Clinical Investigational Plan

Study Title: A Prospective, Randomized, Controlled, Double-Blind Study that Evaluates the Safety and Efficacy of Three Active *REVIAN* Caps versus a Non-Active *REVIAN* Cap (SHAM) in Participants with Pattern Hair Loss (Androgenic Alopecia)

Short Title: REVIAN Trial

Protocol No: REV-01
Version 6.0
2018-08-22

NCT04019795

Study Sponsor:

PhotonMD, Inc.
4222 Emperor Blvd, Suite 470
Durham, NC 27703
(919) 229-4640

Investigator Protocol Signature Page and Protocol Agreement

Study Title: A Prospective, Randomized, Controlled, Double-Blind Study that Evaluates the Safety and Efficacy of Three Active *REVIAN* Caps versus a Non-Active *REVIAN* Cap (SHAM) in Participants with Pattern Hair Loss (Androgenic Alopecia)

Short Title: *REVIAN Trial*
Protocol No: REV-01 Version 6.0

I agree to conduct the investigation in accordance with the agreement and the investigational plan.

I agree to adhere to applicable Good Clinical Practices (GCP) regulations and requirements that govern the conduct of clinical studies as stated in the Code of Federal Regulations, Title 21 (21 CFR):

- 21 CFR 50, *Protection of Human Subjects*, provides the requirements and general elements of informed consent;
- 21 CFR 56, *Institutional Review Boards/Ethic Committee,* covers the procedures and responsibilities for institutional review boards (IRBs) and ethic committees (ECs) that approve clinical investigations protocols;
- 21 CFR 54, *Financial Disclosure by Clinical Investigators*, covers the disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data.

I agree to ensure that all participants will have provided signed Informed Consent prior to enrollment in the study.

I will ensure that the IRB/HREC complies with the requirements of ICH E6, 21 CFR Part 50, and 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the investigation.

I agree to comply with all state and federal laws and regulations governing financial disclosure and to supply updated disclosure information, as it becomes known to me, during the Trial and for one year following completion of the Trial, unless otherwise required by law or regulation.

I agree to supervise all testing of the device involving human participants and ensure that the investigational products supplied by the Sponsor for this study protocol will be used only for participants enrolled for treatment under this protocol, and unused devices will be returned to the Sponsor at the close of the study or sooner as determined by the Sponsor.

I agree to report all unanticipated adverse device effects and serious adverse events as requested to the Sponsor within 24 hours. I agree that all data relevant to the clinical evaluation and regarding the participant response and safety will be documented and forwarded to the Sponsor. I agree to attend a training session on the use of the *REVIAN* Cap prior to the initiation of the clinical investigation.

I have NOT been restricted from participating in clinical research, nor is any action pending that could result in such restriction, nor involved in an investigation or other research that was terminated.

_____ Investigator Signature Date (YYYY-MM-DD)
_____ Investigator Name (please print or type)

REVIAN Protocol Revision History

***REVIAN Investigational* Plan**	**Release Date**
Version 1.0	2016-11-25
Version 2.0	2017-02-14
Version 3.0	2017-03-20
Version 4.0	2017-07-10
Version 5.0	2017-10-01
Version 6.0	2018-08-22

TABLE OF CONTENTS

PROTOCOL SUMMARY

Protocol Title	A Prospective, Randomized, Controlled, Double-Blind Study that Evaluates the Safety and Efficacy of Three Active *REVIAN* Caps versus a Non-Active *REVIAN* Cap (SHAM) in Participants with Pattern Hair Loss (Androgenic Alopecia)
Protocol Number	REV-01, Version 6.0
Investigational Device	REVIAN (PhotonMD, Durham, NC, USA) is a mobile soft dome-shaped Cap using LED modulated light therapy (MLT™) for the treatment of androgenic alopecia. The Cap is controlled and operated by a mobile app and is intended to be used in a home environment.
Study Objective	The primary objective of this study is to collect data on the safety and efficacy of REVIAN in participants with androgenetic alopecia through 26-weeks of treatment.
Study Design	This study is designed as a prospective, randomized, controlled, double-blind, four-arm study. Eligible participants with androgenic alopecia will be enrolled and randomized to one of the four study arms presented below. Study Arm 1: Active *REVIAN* Cap 101 Study Arm 2: Active *REVIAN* Cap 102 Study Arm 3: Active *REVIAN* Cap 103 Study Arm 4: Non-Active *REVIAN* (Sham) Cap 100
Study Population	The study population will consist of adult men and women between 18 and 65 years of age with diagnosis of Androgenic Alopecia, consistent with males who have Norwood Hamilton Classification IIa to V patterns of hair loss and females who have Ludwig-Savin Scale I-1 to I-4, II -1, II-2 or frontal, both with Fitzpatrick Skin Types I – IV. Participants will be excluded for the following conditions: • 12-month usage taking Propecia or any other hair growth supplements prior to enrollment, • using Rogaine or Minoxidil based products for 6-months prior to enrollment, • having previous hair transplant, cell treatment, micro-needling, tattooing, or any other treatment to the scalp, • suffering from an active autoimmune disease such as serum lupus erythematosus or alopecia areata, • photosensitivity to visible light operating within 400 – 850 nm, • currently suffering from a dermatological condition in the treatment area or has a significant scar in the hair treatment area that will make hair growth difficult (such as a systemic burn, malignancy, etc.), • has a sensitivity or allergy to tattoo ink, • using any medication deemed to inhibit hair growth as determined by the physician investigator, or • have had radiation or chemotherapy in the last 12 months
Number of Participants and Sites	Up to a total of 200 (approximately 120 men and 80 women) participants will be enrolled in this study at up to 4 centers.

Primary Efficacy Endpoint	The primary efficacy endpoint of this study is mean change in hair count from baseline to 16-weeks following the initial application at baseline
Primary and Secondary Safety Endpoints	The primary and secondary safety outcomes will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 16- and 26-week period, respectively, for all participants.
Secondary Efficacy Endpoints	**Secondary Efficacy Endpoint(s):** Clinical outcomes will be determined using the following outcome measurement tools to evaluate changes at each follow up visit compared to baseline: 1. *Change from Baseline Hair Count*: Like the primary endpoint, change from baseline hair count, will also be assessed at 8 and 26 weeks. 2. Rate of Change in Hair Growth: The rate of change in hair growth at 8, 16, and 26 weeks will be calculated as a ratio of change from baseline to baseline. 3. *Independent Physician's Global Assessment (iPGA):* An independent reviewer will assess over hair growth over baseline from photographs, using PGA scores at weeks 8, 16 and 26. The PGA score hair growth as: -3=greatly decreased, -2=moderately decreased, -1=slightly decreased, 0=no change, 1=slightly increased, 2=moderately increased and 3=greatly increased 4. *Site Physician's Global Assessment (sPGA)*: The site investigator will assess over hair growth using the PGA scores at weeks 8, 16, and 26. In addition, the percentage of participants who achieve success as defined by a PGA ≥2 will be summarized by treatment and by weeks. 5. *Subjective Scalp Hair Growth Score (SSHG)*: S*SHG* will be administered beginning at 8 weeks and then at 16 and 26 weeks. 6. *Hair Specific Skindex-29 Quality of Life Score Questionnaire (HSSQOL)*: The hair specific Skindex-29 QOL questionnaire will be administered at baseline, 8, 16, and 26 weeks. 7. *Overall Treatment Success (OTS)*: Overall treatment success will be defined as the number of participants who achieve ≥50% reduction in overall QOL scores, plus reported SSHG ≥2 on every question.
Secondary Safety Endpoint	The secondary safety outcome will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 26-week period for all participants.
Statistical Analyses	**Primary Statistical Analysis:** The primary efficacy analysis of this study is to compare the mean change in hair count change from baseline to 16-weeks following the initial application at baseline of *REVIAN* to the Sham. This will be performed using mixed effects analysis of covariance where baseline characteristics and demographics may be considered as covariates. **Safety Analyses:** All Adverse Events (AEs) will be tabulated and summarized as counts and percentages. AEs will also be cross-tabulated per the following categories: • Severity (Mild, Moderate, Severe) • Seriousness (Serious, Non-serious) • Device-Relatedness (Unrelated, Probably Related, Possibly Related, Definite) • Procedure-Relatedness (Unrelated, Probably Related, Possibly Related, Definite)

Study Duration	Study enrollment will be completed over approximately 7-months. All participants included in this clinical investigation will be evaluated for safety and efficacy at 8-, 16- and 26-weeks. The primary study endpoint will be evaluated at 16-weeks and secondary endpoints will be evaluated at 8-, 16- and 26-weeks. The total duration of the enrollment period and completion of the 26-week endpoint is approximately 54-weeks (Approx. 13.5 months) for primary and secondary endpoint evaluation.

PRINCIPAL CONTACTS

	Name, Address and Contact
Study - Principal Investigator	
Study Sponsor/Monitor	
Study Statistician	
Terminal Hair Count and Macro-Photographic Independent Reviewer	
Medical Monitor	
Official Commercial Correspondent	

ABBREVIATIONS AND TERMS

Table 1. Abbreviations and Terms

AE	Adverse Event
AGA	Androgenetic Alopecia
ANCOVA	One-way Analysis of Covariance
CCO	Cytochrome C Oxidase
CRF	Case Report Form
DHT	Dihydrotestosterone
FDA	Food and Drug Administration
FPHL	Female Pattern Hair Loss
FPCB	Flexible Printed Circuit Board
GCP	Good Clinical Practice
HF	Hair Follicles
HREC	Human Research Ethics Committee
ICF	Informed Consent Form
IFU	Instructions for Use
ITT	Intent-to-Treat
ISO	International Organization for Standardization
IRB	Institutional Review Board
LED	Light Emitting Diode
LOCF	Last Observation Carried Forward
LLLT	Low-Level Laser Light Therapy
LTFU	Lost to Follow up
MDD	Medical Device Directive
MLT	Modulated Light Therapy
MPHL	Male Pattern Hair Loss
NO	Nitric Oxide
PCB	Electronically Controlled Circuit Board
PHI	Personal Health Information
PGA	Physician Global Assessment Score
PI	Principal Investigator
PP	Per-Protocol Patient Population
QOL	Quality-of-Life
SAE	Serious Adverse Event
SD	Standard Deviation
SSHG	Subjective Scalp Hair Growth
UADE	Unanticipated Adverse Device Effect

1.0 STUDY PURPOSE

1.1 Introduction and Background

Androgenetic Alopecia

Male and female pattern hair loss is a common, chronic dermatologic disorder. Male pattern hair loss (MPHL) or androgenetic alopecia (AGA) affects 50% of men by 50 years of age, and the frequency and severity increase with age. MPHL is characterized by a dihydrotestosterone-dependent process with miniaturization of terminal hair follicles (HFs) into vellus HFs. The frequency and severity of female pattern hair loss (FPHL) also increase with age, with a prevalence of over 50% in women over the age of 80 years. While the role of androgens in all cases of FPHL is less certain, FPHL also undergoes follicular miniaturization.

Current Care

Pharmacologic Approaches

Current medical treatments for MPHL include pharmaceutical agents such as topical minoxidil (available in 2% and 5% solutions or 5% foam, and sometimes combined with other active ingredients such as tretinoin), finasteride, dutasteride (US FDA approved for the treatment of benign prostatic hyperplasia, and prescribed off-label for treatment of MPHL), topical ketoconazole, anti-androgens and estrogens (for FPHL), and surgical treatment using follicular unit transplantation. Finasteride and minoxidil are well-known, effective treatment methods, but patients who exhibit a poor response to these methods have no additional adequate treatment modalities.

Minoxidil (Rogaine)

This topical medication is available over the counter, and no prescription is required. It can be used in men and women. It works best on the crown, less on the frontal region. Minoxidil is available as a 2% solution, 4% solution, an extra-strength 5% solution, and a new foam or mousse preparation. Rogaine may grow a little hair, but it's better at holding onto what's still there. There are few side effects with Rogaine. The main problem with this treatment is the need to keep applying it once or twice daily, and most men get tired of it after a while. In addition, minoxidil tends to work less well on the front of the head, which is where baldness bothers most men. Inadvertent application to the face or neck skin can cause unwanted hair growth in those areas.

Finasteride (Propecia)

This medication is FDA approved for use in only men with androgenic hair loss. Finasteride is in a class of medications called 5-alpha reductase inhibitors. It is thought to help reduce hair loss by blocking the action of natural hormones in scalp hair follicles. Propecia is a lower-dose version of a commercially available drug called Proscar that helps shrink enlarged prostates in middle-aged and older men. Propecia may grow and thicken hair to some extent for some people, but its main use is to keep (maintain) hair that's still there. Studies have shown that this medication works well in some types of hair loss and must be used for about six to 12 months before full effects are determined. This medication does not "work" in days to weeks, and its onset of visible improvement tends to be gradual. It may be best for men who still have enough hair to retain but also can help some regrow hair. Possible but very unlikely side effects include impotence or a decreased sex drive (libido). Studies have shown that these side effects were possibly slightly more common than seen in the general population and are reversible when the drug is stopped. The cost is about $70-$100/month, which is generally not reimbursed by most health insurers.

