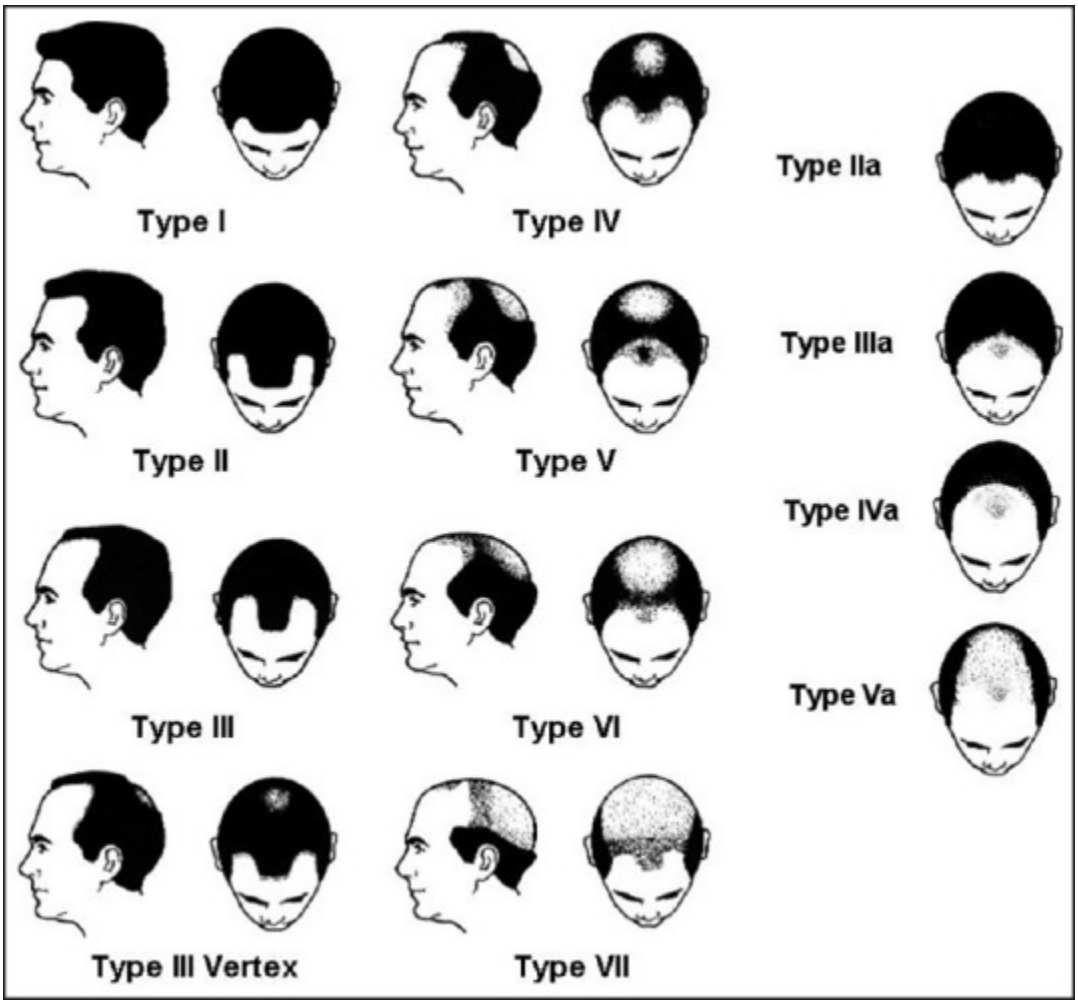
1. Draw up exactly 1 mL of study medication into the dropper. The medication level should be at the 1mL line.
2. During study medication application, avoid any study medication running into your eyes.
3. Squeeze a few drops of study medication onto the center of the identified area of your scalp and gently rub the study medication into your scalp. Keep applying a few drops and rubbing into your scalp until **the entire area** is covered with a thin film of study medication.
4. Draw up additional medication - 1 mL at a time- to cover the entire area on your scalp with hair loss.
5. Replace the screw top cap and make sure it is closed tightly. Dispose of the used dropper(s).
6. It is important to continue to apply study medication to the areas of hair loss throughout the study, even if there is hair growth in the area(s).