Experimental

Dutasteride

Dutasteride is a more potent 5α-reductase inhibitor than finasteride, working by inhibiting both type I and type II 5α-reductase. Whereas type II 5α-reductase concentrations are much higher than those of type I 5α-reductase, the additional inhibitory effect on androgen activity produced by dutasteride may translate into greater clinical efficacy. It is commonly used to treat benign prostatic hypertrophy but is not approved by the US FDA for the treatment of either male or female AGA. Phase 1 and 2 trials conducted exclusively in men demonstrated that at a dose of 2.5–5.0 mg/day, dutasteride suppresses almost 100% of serum Dihydrotestosterone (DHT) activity, whereas finasteride at a dose of 5 mg/day suppresses only 70% of DHT. Phase 2 preclinical trials showed that after 6 months of treatment, there was a 30% increased improvement in hair count when comparing 0.5 mg of dutasteride with 5 mg of finasteride.

Current Surgical Treatment Options

Hair Transplantation

Surgical treatment of AGA has been successfully performed for the past 4 decades. Although the cosmetic results are often satisfactory, the main problem is covering the bald area with donor plugs (or follicles) sufficient in number to be effective. Micrografting produces a more natural appearance than the old technique of transplanting plugs.

A review of surgical procedures concluded that both patients and physicians alike are pleased with the results of contemporary hair transplantation. However, patients with less than 40 follicular units/cm^2 in their donor areas are poor candidates for the procedure.

Scalp Reduction

This option is less popular compared with hair transplantation. It involves bringing hair-bearing skin closer together by removing the central scalp affected by the alopecia. Sometimes it is performed in conjunction with hair transplantation to optimize cosmetic outcomes. Disadvantages of this procedure increase with time and include diminishing efficacy due to the unpredictability of subsequent individual hair loss, increasing cosmetic visibility of excision scars, potential gradual widening of scars due to stretching of adjacent scalp skin, and the usual need for more than one scalp reduction to effectively address hair loss.

In addition, there are numerous oral supplements and topical treatments claimed to have hair growth-promoting or anti-hair loss effects that are marketed directly to the consumers, without independent data supporting the claims.

Alternative Treatments – Light Therapy

Despite the current treatment options for different types of alopecia and given the prevalence of MPHL and FPHL, there is a need for more effective management options. In recent years, low-level laser/light therapy (LLLT), or photobiomodulation or photobiostimulation, has been promoted to prevent hair loss and stimulate hair growth in both MPHL and FPHL. There have been several commercially available devices designed for home use (daily or several times a week), and they are relatively inexpensive compared with current medical treatment and hair transplantation surgery. These low-level laser therapy (LLLT) devices have been evaluated for stimulating hair growth as an effective alternative for pattern hair loss.

Review of prospective, randomized, multicenter clinical studies to determine safety and efficacy of LLLT home devices like the HairMax LaserComb (Lexington International), Handi-Dome Laser (Capillus, LLC), and TOPHAT655 Rejuvenation System (Apira Science, Inc) are considered both safe and effective.

Other products using laser diodes to treat patients with AGA include; iRestore Hair Rejuvenation System (Freedom Laser Therapy) LaserCap 80-300 (Dermascalp, LLC), Capillus 272 Pro and OfficePro (Capillus, LLC), Laser Helmet LH40-EVO (Theradome, Inc), Nutrastim Hair Laser Helmet (Nutra LuxeMD, LLC), and Lasercap 120-300 (Transdermal Cap, Inc.). These medical products have United States FDA clearance without clinical trials.

Conclusions

Both physicians and patients are frustrated with the inconsistent outcomes from these treatment options. Given the increasing prevalence of alopecia in patients and the evident potential of modifying therapies that overcome the limitations of the current treatment options this study is both warranted and necessary.

1.2 Study Rationale

Low level laser therapy (LLLT) utilizing red light (625-680 nm) is clinically proven to be both safe and effective at promoting hair growth in men and women with AGA. The ability of red light to grow hair was accidentally discovered in 1967 by Endre Mester when he observed that shaved mice exposed to red laser light regrew hair faster than mice not exposed.[23] While the exact mechanism of action for light-induced hair growth is unknown, nearly 50 years of research has led to the development of several hypotheses which will be outlined below.

For light to have a therapeutic effect, the light must first be absorbed by molecules in the body, termed photoacceptors. Various wavelengths of light target different photoacceptors. For example 500-600 nm light is absorbed by hemoglobin while IR light (<1050 nm) is absorbed by water.[24-25] Work pioneered by Professor Karu PhD., (Institute on Laser and Informatic Technologies of the Russian Academy of Sciences) discovered that cellular mitochondria are photoacceptors of red light in the skin and scalp.[26-28] The primary hypothesis for why LLLT with red light induces hair growth is that it releases nitric oxide (NO) from the cell mitochondria.[29-30] Nitric oxide is a potent signaling molecule that regulates many physiological processes including vasodilation, the immune response, and neurotransmission. Nitric oxide is generated by nitric oxide synthase enzymes (i.e., endothelial, neuronal, and inducible nitric oxide synthases) that convert L-arginine to NO and L-citrulline.[31-32] The resulting NO is highly reactive and binds to small molecule or proteins to form a non-active state. One protein that NO binds to is Cytochrome C Oxidase (CCO), a protein found in the christa of mitochondria and acts as part of the electron transport chain.[33] When light from LLLT enters a cell, the light energy excites CCO, changing its electronic state and subsequently releasing the bound NO.[30, 34] When NO is bound to CCO, it blocks the respiratory activity of the mitochondria by preventing oxygen from binding to CCO.[33]

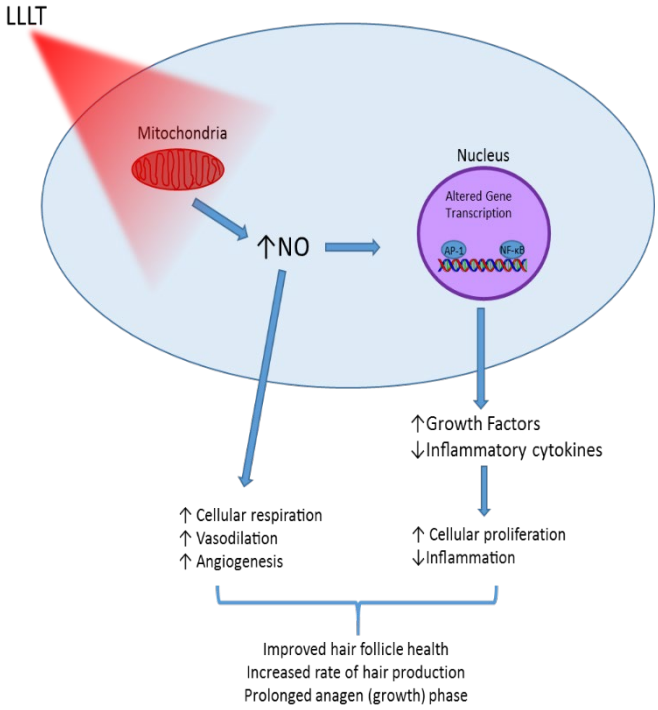

Figure 1. Proposed mechanism of action of LLLT for the treatment of androgenetic alopecia.

Releasing NO from CCO using LLLT therefore increases cellular respiration. In its unbound (bioactive) state, NO alters gene transcription, resulting in increased expression of growth factors and reduced expression of inflammatory cytokines.[29-30] LLLT has been shown to upregulate growth factors associated with the anagen (growth) phase of the hair cycle, which include vascular endothelial growth factor, basic fibroblast growth factor and keratinocyte growth factor.[35,38] By increasing these growth factors, LLLT is believed to prolong the growth phase of the hair cycle and prevent entry into the catagen phases where the hair follicle undergoes massive apoptosis.[29, 39-40]

In the scalp, NO released by LLLT acts as a potent vasodilator, increasing blood flow to the scalp and hair follicles.[41-43] Increased NO levels also stimulate epithelial cell proliferation, leading to

increased angiogenesis and improved microcirculation in the scalp.[44-45 Therefore], LLLT results in short- and long-term improvements to scalp blood flow. This enhanced circulation supports cell metabolism and proliferation while decreasing inflammation, ultimately resulting in healthier follicles which are more capable of producing hair.[29]

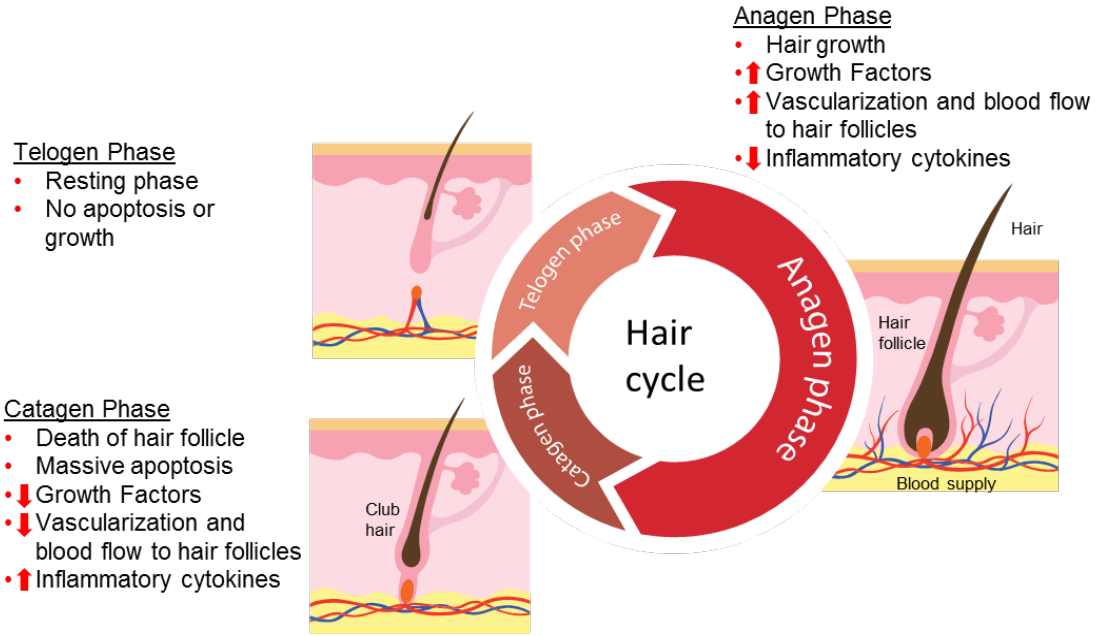

Figure 2. Hair Growth Cycle. The hair growth cycle consists of three main phases: anagen, catagen, and telogen. The length of these phases is controlled by the vascularization and blood flow around the hair follicle and the expression of growth factors and cytokines by cells in the hair follicle. LLLT promotes entry into the anagen (hair growth) phase and prevents transition to the catagen (hair death) phase. This is achieved by improving circulation in the scalp, increasing the expression of growth factors and decreasing inflammation.

Most of the research on LLLT as a treatment for AGA to date has focused on specific wavelengths of light based on historical studies (e.g., Mester's accidental induction of hair growth with red lasers in 1967) and the commercial availability of lasers. Unfortunately, this means the potential to treat AGA with light therapy has been hindered. While current LLLT products release NO from CCO, they do not attempt to generate NO via the upregulation of nitric oxide synthase enzymes. PhotonMD's preclinical work has focused on developing modulated light therapy (MLT)™ via two mechanisms:

1) Increase the concentration of NO in hair follicles by using new wavelengths of light that are more effective at releasing NO from CCO, and the other small molecules and proteins on which it is stored.
2) Regenerate the NO released during LLLT by increasing the expression of nitric oxide synthase enzymes which produce NO from L-arginine.

Systematic *in vitro* experiments were performed to determine the efficacy of different wavelengths of light at releasing NO from its bound, inactive state. Using chemiluminescent detection of NO, it was shown that wavelengths of light used in current LLLT devices were less effective at liberating NO than the wavelengths used in REVIAN 102. These experiments were corroborated by cell studies performed by an unbiased third party which measured intracellular NO generated in human cell lines relevant to hair growth. These studies showed significant improvement in concentration

of unbound (bioactive) NO using the wavelengths of light in REVIAN 102 when compared to traditional forms of red LLLT. Additionally, irradiation with the wavelength of light used in REVIAN 102 enhances the expression of nitric oxide synthase enzymes in human dermal fibroblasts and keratinocytes, while red light had no effect.

These results suggest the REVIAN 102 will increase the amount of NO generated and stored in hair follicles and the surrounding tissue.

REVIAN 103 combines both the current red light therapy technology as well as the new wavelengths of light used in REVIAN 102. As red light therapy is associated with decreased inflammation, combining both treatment modalities may further improve hair growth. By comparing REVIAN 102 and REVIAN 103, we hope to determine whether combining these treatments improves hair growth in an additive or synergistic manner.

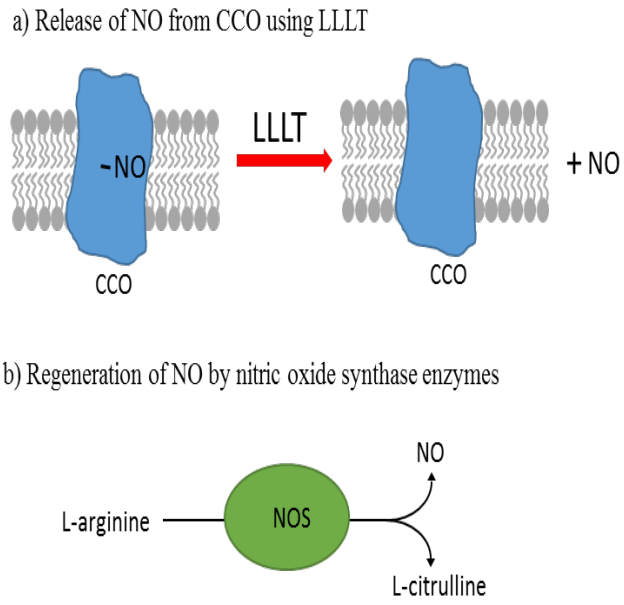

Figure 3. Dual mechanisms of NO generation used by *REVIAN* 102 and 103. The *REVIAN* products a) release NO bound to proteins such as CCO and, b) increase the enzymatic generation of NO by increasing the expression of NOS proteins that convert L-arginine to NO and L-citrulline

While LLLT has been clinically proven to be safe, the design of these devices makes them prone to misuse and risks the potential for eye damage. First, REVIAN 102 and 103 do not use lasers, which can damage the retina due to the intensity of their highly focused light beam. Instead, REVIAN 102 and 103 use light emitting diodes (LEDs), which are inherently safer than lasers due to the wide-angle dispersion of light in LEDs. In addition to improving safety the use of LEDs provides uniform coverage of light to the scalp instead of creating areas of high and low light dosing caused using lasers. Of note, recent scholarship agrees that lasers provide no advantage over LEDS in providing LLLT.[38, 46]

Another safety feature of REVIAN 102 and 103 is the addition of a sensor that automatically dims the LEDS if the Cap is removed from the head to protect the eyes from damage. Finally, the mobile app controls the Cap and helps participants establish a treatment regimen which both improves patient compliance during treatment. The mobile app prevents the Cap from being used more than once a day (ensuring that participants cannot give themselves more light therapy than is necessary), reminds participants to treat daily, and allows them to set reminder alarms.

In summary, the development of new treatments for AGA is highly desirable as current available therapies fail to deliver the outcomes desired by patients. While current light therapy devices for hair growth have proven clinical safety and efficacy, these therapies were

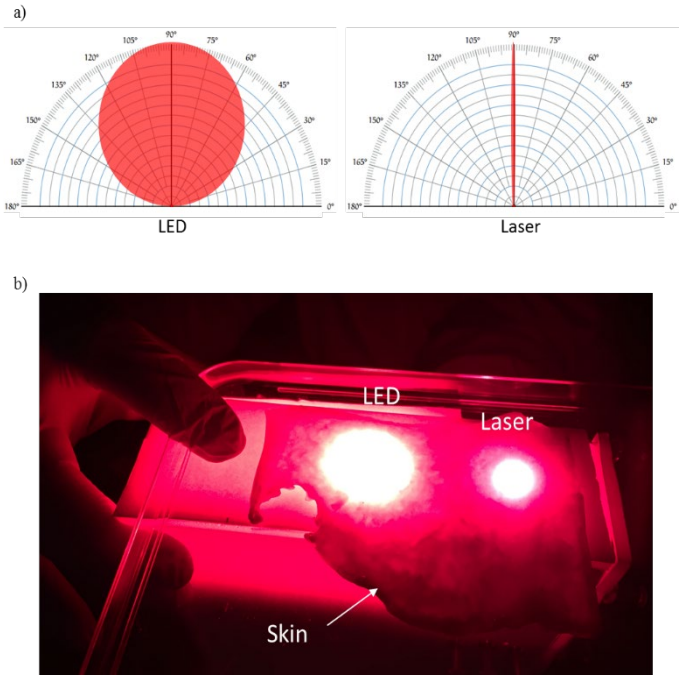

Figure 4. Differences in coverage between LED and Laser medical devices. a) LEDs emit light with a wide distribution angle compared to Lasers, making them both safer and more effective. b) The differences in coverage of light shining from a single LED or single laser through human skin. The irradiance (mW) and distance from the sample was matched for both light sources.

developed based on limited preclinical testing and do not represent optimum modes of treatment including dosing and wavelength. REVIAN 102 and 103 are improvements on the current products because they improve the ability to release NO from its bound form and increase enzymatic generation of NO. The downstream effects of NO in the scalp include improved microcirculation (via vasodilation and angiogenesis), increased proliferation of hair follicle cells, decreased inflammation, and elongation of the anagen phase of hair growth. These downstream effects of NO are believed to improve the health of hair follicles, promote hair growth, and increase hair thickness (diameter). Additionally, the REVIAN products have been designed with safe LEDs, a sensor based automatic turn-off, and programmed treatment schedule to help improve both safety and compliance.

1.3 Device Name

For purposes of this study, "investigational device" or "test device" refers to the REVIAN System (herein after referred to as "REVIAN"). A non-active version of the device will serve as a SHAM comparator (herein after referred to SHAM).

1.4 Brief Description of the Device

The REVIAN is a soft dome-shaped Cap that contains integrated electronics and battery technology to control delivery of modulated light therapy (MLT™) for a daily 10-minute treatment to treat AGA and promote hair growth in men and women. The Cap contains a flexible printed circuit board (FPCB), LEDs, electronic control circuit board (PCB), lithium-polymer battery, elastic fabric and foam fitting pieces. The cap is controlled and operated by a mobile app.

2.0 PROTOCOL

2.1 Study Purpose and Objectives

The primary objective of this study is to collect data on the safety and effectiveness of REVIAN in male and female participants with AGA through 26-weeks of treatment.

2.2 Study Design Overview

This study is designed as a prospective, randomized, controlled, double-blind, four-arm study. Up to 4 clinical sites will enroll up to 200 participants over an approximate 7-month duration. Eligible participants with AGA meeting inclusion and exclusion criteria will be enrolled and randomized to one of four study arms.

Study Arm 1: Active *REVIAN* 101 (___ mW/cm^2 of 625 nm and 660 nm)
Study Arm 2: Active *REVIAN* 102 (___ mW/cm^2 of 425 nm)
Study Arm 3: Active *REVIAN* 103 (___ mW/cm^2 of 425 nm + ___ mW/cm2 of 625 nm and 660 nm)
Study Arm 4: Non-Active *REVIAN* (SHAM) Cap 100

The outcome measures in this study will include the following:

- Quantitative Scalp Hair Growth (Macrophotography of 1-cm^2 area of interest)
- Subjective Scalp Hair Growth (SSHG) score
- Physician's Global Assessment (PGA) score
- Hair Specific Skindex-29 Quality of Life Score Questionnaire

All participants will be asked to complete self-administering scalp hair growth and life quality questionnaires at each follow-up visit. Investigators will be required to complete global assessments of scalp hair growth for each enrolled participant at each follow-up visit.

Macrophotography evaluations will be performed at baseline, 8-, 16-, and 26 weeks for all participants. Global photographs of superior and vertex scalp will be taken by the PI to be assessed by a blinded reviewer once all photos have been captured for each participant per visit.

2.3 Study Scope and Participating Institutions

Participating Institutions

This study will include a maximum of 4 sites. A list of participating institutions will be provided to regulatory authorities as required.

Participant Population

Detailed enrollment criteria are provided in *Section 2.6 Participant Eligibility Criteria* of the protocol. In general, the study population will consist of adult men and women between 18 and 65 years of age with diagnosis of Androgenic Alopecia, consistent with males who have Norwood Hamilton Classification IIa to V patterns of hair loss and females who have Ludwig-Savin Scale I-1 to I-4, II -1, II-2 or frontal, both with Fitzpatrick Skin Types I – IV.

2.4 Study Endpoints

2.4.1 Primary Efficacy Endpoint:

The primary efficacy endpoint of this study is mean change in hair count from baseline to 16 weeks following the initial application at baseline.

2.4.2 Secondary Efficacy Endpoints:

Secondary efficacy endpoints will be determined using the following outcome measurement tools to evaluate changes at each follow up visit compared to baseline:

1. *Change from Baseline Hair Count*: Like the primary endpoint, change from baseline hair count, will also be assessed at 8 and 26 weeks.

2. Rate of Change in Hair Growth: The rate of change in hair growth at 8, 16, and 26 weeks will be calculated as a ratio of change from baseline to baseline.

3. *Independent Physician's Global Assessment (iPGA):* An independent reviewer will assess over hair growth over baseline from photographs, using PGA scores at weeks 8, 16 and 26. The PGA score hair growth as: -3=greatly decreased, -2=moderately decreased, -1=slightly decreased, 0=no change, 1=slightly increased, 2=moderately increased and 3=greatly increased

4. *Site Physician's Global Assessment (sPGA)*: The site investigator will assess over hair growth using the PGA scores at weeks 8, 16, and 26.

   In addition, the percentage of participants who achieve success as defined by a PGA ≥2 will be summarized by treatment and by weeks.

5. *Subjective Scalp Hair Growth Score (SSHG)*: *SSHG* will be administered beginning at 8 weeks and then at 16 and 26 weeks.

6. *Hair Specific Skindex-29 Quality of Life Score Questionnaire (HSSQOL)*: The hair specific Skindex-29 QOL questionnaire will be administered at baseline, 8, 16, and 26 weeks.

7. *Overall Treatment Success (OTS)*: Overall treatment success will be defined as the number of participants who achieve ≥50% reduction in overall QOL scores, plus reported SSHG ≥2 on every question.

2.4.3 Primary Safety Endpoint(s):

At each follow-up visit, participants will be interviewed to determine if any adverse events (AEs) were experienced since the previous follow-up visit. If deemed necessary, a physical assessment may be performed for any participant experiencing a serious adverse event or as required by the Principal Investigator. The primary safety outcomes will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 26-week period for all participants.

2.5 Study Population and Source of Participants

All participants with diagnosis of androgenic alopecia may be eligible for study participation. Potential study candidates will be approached for consent prior to any data collection. A screening and enrollment log will be provided to study sites to maintain a record of all screened participants.

Participants will be identified and recruited by Clinical Investigators and/or their designated research staff at facilities affiliated with a maximum of 4 investigative sites. Clinical Investigators selected to participate in the study should be able to enroll at least 10 participants per month with a maximum of 100 participants enrolled at a single site.

For the purposes of enrollment, only those participants who meet all eligibility criteria, sign an IRB/HREC approved consent form and begin treatment with REVIAN/SHAM will be considered enrolled in the study. Participants who consent to participate but withdraw prior to the first treatment with REVIAN/SHAM will be considered a screening failure and the reasons for screening failure will be documented on the site screening log. All treated participants will be evaluated for the primary endpoints at 16-weeks.

Any participant consented, whether treated or not, will be assigned a screening number. The reason for failure to treat will be recorded in his/her study records and the site screening log.