7. Wash your hands after using this product to prevent any residue being left on your hands.
8. Allow the study medication to dry for at least 15 minutes before you apply any styling products to the hair. All topical products applied to the hair and scalp must be reviewed and approved by your study doctor before use.
9. If you missed a dose or doses, tell the study staff at your next visit.
10. Do not wash your hair or scalp for at least 6 hours after applying study medication.

Missed Doses: If you miss a dose of this study medicine, apply it as soon as possible. However, if it is almost time for your next dose, skip the missed dose, and go back to your regular dosing schedule.

Storage: Store the medicine in the original glass bottle in the carton provided at room temperature, away from heat, moisture, and direct light. Keep from freezing. Keep out of the reach of children.

APPENDIX 2. NORWOOD HAMILTON SCALE



(Gupta M and Mysor V, 2016)

Type I: Minimal or no recession of the hairline

Type II: Triangular, usually symmetrical, areas of recession at the frontotemporal hairline

Type III: Deep symmetrical recession at the temples that are bare or only sparsely covered by hair. In Type III vertex, the hair loss is primarily from the vertex with limited recession of the frontotemporal hairline that does not exceed the degree of recession seen in Type III.

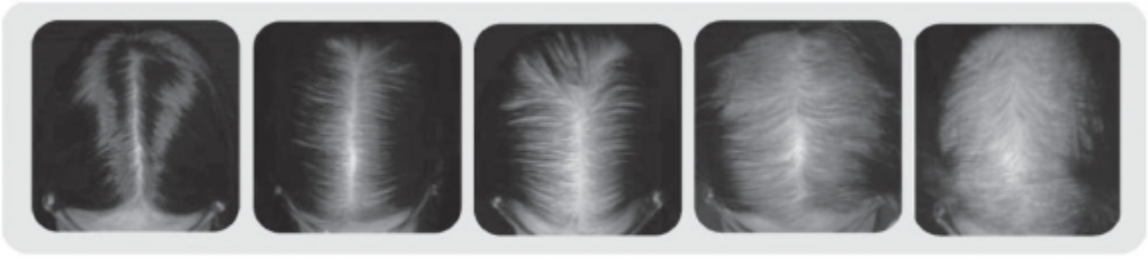
Type IV: Frontotemporal recession is more severe than in Type III and there is sparse hair or no hair on the vertex. The two areas of hair loss are separated by a band of moderately dense hair that extends across the top. The is band connects with the fully haired fringe on the sides of the scalp.

Type V: The vertex hair loss region is still separated from the frontotemporal region but it is less distinct. The band of hair across the crown is narrower and sparser and the vertex and frontotemporal regions of hair loss are bigger.

Type VI: The bridge of hair that crosses the crown is gone with only sparse hair remaining. The frontotemporal and vertex regions are joined together and the extent of hair loss is greater.

Type VII: The most severe form of hair loss and only a narrow band of hair in a horseshoe shape remains on the sides and back of the scalp. This hair is usually not dense and may be quite fine.

APPENDIX 3. SINCLAIR SCALE



(Dinh Q and Sinclair R, 2007)

Grade 1: is normal. This pattern is found in all girls prior to puberty but in only forty-five percent of women aged eighty or over.

Grade 2: shows a widening of the central part.

Grade 3: shows a widening of the central part and thinning of the hair on either side of the central part.

Grade 4: reveals the emergence of a diffuse hair loss over the top of the scalp.

Grade 5: indicates advanced hair loss.

APPENDIX 4. GLOBAL PHOTOGRAPHY PROCEDURE

I. Purpose:

The purpose of these procedures is to ensure that reproducible, registered, serial global photographs are taken of each subject's vertex scalp throughout the study period. These photographs will document hair growth or loss of the vertex scalp and consistency of these photographs permits quality subjective evaluations.

Subjects must not be prepared for macro haircount photography until global photography has been conducted.

II. Photographic locations:

Global photograph of the vertex scalp (male only)

Global photograph of the frontal scalp (male and female)

III. Equipment and Supplies:

- Canon Rebel T6i 18MP D-SLR
- Canon 60mm lens
- Canfield IntelliFlash
- Stereotactic Head Device
- Dedicated laptop computer
- Canfield Capture Software
- Blue Drape cloth

All supplied photographic equipment will remain the property of Canfield.