2.6 Participant Eligibility Criteria

Inclusion Criteria:

*Candidates for this study must meet **ALL** of the following criteria:*

1. Male and Female participants between 18 and 65 years of age
2. Must be able to read and speak English.
3. Participants who are able to give voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained.
4. Participants, who, in the opinion of the Clinical Investigator, are able to understand this clinical investigation, cooperate with the investigational procedures and are willing to return for all the required follow-up visits.
5. Participant must be able to visit clinic site at 8-, 16- and 26-weeks study visits and be available by phone at 4 weeks.
6. Participant must have the ability to communicate effectively with study personnel in person or over the phone.
7. Participant must have diagnosis of Androgenic Alopecia (pattern hair loss).
8. Participant must have active hair loss consistent with Grades IIa to V, based on Norwood-Hamilton Scale or Ludwig-Savin Scale I-1 to I-4, II -1, II-2 or frontal and Grades I - IV using Fitzpatrick Skin Type Scale.
9. Participant's hair must be at least 1 inch in length. The hair style and length shall be the same for each follow-up visit. Participants will be instructed to not have their hair cut/styled within 5 days prior to a follow-up visit.
10. Participant is willing to have a dot tattoo placed on or around the target area of the scalp.
11. Participant is willing to undergo all study procedures including consent for global photographs of hair loss/growth and a 1 mm tattoo to mark the macrophotography site along the indicated transition area of the scalp between the hairline and the balding/thinning vertex area.
12. Participant is willing to avoid the use of wigs, hairpieces, and/or hair extensions during the study period.
13. Hair Specific Skindex-29 Quality of Life total overall score of ≥ 45.
14. Participant is willing to maintain their natural hair colour or including the use of coloring throughout the study period.
15. Participant agrees to refrain from using all other hair growth products or treatments (oral or topical medication including over the counter herbal medications, or Dutasteride) during the study period.
16. Participant has the ability to utilize a Bluetooth device and application on a smart device connected to Wi-Fi.

Exclusion Criteria:

*Candidates will be excluded from the study if **ANY** of the following apply:*

1. Female participants of childbearing potential who are not on some form of birth control and do not have a confirmed negative pregnancy test at baseline
2. Use of Propecia or any other hair growth supplements within 12 months prior to enrollment.
3. Use of Rogaine or Minoxidil based products within 6 months prior to enrollment.
4. Participants have a previous hair transplant, cell treatment, micro needling, tattooing, or any other treatment to the scalp.
5. Participant is suffering from an active autoimmune disease such as lupus erythematosus (systemic and cutaneous) or alopecia areata.
6. Photosensitivity to visible light operating within 400 – 850 nm or taking medication that

increases photosensitivity.

7. Currently suffering from a dermatological condition in the treatment area or has a significant scar in the hair treatment area that, in the opinion of the investigator, will make hair growth difficult (such as a systemic burn, malignancy, etc.)
8. Participant has a sensitivity or allergy to tattoo ink.
9. Using any medication deemed to inhibit hair growth as determined by the physician investigator.
10. Employed by the sponsor, clinic site, or entity associated with the conduct of the study.
11. Has had radiation or chemotherapy in the last 12 months.
12. Have any condition or situation which, in the Investigator's opinion, puts the participant at significant risk, could confound the study results, or may interfere significantly with the participant's participation in the study.
13. Known prior inability to complete required study visits during treatment period;
14. Use of any other investigational drug, therapy, or device within the past 30 days of enrollment or concurrent participation in another research study;
15. Are unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
16. Participants who are currently involved in any investigational drug or device trial or have been enrolled in such trials within the last 3 months.

2.7 Study Duration

It is anticipated that the enrollment of participants will take approximately 7-months. All participants included in this clinical investigation will return for follow-up visits at 8-, 16- and 26-weeks post-baseline visit. Evaluation of the primary efficacy and safety endpoints will be completed on all participants at the 16-weeks post-baseline period and secondary efficacy and safety endpoints will be completed at 26-weeks post-baseline.

3.0 STUDY PROCEDURES

3.1 Enrollment Procedure

Participants will not be recruited until the appropriate governmental regulatory agencies (as applicable) and the local Institutional Review Board (IRB) or Human Research Ethics Committee (HREC) have approved the study. The Investigator or the Investigator's designee will inform all participants of the purpose of the study, expected duration, number of participants, as well as all conditions of the study to include the potential risks and benefits that may result from participation, follow-up duration, and study requirements.

The Investigator or designee will review the participant's history to determine the participant's initial eligibility for study entry. Upon determination of participant eligibility, the participant will be given the opportunity to discuss any aspect of the study, the informed consent, procedure, risks, benefits, alternative therapies, and the study requirements with the Investigator or Investigator's designee prior to signing the informed consent document.

Upon determining a participant's eligibility status, the participant will be offered the opportunity to participate in the study, and the participant's initials will be entered into the study site's screening log regardless of their decision to participate in the study or not. After the participant has signed the Informed Consent, all inclusion and exclusion criteria will be verified. If the participant meets all the inclusion and none of the exclusion criteria, the participant will then become eligible for enrollment.

3.2 Process for Obtaining Informed Consent

The patients will be informed by the Investigator or Investigator's designee that they are free to refuse participation in this research study. If they elect to participate, it will be made clear that they may withdraw from the study at any time without prejudicing further care.

The Investigator or the Investigator's designee will inform participants that their medical records will be subject to review by the sponsor or appropriate regulatory bodies. This information will be used during the analysis of the results of the clinical study, but the participants' identities will be treated as confidential. Participants will be assigned a unique study participant code that will not reveal the participants' identity. This code will be used on all data and data collection forms during the study period.

The Investigator will explain the conditions of the study, giving the participant sufficient time to ask questions and to consider whether to participate. Eligible participants who agree to participate will be asked to sign and date an IRB/HREC approved informed consent form (ICF). One copy of the ICF shall be returned to the Investigator and filed in the participant's case history; the other copy is for the participant to keep.

3.3 Blinding Procedure

The participants, Principal Investigator and Study Coordinators will be blinded to treatment, except in the case of an emergency that requires unblinding of a participant. In order for each Principal Investigator to remain blinded for all participants throughout the study, each site will designate a minimum of one, but no more than two, licensed members of the study staff (e.g., M.D., D.P.M., P.A., Nurse Practitioner, study assistant, etc.) to be the unblinded Treatment Administrator. The role of the Treatment Administrator(s) will be to administer the study device (both active and SHAM) and maintain and complete the Device Treatment and Training logs. In order to verify that the correct application was being used for each participant at each study visit, the code will be reviewed by the local Study Sponsor during monitoring visits and throughout the study when a participant is enrolled.

Each participant will register their user name in the mobile app and run an application for the first treatment prior to leaving the clinic. The Principal Investigator and/or designated Sub-Investigators will serve as the blinded evaluators for all study visits.

3.4 Participant Assessments

3.4.1 Screening – Visit 1

Participants will be preliminarily qualified to determine eligibility, i.e., those who meet all applicable inclusion/exclusion criteria that do not require a study related procedure to be performed. Those participants that meet the preliminary qualification and who agree to participate in the study will sign an Informed Consent. At the initial screening visit, participants will have their demographic information collected, their medical and medication history collected (including duration and severity of AGA); as well as a urine pregnancy test, for females of child bearing potential.

Demographic information will be collected as follows:

- Details including age and date of birth
- Gender
- Co-morbid conditions
- Work status
- Education level
- Smoking history

3.4.2 Baseline – Visit 2

The Baseline visit is the time remaining screening procedures will be completed, with the participant enrolled and randomised to a device, if eligible. This visit can take place up to 7 days from Visit 1, or it can be conducted the same day. Participants will have a physical examination and will then fill out a baseline Hair Specific Skindex-29 Quality of Life Questionnaire. This questionnaire is a well-established, three-dimensional, dermatology-specific health-related quality-of-life (HRQoL) instrument designed to evaluate the impact of androgenetic alopecia (AGA) and treatment outcome on a participant's physical, psychological, social functioning and well-being. A participant must have a Hair Specific Skindex-29 total overall score of ≥ 45 at baseline to be eligible for enrollment. The Skindex-29 consists of 29 items loading on emotional (10-50), functioning (12-60) and symptom (7-35) categories with total scoring ranging from 29-145. The questions refer to the previous 4-week period, and scores are given on a 5-point scale, from 'never' to 'all the time'. Greater scores indicate poorer quality of life. The scale scores are computed by transforming responses to a 100-point scale, with higher

scores indicating a lower level of quality of life. The overall score and individual category scores will be used to demonstrate improvement over the course of the trial. Corresponding Skindex-29 cut-off scores for severely impaired HRQL are as follows: ≥ 52 points on symptoms, ≥ 39 on emotions, ≥ 37 on functioning, and ≥ 44 on the overall score. The estimated cut-off scores can be used in clinical practice to identify patients with (very) severely impaired HRQL

The Investigator will conduct a routine physical exam and record the following:

i. Medical Assessment will be performed and the following information recorded:

- Complete history
- Physical Exam (including vital signs)
- Previous treatments for AGA
- Co-morbid conditions and any disabilities
- Duration and severity of AGA
- Concomitant medication usage
- Pregnancy Test – urine dipstick (as required)

ii. Assessments and Procedures will be collected as follows:

- Hair Specific Skindex-29 Quality of Life Score Questionnaire

If a participant remains eligible, the Investigator will enter the participant into the study. Eligible participants will then have photographic assessments conducted and be trained on the components and use of REVIAN/SHAM and will undergo the first treatment at the PI's office. The day of the first treatment will be considered as the date of participant enrollment.

- Global Photography Image of Two Views (superior and vertex scalp)
- Shave and Tattoo Scalp
- Hair Count - Macrophotography (1cm^2 Area)
- Instruction and 1st REVIAN/SHAM 10 Minute Treatment
- Adverse Events

A standard macrophotography technique will be provided to all investigational sites. Please refer to the Macrophotography Technique Manual for full instructions on the proper site selection for shaving and tattooing the scalp and macrophotography.

All participating investigators will undergo training on the appropriate use of the REVIAN/SHAM device. Only investigators and co-investigators qualified by training or experience in dermatological conditions of the scalp will be selected for this clinical trial.

All participants will be seen at 8-weeks, 16-, and 26-weeks following enrollment.

3.4.3 Randomization of Treatment Device

All participants will be randomized to one of four study arms. The randomization will be a block design, stratified across the sites and maintained by the local Study Sponsor. Each site will be blinded to the randomization code and will only receive a pre-assigned code to use for each participant at time of enrollment. The code will be pre-assigned to one of the four caps below:

Study Arm 1: Active REVIAN Cap 101
Study Arm 2: Active REVIAN Cap 102
Study Arm 3: Active REVIAN Cap 103
Study Arm 4: Non-Active REVIAN (SHAM) Cap 100

3.4.4 Week 1 Phone Call – (7±3 Days), Visit 3

- Concomitant medication usage
- Adverse Events
- Compliance Follow-up

3.4.5 Week 8 Follow-Up Visit – (56±5 Days), Visit 4

- Subjective Scalp Hair Growth (SSHG) Score
- Physician's Global Assessment (PGA) Score
- Hair Specific Skindex-29 Quality of Life Questionnaire
- Global Photography Image of Two Views (superior and vertex scalp)
- Shave and Tattoo Scalp
- Hair Count - Macrophotography (1cm^2 Area)
- Concomitant medication usage
- Adverse Events
- Compliance Follow-up

3.4.6 Week 16 Follow-Up Visit – (112±10 Days), Visit 5

- Subjective Scalp Hair Growth (SSHG) Score
- Physician's Global Assessment (PGA) Score
- Hair Specific Skindex-29 Quality of Life Score Questionnaire
- Global Photography Image of Two Views (superior and vertex scalp)
- Shave and Tattoo Scalp
- Hair Count - Macrophotography (1cm^2 Area)
- Concomitant medication usage
- Adverse Events
- Compliance Follow up

3.4.7 Week 26 Follow-Up Visit – (182±10 Days), Visit 6

- Physical Exam (including vital signs)
- Subjective Scalp Hair Growth (SSHG) Score:
- Physician's Global Assessment (PGA) Score:
- Hair Specific Skindex-29 Quality of Life Score Questionnaire
- Global Photography Image of Two Views (superior and vertex scalp)
- Shave and Tattoo Scalp
- Hair Count - Macrophotography (1cm^2 Area)
- Concomitant medication usage
- Adverse Events
- Compliance Follow up
- Exit/Termination Form

3.4.8 Unscheduled Visit: Visit within 26-weeks Follow-Up

If the participant returns for a study-related unscheduled visit within the 26-weeks follow-up the following evaluations will be performed:

- Medical treatment
- Adverse event
- Concomitant medication

The following Study Assessment Table provides an overview of activities to be performed at each study visit.