IV. Global Photography Schedule Overview:

- Visit 1 (Screening)
- Baseline reshoot (Visit 2) (if applicable)

- Visit 5 (Day 56)
- Visit 7 (Day 112)
- Visit 10 (Day 182)

V. Image Capture Procedures:

1. The supplied equipment is to be used exclusively for this study. Modifications, adjustments or repairs of the camera equipment are not to be undertaken without the expressed instruction of Canfield Scientific, Inc.

2. Prior to capturing the subject photographs, Site Photographer launches Canfield Capture software by selecting the icon from the laptop desktop.

3. Site Photographer logs in using unique Username/Password and selects study protocol.

4. Site Photographer either creates a New Subject for an initial visit or, for a return subject, highlights the appropriate existing Subject ID listed in the Canfield Capture database. The visit name (as per Section IV above) is selected by Site Photographer and the photo date is captured by the software.

5. Site Photographer follows the application software prompts to make the capture set. The capture set consists of the vertex view of the head/scalp.

6. Vertex View Hair Preparation: The hair has to be clean, dry, and combed out radially from the vertex like the spokes of a wheel. The blue drape cloth has to be placed over the subject's shoulders to mask the shirt and collar color.

7. For each photograph captured in the Screening capture sequence, the photographer matches orientation to the reference diagrams in Canfield Capture while utilizing the live-preview available. At the Follow-Up sessions, the live-preview with image overlay/ghosting helps maintain photo consistency i.e. magnification and head positioning relative to the camera.

VI. Image Transfer Procedure:

1. After each capture, Site Photographer is prompted to review the photograph for acceptability. The Site Photographer either accepts the photograph and moves on to

the next capture or does not accept it and recaptures.

2. Following the session, the Photographer submits the photographs to Canfield. Upon exiting, the software automatically reads, checksums, encrypts, packages, and duplicates the data to submit to Canfield via internet or removable media submission.

3. Modes of image transfer:

   - Internet: A secure, validated, compliant web server set up at Canfield is used for secure transfer of study photographs by study sites. Photographs are to be transferred the day of capture.
   - Removable Media: a dedicated flash media drive (connected to the PC's USB port). The Photographer removes the flash drive containing the study photographs from the PC, and ships it to Canfield via courier on the same day the photographs are acquired.

   Canfield Capture logs a record of this action to a local database and prompts the Site Photographer when completed.

4. Trained Canfield staff review the photographs with the associated data for technical quality and acceptability and communicate comments and issues to the site.

5. At the end of the study, a copy of site specific subject photographs with all associated data is provided to each Study Site. This copy is in addition to the Photography Result Report forms made available on the Canfield Clinical Services website on a rolling basis for printing after each session. Remote access to all photographs by the Sponsor and CRO (if applicable) is also provided.

6. Canfield provides each Study Site with the necessary hardware as well as technical support as needed. All supplied photographic equipment remains the property of Canfield. Any questions regarding the photographic portion of this study are to be forwarded to the assigned Project Manager at Canfield Scientific.

VII. Electronic Assessments

1. An Investigator Global Assessment (IGA) and Subject Self-Assessment (SSA) web based application is made available for viewing on the supplied laptop. Approved Screening photographs are presented alongside Follow-Up photographs for real-time assessments immediately following Follow-Up photographic capture.

2. Canfield is responsible for programming and installing the application on the laptop. The study specific work instruction outlines the randomization and layout for the assessment application.

3. Canfield electronically captures the assessment scores. The decode listing specifying photograph position is provided and details described in the Data Transfer Specification document.

Questions, issues and comments regarding the photographic portion of this protocol are directed to the assigned Project Management Team at:

Canfield Scientific, Inc.

4 Wood Hollow Road

Parsippany, NJ 07054

Telephone: 973-434-1200

APPENDIX 5. MACRO HAIRCOUNT PHOTOGRAPHY AND IMAGE ANALYSIS PROCEDURE

Purpose:

The purpose of these procedures is to ensure that reproducible, registered, serial macro haircount photographs are taken of each subject throughout the study period. These photographs document hair growth or loss through quantitative image analysis (Target Area Haircount [TAHC] and, Target Area Hair Width. The quality of these photographs is essential in order to allow for accurate image analysis.

Subjects must not be prepared for macro haircount photography until global hair photography has been conducted.