PROCEDURES	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening (Day -7)	Baseline (Day 0)	Phone Call (7 ±3 Days)	Week 8[1,2] (56 ±5 Days)	Week 16[1,2] (112 ±10 Days)	Week 26[1,2] (182 ±10 Days)
Informed Consent	X	X				
Demographics	X	X				
Medical History	X	X				
Medication History	X	X				
Inclusion/Exclusion Criteria	X	X				
Pregnancy Test (As required)	X	X				
Physical Examination		X				X
Instruction on Device and 1st Application		X				
Shave and Tattoo Scalp		X		X[3]	X[3]	X[3]
Hair Count - Macrophotography (1cm^2 Area)		X		X	X	X
Global Assessment Photography (superior and vertex scalp)		X		X	X	X
Growth Assessment and Questionnaires:						
(1) Subjective Scalp Hair Growth (SSHG) score[4]				X	X	X
(2) Physician's Global Assessment (*sPGA*) score[4]				X	X	X
(3) Hair Specific Skindex-29 QoL Questionnaire		X		X	X	X
Blinded Review of Global Photographs (*iPGA*)[4]				X	X	X
Follow-up on Compliance and Use of REVIAN/SHAM		X	X	X	X	X
Concomitant Medications		X	X	X	X	X
Adverse Events		X	X	X	X	X
End of Study / Termination / Return Device						X

[1]All visit dates are in reference to Baseline, i.e., Visit 4 occurs approximately eight weeks (56 days) after the Baseline Visit.
[2] Participants will continue treatments throughout the 26-weeks with a daily 10-minute treatment for a total of 56 treatments over 8 weeks, 112 treatments over 16-weeks, and 182 treatments over 26-weeks.
[3] Participants may have tattoo ink reapplied to original site of ink dot application at these time periods.
[4] SSHG, *sPGA* and *iPGA* are not taken at baseline. These assessments are conducted at the follow-up visits only.

3.5 Termination of Participants

Participants may voluntarily withdraw from the study at any time for any reason. The Investigator(s) may elect at any time to withdraw a participant from the study for any reason unrelated to the study treatment if such a decision is in the participant's best medical interest. If a participant discontinues the study, or is withdrawn by the Investigator(s), as much follow-up data as possible will be obtained. The primary reason for termination or discontinuation will be documented on the End of Study case report form. Participants who are withdrawn from the study after treatment for any reason will not be replaced.

Anticipated reasons for not evaluating a participant through the primary endpoint include:

Participant Lost to Follow-Up: Unable to locate participant despite documented attempts to notify the participant via telephone and by certified mail. A participant will not be considered lost to follow-up until the last scheduled follow-up visit (26-week secondary study time point).

Participant Request to Terminate: The participant requests to terminate his/her involvement in the study, therefore withdrawing his/her consent to participate in the study (the investigator must thoroughly document the reasons for termination). Attempts will be made to retrieve any follow-up data, prior to the time point at which voluntary consent was withdrawn, when available, regarding possible AEs at the time of study discontinuation

Participant Death: If possible, an autopsy and/or death certificate should be obtained to document the cause of death.

4.0 SAFETY REPORTING

All adverse events (AEs), whether device- related or not will be recorded and reported. Pain and function symptoms are categorized as complications when a participant's complaint for any of these symptoms results in an unscheduled visit or when a participant presents with new or worsening symptoms as compared to the previous visit.

4.1 Adverse Events

An AE is any undesired clinical response or complication experienced by a participant. All AEs, whether device-related or not, will be recorded on the AE case report forms. Data to be collected will include the description of the AE, onset and resolution dates (or whether the AE is ongoing), severity, management/treatment, outcome, and determination of the relationship to the device and/or procedure. In general, AEs should be reported and classified by the Investigator using a diagnosis. The diagnosis should be confirmed through specific signs, symptoms, and (if necessary) laboratory tests. The Investigator will determine the relationship of the AE to the device or the study procedure.

The Investigator, based on his or her clinical judgment using the following categories (detailed definitions provided in Appendix A), will determine the relationship and severity of the AE to the device and/or treatment procedure:

1. *Unrelated:* *The adverse event is clearly not related*
2. *Possibly related:* *The adverse event may be related*
3. *Probably related:* *The adverse event is likely related*
4. *Definite:* *The adverse event is clearly related*

An AE or an adverse device effect may be mild, moderate or severe.

The term "severe" is used to describe intensity (severity) of a specific event; the mild, moderate and severe definitions are listed below. An event itself, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on participant/event outcomes or action criteria usually associated with events that pose a threat to the participant's life or functioning.

Severity will be determined by the Investigator and coded as to the degree of severity as follows:

1. *Mild:* Awareness of the event but easily tolerated.
2. *Moderate*: Discomfort enough to cause interference with usual activity.
3. *Severe*: Inability to carry out usual activity (not necessarily the same as a Serious Adverse Event)

For the purposes of safety reporting in this study, the following definitions will be applied:

- An **adverse event** (**AE**) is any untoward medical occurrence in a participant whether it is considered device related or not. Diseases, signs, symptoms, or laboratory abnormalities already existing at enrollment are not considered AE's unless they worsen (i.e., increase in intensity or frequency). Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event. Surgical procedures planned prior to enrollment and the conditions leading to these measures are not adverse events.

- An **adverse device effect (ADE)** is any untoward and unintended response to a medical device, including events arising from insufficient or inadequate instructions for the employment of the device or its use.

- A **Serious Adverse Event** (**SAE**) is any AE that 1) results in death, 2) is life threatening, 3) results in or prolong hospitalization, 4) results in permanent impairment of a body function or permanent damage to a body structure, 5) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

  Note: a device malfunction may or may not result in an AE. If a device malfunctions in a manner that causes an AE or a SAE as defined above, then the consequence of the malfunction will be reported as an AE or SAE, as appropriate. However, all device malfunctions will also be tabulated separately, regardless of whether or not an adverse event results from the malfunction.

Any SAE must be reported to the sponsor or designee by the Investigator within 24 hours of first learning about the event. A written report must be sent to the sponsor within ten working days of knowledge of the event to the fax number listed on the Serious Adverse Event Report Form.

The investigator is required to notify the IRB or EC in accordance with local reporting requirements.

4.2 Anticipated Adverse Events

The following AEs may be associated with the REVIAN device:

- Mechanical or electrical failure of the device or components
- Materials of Cap that may cause irritation or tissue reaction
- Allergies to Materials of Cap
- Failure to improve symptoms and/or function
- Hyperpigmentation of the treatment area

4.3 Unanticipated Adverse Device Effects

ISO 14155:2011 (Clinical Investigation of Medical Devices – Good Clinical Practice) defines an unanticipated adverse device effect (UADE) as any *serious* adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan or risk analysis; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB/EC, as described below:

- Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB/HREC as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

- PhotonMD will immediately conduct an evaluation of an UADE and report the results of the evaluation to the appropriate regulatory agency, all reviewing IRB/HRECs and participating investigators within 10 working days after first notice of the effect (§§ 812.46(b), 812.150(b)(1)).

All serious reported events will be followed until resolution, stabilization or 30 days after the last participant enrolled has completed the trial, whichever occurs first.

ALL UNANTICIPATED ADVERSE DEVICE EFFECTS AND SERIOUS ADVERSE EVENTS OCCURRING THROUGHOUT THE STUDY PERIOD MUST BE RECORDED ON THE ADVERSE EVENT CRF AND FAXED TO THE STUDY SPONSOR AS SOON AS POSSIBLE (WITHIN 24 HOURS).

4.4 Medical Monitor

To promote early detection of any safety issues routine medical monitoring may be conducted on an ongoing basis. A medical monitor would provide evaluation of safety events at routine intervals. Process flow, supporting documents, and software programming will allow for 21 CFR Part 11 compliant electronic database access, to the medical monitor for real time case review and event adjudication.

The medical monitor may be un-blinded due to the fact the dataset will contain obvious AEs/SAEs specific to the active treatment compared to non-active treatment that will, simply by their presence, un-blind the individual reviewing the data. This process requires the dynamic collection of unmonitored data as soon as an event is reported. The medical monitor will be responsible to review and adjudicate the safety outcome measures and relevant adverse events reported by study investigators. Relevant information and source documents will be provided to assist with their

review and adjudication of events. During regularly scheduled monitoring visits, the clinical research monitors will support the dynamic reporting process through their review of source document information.

The medical monitor would review accumulating safety data to monitor the incidence of Adverse Events and other trends that would warrant modification or termination of the trial. The medical monitor would review the safety outcomes in both arms to ensure that the risks do not exceed the benefits. All reviews conducted by the medical monitor would be reported to the sponsor.

5.0 STATISTICAL ANALYSIS PLAN

5.1 Study Objective/Purpose

The purpose of the study is to collect data on the safety and effectiveness of REVIAN in participants with AGA. In general, for continuous variables, the sample size, mean, standard deviation, and range will be presented. For categorical variables, the number and percentage in each category will be presented.

Primary Efficacy Endpoint: The primary efficacy endpoint of this study is the mean change in hair count from baseline to 16 weeks following the initial application.

Primary Safety Endpoint: The primary safety outcome will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 16 week period for all participants.

Secondary Efficacy Endpoints: The secondary efficacy endpoints include the following:

(1) *Change from Baseline Hair Count*: Like the primary endpoint, change from baseline hair count, will also be assessed at 8 and 26 weeks.

(2) *Rate of Change in Hair Growth*: The rate of change in hair growth at 8, 16 and 26 weeks will be calculated as ratio of change from baseline to baseline.

(3) *Independent Physician's Global Assessment (iPGA*): An independent reviewer will assess over hair growth from photographs, using PGA scores at weeks 8, 16 and 26. The PGA score hair growth as: -3=greatly decreased, -2=moderately decreased, -1=slightly decreased, 0=no change, 1=slightly increased, 2=moderately increased and 3=greatly increased.

(4) *Site Physician's Global Assessment (sPGA)*: The site investigator will assess over hair growth using the PGA scores at weeks 8, 16 and 26. In addition, the percentage of participants who achieve success as defined by a PGA ≥2.0 will be summarized by treatment and by weeks.

(5) *Subjective Scalp Hair Growth Score (SSHG)*: Beginning at Week 8, participants will complete a subjective hair growth questionnaire. The participants choose the answer that best fits the following statements:

1) Since the start of the study, I can see my bald spot getting smaller. (1="strongly agree" to 5= "strongly disagree")
2) Because of the treatment, I have received since the starts if the study, the appearance of my hair is: (1="a lot better" to 5="a lot worse")
3) Ever since the start of the study, how would you describe the growth of your hair? (1="greatly increased" to 7="Greatly decreased")
4) Ever since the start of the study, how effective do you think the treatment has been in slowing down your hair loss? (1="Very effective" to 4="Not effective at all")
5) Compared to the beginning of the study, which statement best describes your

satisfaction with your appearance of:

a. The hairline in front of your head? (1="very satisfied" to 5="very dissatisfied")
b. The hair on top of your head? (1="very satisfied" to 5="very dissatisfied")
c. Your hair overall? (1="very satisfied" to 5="very dissatisfied")

SSHG will be administered at 8 weeks, 16 weeks and 26 weeks

(6) *Hair Specific Skindex-29 Quality of Life Questionnaire (HSSQOL*): The hair specific Skindex-29 QOL questionnaire is a 29-item questionnaire with 3 domains: 7 questions for symptoms domain, 10 questions emotion domain and 12 questions for function domain. Participants score each question on a scale from 1 (never) to 5 (all the time). Scores are then summed within each domain and overall. HSSQOL will be administered at baseline, 8, 16 and 26 weeks.

(7) *Overall Treatment Success (OTS)*: Overall treatment success will be defined as the number of participants who achieve ≥50% reduction in overall QOL scores, plus reported SSHG ≥2 on every question.

Secondary Safety Endpoint: The primary safety outcome will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 26-week period for all participants.

5.2 Study Analysis, Sample Size and Pooling of Data

Study Analysis:
The primary efficacy analysis of this study is to compare the mean change in hair count change from baseline to 16-weeks following the initial application at baseline of REVIAN to the SHAM. This will be performed using mixed effects analysis of covariance (ANCOVA) where baseline characteristics and demographics may be considered as covariates. Comparison between active groups will not be tested for statistical significance as the study is not powered for these comparisons. Instead, each active will be compared to the SHAM individually. Details on adjustments for multiple testing to a single SHAM will be provided in a statistical analysis plan.

Power Calculation, Sample Size:

Prior hair growth studies, regardless of potential efficacy of the SHAM device, showed the delta between active treatments and control treatments was consistently at around 15-22 hairs/cm^2 which appears to be the expected level of improvement. It is estimated that participants in the active group will have greater than 15 hairs/cm^2 by 16-weeks. The study design is a parallel arm study of superiority of PhotonMD devices to SHAM with a minimum of 40 participants per arm. Assumptions are 15 hair difference between treatments, standard deviation (SD)=20, 10% drop-out rate, 5% alpha level, 90% power and 2-sided t-test.

The study will accrue a total of 200 participants (50 per each Active Study Arm and 50 control participants) to make sure, after lost to follow-up, that there is a minimum of 160 evaluable (40 per arm) participants.

Pooling of Data:

The clinical study will be conducted under a common protocol for each of 3 investigational sites with the intention of pooling the data over all sites for analysis. Every effort will be made to promote consistency in study execution at each investigational site.