I. Photographic locations:

- Subject ID
- Macro haircount photograph of the clipped target area

II. Equipment and Supplies:

- Canfield VEOS SLR (18 MP)
- Canfield LED
- Secure Digital (SD) Memory Card

III. Macro Photography Schedule Overview

- **Visit 2 (Baseline)**
- **Visit 5 (Day 56)**
- **Visit 7 (Day 112)**
- **Visit 10 (Day 182)**

IV. Target Area Preparation/Image Capture Procedures:

(Full details of hair clipping and macrophotography procedures are provided to the Study Sites in a Canfield Photography Manual prior to study site initiation)

1. The supplied equipment is to be used exclusively for this study. Modifications, adjustments or repairs of the camera equipment are not to be undertaken without the expressed instruction of Canfield Scientific, Inc.

2. Magnification/Aperture: The lens and camera is fixed at a predetermined reproduction ratio and F-Stop.

3. A circular haircount target area approximately 1.9 cm in diameter is identified in the actively balding area (detailed information and diagrams provided in the Canfield Photo Manual). Care is taken to ensure that the target area is a representative area of active hair loss. The target area is clipped short (approximately one [1] mm in length). A small dot tattoo is placed in the center of the target area and is used as a permanent reference point. The same circular haircount target area is clipped and photographed at subsequent study visits. If the ink intensity of the tattoo has faded severely at any subsequent visit, the tattoo is to be reapplied prior to conducting of macrophotography.

4. Only one subject session captured on each SD card. Additional photographs are encouraged if there is any doubt as to the correctness or quality of the photographic technique.

5. Two exposures of subject's ID card include the following legible information in black indelible ink:

    - Protocol No.
    - Date
    - Investigator Number
    - Visit Day
    - Subject's Initials
    - Subject's ID number
    - Photographer's Initials

6. A minimum of 2 exposures of the target haircount area is captured.

V. Image Transfer Procedure:

1. Upon completion of the photographic session, the contents of the SD memory card are uploaded to the Canfield Clinical Services Website. A secure, validated, compliant web server set up at Canfield is used for this secure transfer of study photographs by the study site. Photographs are transferred the day recorded. Remote access to all photographs by the sponsor and CRO (if applicable) is also provided. Only approved individuals by Sponsor have access to the website.

2. After the Site Photographer confirms that the photographs have been successfully uploaded to Canfield, all photographic files are deleted on the memory card by opening Windows Explorer and navigating to the card directory

   - Select all files by clicking on **Edit /Select All**
   - Delete the photographs by clicking on **File / Delete**

3. After clearing the card of all files, the memory card is removed from the card slot and stored for re-use.

VI. Image Archiving and Monitoring:

1. Once the photographs are received at Canfield from the study site, the photographs are copied to a dedicated, secure archival server.

2. Trained Canfield staff review the photographs with the associated data for technical quality and acceptability and communicate comments and issues to the site.

3. At the end of the study, a copy of site specific subject photographs with all associated data is provided to each Study Site. This copy is in addition to the Photography Result Report forms made available on the Canfield Clinical Services website on a rolling basis for printing after each session. Remote access to all photographs by the Sponsor and CRO (if applicable) is also provided.

4. Canfield provides each Study Site with the necessary hardware as well as technical support as needed. All supplied photographic equipment remains the property of Canfield. Any questions regarding the photographic portion of this study are to be forwarded to the assigned Project Manager at Canfield Scientific.

VII. Image Analysis Procedures:

On the digital images, a circular 1-cm^2 target area is identified using the landmark dot tattoo placed in the center of the circle of clipped hairs as a reference point. From the identified 1- cm^2 target area, the width of each hair is determined using an electronic caliber measurement. All hairs >30 μm are classified as terminal hairs.

Hair image analysis is randomized and blinded; subject identity and photographic sequence is unknown to the Canfield technicians conducting the image analysis.

Parameters derived from hair measurement analysis include:

- Target Area Haircount (TAHC)
- Target Area Hair Width (TAHW)

Questions, issues and comments regarding the photographic portion of this protocol are directed to the assigned Project Management Team at:

Canfield Scientific, Inc.

4 Wood Hollow Road

Parsippany, NJ 07054

Telephone: 973-434-1200