5.3 Analysis Populations

Participants receive either an active *REVIAN* Cap in three arms or a non-active *REVIAN* Cap (three versions of an active *REVIAN* Cap and one non-active *REVIAN* Cap). The following participant groups or analysis populations will be used to complete the analysis of data:

Intent-to-Treat participant population (ITT): The ITT participant population will include all participants that started a treatment at Baseline. All baseline characteristics, demographics and primary efficacy analyses will be performed on the ITT population.

Per-Protocol participant population (PP): The PP participant population will include all participants in the ITT population with 16-week follow-up data, with no major protocol deviations. The primary and secondary efficacy analyses will be performed on the PP population.

Safety participant population (SAF): The SAF participant population is the same as the ITT population. All safety summaries will be performed on the SAF population.

5.4 Safety Outcomes

Safety outcomes will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 26-weeks timepoint for all participants. All Adverse Events (AEs) will be tabulated and summarized as counts and percentages. AEs will also be cross-tabulated according to the following:

- Severity (Mild, Moderate, Severe)
- Seriousness (Serious, Non-serious)
- Device-Relatedness (Unrelated, Possibly Related, Probably Related, Definite)
- Procedure-Relatedness (Unrelated, Possibly Related, Probably Related, Definite)

In addition, the occurrence of any Unanticipated Adverse Device Effects (UADE) will be listed. The classification of severity, relatedness, and anticipated nature of AEs will be made by the investigator.

5.5 Baseline Variables

Demographic and baseline variables will be summarized. Sample sizes, means, standard deviations and ranges will be presented for all continuous variables.

5.6 Participant Accountability

Lost-to-Follow-Up: The primary analysis will be done on the ITT group. Those participants who withdraw or who are lost (LTFU) after enrollment will be included in the primary analysis using a last observation carried forward (LOCF) approach where the outcome at the most recent visit will be carried forward to all subsequent missing assessment times. Participants without at-least an 8-week visit will have their baseline observation carried forward (BOCF).

5.7 Missing Values

Every effort will be undertaken to fulfill all the requirements of the protocol concerning the collection of data. If participants refuse to return for data collection, but agree to continue in the study, questionnaire data will be collected over the telephone or at home if necessary. Missing values may occur under the following conditions.

- Participants fail improvement and exit the study.
- Participants do not return to the clinic but information regarding REVIAN can be obtained.
- Participants do not return to the clinic but will complete one or more of the questionnaires.
- Participants do not return to the clinic and cannot be contacted.

For other secondary endpoints, analyses will be performed first on all available data with no imputation and additionally with imputed 26-week data.

5.8 Follow-Up and Reporting

All participants enrolled and devices used in the clinical investigation will be accounted for in the final report. All reasons for exclusion from analysis will be carefully documented. Similarly, for all participants and devices included in an analysis population, the measurements of all important variables must be accounted for at all relevant time points. Additional information that is available on participants screened for entry but not enrolled will also be summarized.

Participants lost to follow-up or withdrawn from the study will be identified and a descriptive analysis of them provided, including the reasons for their loss to follow-up and known treatment outcome.

For participants with device failures, data up to the time of the participant's last visit will be pooled with all other participants and analyzed on a per protocol (PP) basis.

5.9 Protocol Deviations

A protocol deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the Investigational Plan or the Investigator Agreement.

Investigators are required to obtain prior approval from study management before deviating from the investigational plan or protocol, except where necessary to protect the life or physical well-being of a participant in an emergency. Such approval will be documented in writing and maintained in study files. Prior approval is generally not expected in situations where circumstances are beyond the Investigator's control, (e.g., participant did not attend scheduled follow-up visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation.

Deviations shall be reported to the study sponsor regardless of whether medically justifiable, pre-approved, or taken to protect the participant in an emergency. Participant specific deviations will be reported on the Case Report Form. Non-participant specific deviations will be reported to the sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB/HREC in accordance with their specific IRB/HREC reporting policies and procedures.

GCP regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates and reasons for each deviation from the protocol.

6.0 STUDY MANAGEMENT

6.1 Sponsor Ethical and Regulatory Considerations

As the Sponsor of this clinical study, PhotonMD has the overall responsibility for the conduct of the study, including assurance that the study meets US federal and local regulatory requirements appropriate to the conduct of the study and is conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). PhotonMD will have certain direct responsibilities and may delegate responsibilities to a Contract Research Organization (CRO). The study sponsor will adhere to sponsor general duties as described in ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice, and CFR Part 812, 50, 56, 54 and the World Medical Association Declaration of Helsinki.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a unique participant identification code (ID number and participant name code – initials only). All study records will be kept in a locked file cabinet and code sheets linking a participant's name to a participant identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

General Duties

PhotonMD will ensure that the application is submitted to the appropriate regulatory authorities, obtaining copies of IRB/HREC approvals and ensuring documentation of IRB/HREC approvals prior to the shipping of devices, ensuring proper clinical site monitoring, ensuring participant informed consent is obtained, providing quality data that satisfies regulations and informing the Investigators and IRB/ECs of unanticipated adverse device effects, events, and deviations from the protocol as appropriate.

The investigation must be reviewed and approved by the appropriate IRB/HRECs before participant enrollment may begin. All proposed changes to the investigational plan must be reviewed and approved by PhotonMD. PhotonMD will also obtain any necessary regulatory approval, per local requirements.

Selection of Clinical Sites

The primary requirements of site and Investigator selection and continued participation in the Trial are: adequate experience, commitment to safety, consistency in adherence to the protocol, and participant volume. Participating sites will be screened to ensure they have sufficient numbers of eligible participants who are representative of the target population. Each center must have facilities that are capable of processing participants in the manner prescribed by the protocol.

The study sponsor, PhotonMD, and its designees will select qualified Investigators, ship or deliver devices only to participating Investigators, obtain signed study agreements, and provide Investigators with the information necessary to conduct the study.

Site Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or designee. The Investigator is responsible for ensuring that his/her staff conduct the study according to the protocol. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present a formal training session to study site personnel which will review the instructions for use of the device, the Investigational Plan, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor or designee through the regular site monitoring.

Investigator Training

The Sponsor will provide appropriate Investigator training on the use of the *REVIAN* System, including the mobile app and the *REVIAN* Cap. Training will take place prior to the initiation of the clinical investigation. Training will address topics including indications for use of the device, management of complications, and instructions to participants. Training will be documented for each physician on a training log, signed by both the physician and training representative

Participant Confidentiality

Participant confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique participant identification code (ID number and participant name code) will be used that allows identification of all data reported for each participant.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the participant's privacy is guaranteed.

Record Retention

PhotonMD will maintain copies of correspondence, data, shipment of devices, adverse device effects, Investigator agreements and other records related to the clinical trial. All study records and reports will remain on file at the sites for a minimum of 2 years after completion of the Study, and will further be retained in accordance with local guidelines as identified in the clinical study agreement. Study records are to be discarded only upon notification by the study sponsor. The Investigator must contact the study sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the sponsor should be contacted if the Investigator plans to leave the investigational site. All required data for this study will be collected on standardized CRFs or an electronic data capture system. All information and data sent to the Sponsor or Contract Research Organizations (CROs) concerning participants or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the participant. The principal Investigator consents to visits by the staff of the Sponsor and its authorized representatives and the U.S. Food and Drug Administration or any other local governmental body to review the study participants' medical records including any test or laboratory data that might have been recorded on diagnostic tests media (e.g., photographs, etc.).

6.2 Investigator Responsibilities

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice. The Investigator will provide current copies of the study protocol to all Sub-Investigators or other site personnel responsible for study conduct.

Upon completion or termination of the study, the Investigator will submit a final written report to the study sponsor and the reviewing IRB/EC. The report should be submitted to the study sponsor within three (3) months of study completion or termination. The Investigator will provide the study sponsor or designee with copies of all IRB/HREC actions regarding the study.

6.2.1 IRB/HREC Approval and Informed Consent

The investigation must be reviewed and approved by the appropriate IRB/HREC before participant enrollment may begin. All proposed changes to the investigational plan must be reviewed and approved by PhotonMD.

Prior to shipment of study devices, a signed copy of the IRB/HREC Committee approval letter identifying the clinical study must be submitted to PhotonMD, signifying study approval. Investigators are responsible for obtaining and maintaining approval of the study by the IRB/EC.

Written informed consent is mandatory and must be obtained from all participants prior to performing any study procedures in this clinical study. PhotonMD will provide each investigator site with a Sponsor approved consent template. Each site is expected to modify the template, if necessary, to meet their facilities requirements. Modified ICF templates must be reviewed by the Sponsor prior to submission to their IRB/EC.

Informed consent must be obtained and shall inform the participant as to the objective and procedures of the study and possible risks involved. The participants must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the participant is otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. The clinical study informed consent must be used in addition to any institutional standard consent form for participation in clinical research. The institutional standard informed consent form does not replace the study consent form.

It is the responsibility of the investigator to obtain both an authorization for participant health information and study consent.

The IRB/HREC approved Informed Consent Forms must be retained at the investigational site along with the other investigational case report forms. A signed copy of the consent form must be given to each participant enrolled in the study.

6.2.2 Data Collection and Reporting

Case report forms will be used to record demographic, procedural, and follow-up data, as well as any unscheduled visits or adverse clinical events which may occur during the study period. The AEs and incidence of morbidity and mortality will be reviewed with Investigators to assess the safety of the device and the procedure.

Qualified study staff at each clinical site will perform primary data collection drawn from source-document (hospital chart) reviews. The clinical monitor will perform clinical monitoring, including review of CRFs with verification of study eligibility, informed consent process, scheduled and unscheduled follow-up visits and AEs to the source documentation.

6.2.3 CRF Completion and Submission

Investigators should complete case report forms (CRF)s in a timely fashion, preferably within 7 days after participant enrollment or follow-up visit. This will enable timely monitoring visits.

Serious adverse events and reports of device failures should be faxed to the study sponsor within 24 hours of first knowledge of the event. Contact information is included on the CRF form.

6.2.4 Data Management

PhotonMD or a representative of the Sponsor will be responsible for database creation and validation. Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data from the analysis for each participant will be determined by appropriate clinical and statistical personnel. All exclusions related to either safety or efficacy will be documented in participant listings.

6.2.5 Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all study devices. When the enrollment is complete, the Investigator shall return any unused devices to the study sponsor. At the completion of the study, all devices shall be returned to the sponsor. The Investigator's copy of the Device Accountability Log must document devices that have been returned to the sponsor.

The device accountability log will include records of receipt, use or disposition of a device that relate to:

1. The type and quantity of the device, the dates of its receipt, and the lot number.
2. The names of all persons who received, used, or disposed of each device.
3. Why and how many units of the device have been returned to the sponsor, or otherwise disposed of.

6.2.6 Source Documents

The investigator shall maintain accurate, complete, and current records relating to the investigator's participation in an investigation including records of each participant's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

1. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each participant shall document that informed consent was obtained prior to participation in the study.

2. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering, and during the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

3. A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other therapy.

The following records must be maintained in designated study administrative files:

- Clinical Protocol and all amendments
- Signed Investigator Agreement
- IRB/HREC approval letter(s) and approved Informed Consent(s) (including any revisions)
- Correspondence relating to this study (with Sponsor, Clinical Monitors, other Investigators, etc.)
- Correspondence with the IRB/HREC
- Instructions for Use
- Curriculum Vitae for all Investigators
- Device log
- Device related paperwork (including shipping documents, invoices, device return log)
- Monitor sign-in log
- Site authorized personnel signature list
- Blank set of CRFs and instructions for completion
- CRF monitoring forms
- Reports (including Adverse Event reports, annual reports and final reports from Investigator and Sponsor)

The following records must be maintained for each participant enrolled in the study:

- Signed participant Informed Consent Form
- All completed CRFs
- Record of any side effects/adverse events, device malfunctions, and treatment failures (with supporting documentation)
- Procedure reports, physician dictations, nursing notes, and participant medical records
- Copies of all participant photographs
- Records of any interventions (procedure reports, physician dictations, nursing notes, etc.)
- Records related to participant deaths during the investigation (including death records, death certificate and autopsy report, if performed).

Investigator files containing all records and reports of the investigation should be retained for a minimum of 5 years after the completion or termination of the investigational study or until two years after they are no longer needed to support product approval. They may be discarded upon notification by PhotonMD. To avoid any error, the Investigator should contact PhotonMD before destroying any records and reports pertaining to the study to ensure they no longer need to be retained.

6.2.7 Audits/Inspections

In the event that audits are initiated by the Sponsor (or its designate), or national/international regulatory authorities, the Investigator shall allow access to the original medical records and provide all requested information.

6.2.8 Publication Policy

At the conclusion of the study, the sponsor will decide whether a multi-center manuscript will be prepared for publication. The publication of the principal results from any single-site experience within the study is not allowed until the preparation and publication of the multi-center results have been published.

7.0 RISK ANALYSIS

7.1 Potential Risks

There are always risks associated with any medical device and to the medical procedure used to treat a disease. The risks associated with the use of the REVIAN System are minimal because of the unique design and use of low-risk electronic components in the system, including LEDs and low voltage battery. In comparison to other medical devices that use Helmets, Caps or Wand Devices for the treatment of alopecia, the risk to the participant using the REVIAN System is extremely low or negligible. The risk of retinal or thermal damage due to laser exposure is not present with REVIAN. The LEDs are non-coherent (radiating in all directions) and divergent as compared to devices using laser diodes. It is expected that the risks and complication rates strictly associated with the procedure using REVIAN would be like other products that are currently used in the home setting to treat alopecia. In addition, as compared to using Minoxidil (Rogaine) or Finasteride (Propecia) REVIAN has no systemic adverse effects like current pharmaceutical agents, especially in women of child-bearing potential.

In addition to the safety profile discussed above the only other additional risk with REVIAN are the fabric and plastic materials used in the inner construction of the cap, however materials are medical grade. In rare circumstances, the fabric or continued use may cause allergies, irritation, tissue reactions, allergic reactions or inflammation that may result in discomfort; or the REVIAN may fail to improve symptoms.

7.2 Justification for Investigation

In summary, the development of new treatments for AGA is highly desirable as current available therapies fail to deliver the outcomes desired by participants. While current light-therapy devices for hair growth have proven clinical safety and efficacy, these therapies were developed based on limited preclinical testing and do not represent optimum modes of treatment including dosing and wavelength. REVIAN 102 and 103 are improvements on the current therapies because they may improve both the ability to release Nitric Oxide (NO) from its bound form and increase enzymatic generation of NO. The downstream effects of NO in the scalp may include improved microcirculation (via vasodilation and angiogenesis), increased proliferation of hair follicle cells, decreased inflammation, and elongation of the anagen phase of hair growth. These downstream effects of NO are believed to progress the health of hair follicles, promote hair growth, and increase hair thickness (diameter). Additionally, the REVIAN products have been designed with safe LEDs, a sensor based automatic turn-off, and programmed treatment schedule to help improve both safety and compliance.

The proposed study will collect data on the safety and effectiveness of the REVIAN System for the treatment of symptoms associated with AGA.

7.3 Study Population

The study population will consist of up to 200 participants (120 men and 80 women) who are between the ages of 18 and 65 years of age, with diagnosis of Androgenic Alopecia, consistent with males who have Norwood Hamilton Classification IIa to V patterns of hair loss and females who have Ludwig-Savin Scale I-1 to I-4, II -1, II-2 or frontal, both with Fitzpatrick Skin Types I – IV.

8.0 ANTICIPATED CHANGES DURING INVESTIGATION

The only product change that is anticipated during the investigation are modifications to the cap assembly for mass production but no changes that affect function or delivery of energy.

The anticipated change will not alter the mechanism of operation or functional requirements of the system. Any potential changes will be managed through the PhotonMD design control process and verified prior to implementation.

9.0 MONITORING PLAN

The monitoring for this study will be conducted by Sponsor or designee. The study will be monitored to ensure that the protocol, applicable regulations, and Good Clinical Practice Guidelines are followed. The study monitor will ensure that the rights and well-being of participants are protected and the clinical trial data are accurate, complete, and verifiable.

Prior to participant enrollment, the sponsor (or designee) will obtain the essential regulatory documents required to initiate the study. The sponsor will be responsible for the review and approval of the following essential documents:

- Protocol Signature Page
- Current Protocol Revision
- Investigator Agreement
- Financial Disclosure or Certification
- IRB/HREC approval letter for the protocol and consent form
- IRB/HREC approved consent form
- IRB/HREC membership roster or assurance number Copies of file documents will be maintained by the sponsor.

9.1 Site Qualification/Initiation

All sites will undergo qualification process to confirm acceptability for participation into the study. SOPs will be followed to determine that a site is qualified for participation in the study. The study monitor or designee will perform an on-site visit to verify the site qualifications and record his or her findings on the site report.

Study initiation visits are performed at the start of the clinical study to ensure that the study personnel have a complete understanding of the protocol, procedures, responsibilities, and regulations involved with the conduct of a clinical trial. Study personnel will be trained on all essential aspects of the trial prior to the first participant being enrolled in the study. This training will include an in-depth review of the protocol and case report forms, regulatory requirements, serious adverse experience reporting, and other activities as documented in the site initiation plan. Following the visit, a report is generated and circulated for review.

9.2 Periodic Monitoring

Periodic monitoring visits will be made at all active investigational sites throughout enrollment of the clinical study to assure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will assure that the facilities are still acceptable; the protocol and investigational plan are being followed, the IRB/HREC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and the IRB/EC, device and device inventory are controlled and the Investigator is carrying out all agreed activities. The monitor will verify accuracy of CRF completion against source documents maintained at the site.

During monitoring visits, the Monitor will perform a review of study eligibility, Inclusion/Exclusion criteria, informed consent, all reports of device malfunction, all events meeting criteria for serious adverse event reporting as well as safety and efficacy endpoints.

Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits.

The monitor will ensure that Investigators are aware of the regulatory requirement to maintain information in the study participant's medical records which corroborate data collected on the CRF. To comply with these regulatory requirements, the following information will be maintained and made available as required by the sponsor and/or regulatory inspectors:

- Medical history/physical condition of the study participant before involvement in the study sufficient to verify protocol entry criteria.
- Medical record documenting that informed consent was obtained for the participant's participation in the study.
- Description of device accountability and treatment details.
- Dated and signed notes for each study participant visit including results of examinations.
- Description of AEs and follow-up of the AEs (minimal event description, severity, onset date, duration, relation to study device, outcome and treatment for AE).
- Notes regarding concomitant medications taken during the study (including start and stop dates).
- Study participant's condition upon completion of or withdrawal from the study.

The monitor will compare key variables (demographics, inclusion/exclusion criteria, and safety) on the CRFs with each participant's source documents. Any discrepancies will be noted and resolved. Following the visit, a report will be generated and circulated to the sponsor for review.

9.3 Site Close-Out

Upon completion of the clinical study (when all participants enrolled have completed the follow-up visits and the CRFs and queries have been completed), the Sponsor or designee will notify the site of closeout and a study closeout visit will be performed. All CRFs, unused study devices, and any unused study materials will be collected and returned to the Sponsor. The Monitor will ensure that the Investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include: discussing retention of study files, possibility of site audits, publication policy, and notifying the EC of study closure. Following the visit, a report is generated and circulated for review.

9.4 Monitoring Trip Reports and Follow up Letters

The following reports will be completed, and submitted to the Project Manager for review within one week following the conclusion of any given visit: initiation visit reports, periodic site monitoring reports and closeout reports. A follow up letter summarizing the monitoring trip report will be sent to the study staff within two weeks following the visit.

9.5 Frequency of Monitoring Visits

Study monitoring will be carried out in compliance with FDA regulations (21CFR 812) and all Good Clinical Practices (GCP) guidelines. The clinical investigation will be monitored throughout its active phase. The first Monitoring Visit will occur shortly after the first participant has been enrolled and treated at any site. Subsequent Monitor Visits will occur as the frequency of enrollment dictate but no less than 2 times annually through the conclusion of the primary endpoint.

9.6 Qualifications of Study Monitor

PhotonMD's study monitor is qualified by training and experience to monitor the progress of the investigation. The study monitor has suitable academic training, applicable clinical experience, and knowledge of the investigational device.

9.7 Name and Address of Monitor

10.0 REFERENCES

1. Olsen EA, Messenger AG, Shapiro J, Bergfeld WF, Hordinsky MK, Roberts JL, et al. Evaluation and treatment of male and female pattern hair loss. J Am Acad Dermatol. 2005;52(2):301–311.

2. Hoffmann R, Happle R. Current understanding of androgenetic alopecia: Part I. Etiopathogenesis. Eur J Dermatol. 2000;10(4):319–327.

3. Gan DC, Sinclair RD. Prevalence of male and female pattern hair loss in Maryborough. J Investig Dermatol Symp Proc. 2005;10(3):184–189.

4. McElwee KJ, Shapiro JS. Promising therapies for treating and/or preventing androgenic alopecia. Skin Therapy Lett. 2012;17(6):1–4.

5. Rangwala S, Rashid RM. Alopecia: a review of laser and light therapies. Dermatol Online J. 2012;18(2):3.

6. Avram MR, Rogers NE. The use of low-level light for hair growth: part I. J Cosmet Laser Ther. 2009;11(2):110–117.

7. Lanzafame RJ, Blanche RR, Bodian AB, Chiacchierini RP, Fernandez-Obregon A, Kazmirek ER. The growth of human scalp hair mediated by visible red light laser and LED sources in males. Lasers Surg Med. 2013;45(8):487–495.

8. Leavitt M, Charles G, Heyman E, Michaels D. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: a randomized, double-blind, sham device-controlled, multicentre trial. Clin Drug Investig. 2009;29(5):283–292.

9. Satino JL, Markou M. Hair regrowth and increased hair tensile strength using the HairMax LaserComb for low-level laser therapy. Int J Cosmetic Surg Aesthetic Dermatol. 2003;5(2):113–117.

10. Norwood OT. Male pattern baldness: classification and incidence. South Med J. 1975;68(11):1359–1365.

11. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. Br J Dermatol. 1977;97(3):247–254.

12. Price VH, Roberts JL, Hordinsky M, Olsen EA, Savin R, Bergfeld W, et al. Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. J Am Acad Dermatol. 2000;43(5 Pt 1):768–776.

13. Savin R. Evaluating androgenetic alopecia in male and female patients: an improved visual method of classifying and tracking hair loss using computer-generated male and female pattern and density scales. Kalamazoo: The Upjohn Company; 1994.

14. Chren MM, Lasek RJ, Flocke SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. Arch Dermatol. 1997;133:1433–1440.

15. Han SH1, Byun JW, Lee WS, Kang H, Kye YC, Kim KH, Kim DW, Kim MB, Kim SJ, Kim HO, Sim WY, Yoon TY, Huh CH, Hwang SS, Ro BI, Choi GS. Quality of life assessment in male patients with androgenetic alopecia: result of a prospective, multicenter study. Ann Dermatol. 2012 Aug;24(3):311-8.

16. Cash TF. The psychosocial consequences of androgenetic alopecia: a review of the research literature. Br J Dermatol. 1999;141:398–405.

17. Schmidt S, Fischer TW, Chren MM, Strauss BM, Elsner P. Strategies of coping and quality of life in women with alopecia. Br J Dermatol. 2001;144:1038–1043.

18. Fischer TW, Schmidt S, Strauss B, Elsner P. Hairdex: a tool for evaluation of disease-specific quality of life in patients with hair diseases. Hautarzt. 2001;52:219–227.

19. Chren MM, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. J Cutan Med Surg. 2001;5:105–110.

20. Kim HJ, Sim WY, Song JY. Assessment of the characteristics of illness behavior and quality of life in patients with androgenetic alopecia. Korean J Dermatol. 2001;39:1094–1099.

21. Cash TF. The psychological effects of androgenetic alopecia in men. J Am Acad Dermatol. 1992;26:926–931.

22. Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, et al. Guidelines of care for androgenetic alopecia. J Am Acad Dermatol. 1996;35:465–468.

23. Mester, E.; Szende, B.; Gärtner, P., The effect of laser beams on the growth of hair in mice. Radiobiol. Radiother. (Berl.) 1968, 9 (621-626).

24. Chung, H.; Dai, T. Sharma, S. K.; Huang, Y.-Y.; Carroll, J. D.; Hamblin, M. R., The nuts and bolts of low-level laser (light) therapy. Ann. Biomed. Eng. 2012, 40 (2), 516-533.

25. Hamblin, M. R.; Demidova, T. N., Mechanisms of low level light therapy. Proc. SPIE 2006.

26. Karu, T., Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP. Photomed. Laser. Surg. 2010, 28 (2), 159-160.

27. Eells, J. T.; Wong-Riley, M. T.; VerHoeve, J.; Henry, M.; Buchman, E. V.; Kane, M. P.; Gould, L. J.; Das, R.; Jett, M.; Hodgson, B. D., Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy. Mitochondrion 2004, 4 (5), 559-567.

28. Karu, T. I., Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. IUBMB Life 2010, 62 (8), 607-610.

29. Avci, P.; Gupta, G. K.; Clark, J.; Wikonkal, N.; Hamblin, M. R., Low-level laser (light) therapy (LLLT) for treatment of hair loss. Lasers Surg. Med. 2014, 46 (2), 144-51.

30. Hamblin, M. R., The role of nitric oxide in low level light therapy. Proc. SPIE 2008.

31. Daniela, B.-G.; Thomas, R.; Kolb-Bachofen, V., Nitric oxide in human skin: current status and future prospects. J. Invest. Dermatol. 1998, 110 (1), 1-7.

32. Cals-Grierson, M.-M.; Ormerod, A., Nitric oxide function in the skin. Nitric Oxide 2004, 10 (4), 179-193.

33. Brown, G. C., Nitric oxide and mitochondrial respiration. BBA-Bioenergetics 1999, 1411 (2), 351-369.

34. Karu, T., Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J. Photochem. Photobiol. B, Biol. 1999, 49 (1), 1-17.

35. Goralczyk, K.; Szymanska, J.; Lukowicz, M.; Drela, E.; Kotzbach, R.; Dubiel, M.; Michalska, M.; Goralczyk, B.; Zajac, A.; Rosc, D., Effect of LLLT on endothelial cells culture. Lasers Med. Sci. 2015, 30 (1), 273-8.

36. Saygun, I.; Karacay, S.; Serdar, M.; Ural, A. U.; Sencimen, M.; Kurtis, B., Effects of laser irradiation on the release of basic fibroblast growth factor (bFGF), insulin like growth factor-1 (IGF-1), and receptor of IGF-1 (IGFBP3) from gingival fibroblasts. Lasers Med. Sci. 2008, 23 (2), 211-215.

37. Song, S.; Zhang, Y.; Fong, C.-C.; Tsang, C.-H.; Yang, Z.; Yang, M., cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light. J. Invest. Dermatol. 2003, 120 (5), 849-857.

38. de Freitas, L. F.; Hamblin, M. R., Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J. Sel. Top. Quantum Electron. 2016, 22 (3), 1-17.

39. Jimenez, J. J.; Wikramanayake, T. C.; Bergfeld, W.; Hordinsky, M.; Hickman, J. G.; Hamblin, M. R.; Schachner, L. A., Efficacy and safety of a low-level laser device in the treatment of male and female pattern hair loss: a multicenter, randomized, sham device-controlled, double-blind study. Am. J. Clin. Dermatol. 2014, 15 (2), 115-127.

40. Leavitt, M.; Charles, G.; Heyman, E.; Michaels, D., HairMax LaserComb® Laser Phototherapy Device in the Treatment of Male Androgenetic Alopecia. Clin. Drug Investig. 2009, 29 (5), 283-292.

41. Lohr, N. L.; Keszler, A.; Pratt, P.; Bienengraber, M.; Warltier, D. C.; Hogg, N., Enhancement of nitric oxide release from nitrosyl hemoglobin and nitrosyl myoglobin by red/near infrared radiation: potential role in cardioprotection. J. Mol. Cell. Cardiol. 2009, 47 (2), 256-263.

42. Makihara, E.; Masumi, S.-i., Blood flow changes of a superficial temporal artery before and after low-level laser irradiation applied to the temporomandibular joint area. J. Jpn. Prosthodont. Soc. 2008, 52 (2), 167-170.

43. Samoilova, K. A.; Zhevago, N. A.; Petrishchev, N. N.; Zimin, A. A., Role of nitric oxide in the visible light-induced rapid increase of human skin microcirculation at the local and systemic levels: II. Healthy volunteers. Photomed. Laser Surg. 2008, 26 (5), 443-449.

44. Lee, P. C.; Salyapongse, A. N.; Bragdon, G. A.; Shears, L. L.; Watkins, S. C.; Edington, H. D.; Billiar, T. R., Impaired wound healing and angiogenesis in eNOS-deficient mice. Am. J. Physol. Heart Circ. Physiol. 1999, 277 (4), H1600-H1608.

45. Chen, C. H.; Hung, H. S.; Hsu, S. h., Low-energy laser irradiation increases endothelial cell proliferation, migration, and eNOS gene expression possibly via PI3K signal pathway. Lasers Med. Sci. 2008, 40 (1), 46-54.

46. Chaves, M. E. d. A.; Araújo, A. R. d.; Piancastelli, A. C. C.; Pinotti, M., Effects of low-power light therapy on wound healing: LASER x LED. An. Bras. Dermatol. 2014, 89 (4), 616-623.

APPENDIX A: DEFINITIONS

ADVERSE EVENT

An **adverse event (AE)** is any untoward medical occurrence in a participant whether it is considered device related or not. Diseases, signs, symptoms, or laboratory abnormalities already existing at enrollment are not considered AE's unless they worsen (i.e., increase in intensity or frequency). Surgical procedures themselves are not described as adverse events in this study. The condition for which the surgery is required may be an adverse event. Surgical procedures planned prior to enrollment and the conditions leading to these measures are not adverse events.

The Investigator, based on his or her clinical judgment and the following definitions, will determine the relationship and severity of the AE to the device and/or surgical procedure:

1. Unrelated: The adverse event is determined to be solely caused by the underlying disease, disorder or condition of the participant, or attributable solely to other extraneous causes (unrelated to the device, device malfunction, or the procedure.

2. Possibly related: The adverse event has onset within a clinically relevant temporal relationship to exposure to the device or procedure, and is plausibly at least partially caused by or aggravated using the device, device malfunction, or the procedure. It must also meet one of the following criteria: (1) follows a known or easily foreseen pattern of response to device use or procedure and (2) is not fully attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes.

3. Probably related: The adverse event has onset within a clinically relevant temporal relationship to exposure to the device or procedure, and is more likely than not to be at least partially caused by or aggravated using the device, device malfunction, or the procedure. It must also meet both criteria: (1) follows a known or easily foreseen pattern of response to device use or procedure; and (2) is not fully attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.

4. Definitely related: The adverse event is clearly caused by using the device, device malfunction, or the procedure. It must meet all following criteria: (1) has a clear temporal relationship between device exposure and onset of the event; (2) follows a known pattern of response to device use or procedure; and (3) is not reasonably attributable to the underlying disease, disorder or condition of the participant, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.

ANTICIPATED ADVERSE EVENT

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a patient, whether or not considered related to the investigational product(s) prescribed as part of the protocol, predefined in the protocol and/or Instructions For Use (IFU), that is identified or worsens during a clinical study.

DEVICE FAILURE:

A device has failed if it is used in accordance with the Instructions for Use, but does not perform according to the Instructions for Use.

DEVICE MISUSE

A misused device (one that is used by the Investigator in a manner that is contradictory to the Instructions for Use) will not be considered a malfunction.

DEVICE RELATED ADVERSE EVENT

A device related adverse event is defined as any adverse event, for which a causal relationship between the device and the event is at least a reasonable possibility, i.e., the relationship cannot be excluded.

LIFE THREATENING

Life-threatening means that the participant was, in the view of the investigator, at immediate risk of death from the adverse event as it occurred. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

LOW-LEVEL LASER THERAPY (LLLT)

Low-level laser therapy is a form of alternative medicine that uses low-level lasers or light-emitting diodes (LEDs). Whereas high-power lasers used in laser medicine destroy or cut tissue, low-power lasers are claimed to stimulate it and to encourage the cells to function.

MODULATED LIGHT THERAPY (MLT™)

Modulated light therapy is a form of alternative medicine that uses modulated light-emitting diodes (LEDs) customized by PhotonMD to treat participants with AGA.

PROTOCOL DEVIATION

An incident where the Investigator or site personnel did not conduct the study according to the investigational plan, protocol or the Investigator agreement.

***Major deviation*:** Any deviation from participant inclusion and exclusion criteria or participant informed consent procedures.

***Minor deviation*:** Deviation from a protocol requirement such as incomplete/inadequate participant testing procedures, non-compliance with medication regimens, follow-ups performed outside specified time windows, etc.

SERIOUS ADVERSE EVENT

A **Serious Adverse Event** (SAE) is any AE that 1) leads to death, 2) leads to serious deterioration in health resulting in a life-threatening illness or injury, 3)results in permanent impairment of a body structure or a body function, 4) requires in-patient hospitalization or prolongs existing hospitalization, 5) results in medical or surgical intervention to prevent permanent impairment to body structure or a body function, or 6) leads to fetal distress, fetal death or a congenital abnormality or birth defect.

Note:
A device malfunction may or may not result in an AE. If a device malfunctions in a manner that causes an adverse event (AE) or a serious adverse event (SAE) as defined above, then the consequence of the malfunction will be reported as an AE or SAE, as appropriate. However, all device malfunctions will also be tabulated separately, regardless of whether an adverse event results from the malfunction. Any surgical interventions for device malfunctions will also be reported as subsequent surgical interventions.

SOFT TISSUE IRRITATION

Superficial Tissue Irritation An inflammatory condition of superficial layers of the skin as a result of an aseptic irritant, such as skin reaction to suture or dressings.

Periprosthetic Soft Tissue Irritation An inflammatory condition of the tissues about the implant resulting from aseptic tissue irritation. Fluid may accumulate in the periprosthetic tissues possibly resulting in the tissue swelling, localized tenderness, pain and/or joint motion is restriction.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

The investigational device exemption (IDE) regulations and ISO 14155:2011 (Clinical Investigation of Medical Devices – Good Clinical Practice) defines an unanticipated adverse device effect (UADE) as any *serious* adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan or risk analysis; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB/EC.

APPENDIX B: HAIR SPECIFIC SKINDEX-29 QUALITY OF LIFE QUESTIONNAIRE

	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My scalp hurts (Sx).	☐1	☐2	☐3	☐4	☐5
2. My alopecia affects how well I sleep (Fx).	☐1	☐2	☐3	☐4	☐5
3. I worry that my alopecia may be serious (Em).	☐1	☐2	☐3	☐4	☐5
4. My alopecia makes it hard to work or do hobbies (Fx).	☐1	☐2	☐3	☐4	☐5
5. My alopecia affects my social life (Fx).	☐1	☐2	☐3	☐4	☐5
6. My alopecia makes me feel depressed (Em).	☐1	☐2	☐3	☐4	☐5
7. My scalp burns or stings (Sx).	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my alopecia (Fx).	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my alopecia (Em).	☐1	☐2	☐3	☐4	☐5
10. My scalp itches (Sx).	☐1	☐2	☐3	☐4	☐5
11. My alopecia affects how close I can be with those I love (Fx).	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my alopecia (Em).	☐1	☐2	☐3	☐4	☐5
13. I worry that my alopecia may get worse (Em).	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my alopecia (Fx).	☐1	☐2	☐3	☐4	☐5
15. I am angry about my alopecia (Em).	☐1	☐2	☐3	☐4	☐5
16. Water bothers my scalp (bathing, washing hands) (Sx).	☐1	☐2	☐3	☐4	☐5
17. My alopecia makes showing affection difficult (Fx).	☐1	☐2	☐3	☐4	☐5
18. My scalp is irritated (Sx).	☐1	☐2	☐3	☐4	☐5
19. My alopecia affects my interactions with others (Fx).	☐1	☐2	☐3	☐4	☐5
20. I am embarrassed by my alopecia (Em).	☐1	☐2	☐3	☐4	☐5
21. My alopecia is a problem for the people I love (Fx).	☐1	☐2	☐3	☐4	☐5
22. I am frustrated by my alopecia (Em).	☐1	☐2	☐3	☐4	☐5
23. My scalp is sensitive (Sx).	☐1	☐2	☐3	☐4	☐5
24. My alopecia affects my desire to be with people (Fx).	☐1	☐2	☐3	☐4	☐5
25. I am humiliated by my alopecia (Em).	☐1	☐2	☐3	☐4	☐5
26. My scalp bleeds (Sx).	☐1	☐2	☐3	☐4	☐5
27. I am annoyed by my alopecia (Em).	☐1	☐2	☐3	☐4	☐5
28. My alopecia interferes with my sex life (Fx).	☐1	☐2	☐3	☐4	☐5
29. My alopecia makes me tired (Fx).	☐1	☐2	☐3	☐4	☐5

Scoring:
Sx: Symptom (7-35), Em: Emotion (10-50), Fx: Function (12-60)
Total Scoring = (29-145)

APPENDIX C: Physician's Global Assessment (PGA) Scoring and Subjective Scalp Hair Growth (SSHG) Evaluations

A Canfield stereotactic positioning device will be used for obtaining global photographs where the participant's chin and forehead are fixed, and on which a given camera and flash device are mounted to standardize the view, magnification and lighting at consecutive study visits. Participants will be asked to keep the same hair style and colour and the coordinators attempt to duplicate baseline hair parting and combing in subsequent follow-up visits. Two standard views (superior and vertex) will be taken at baseline, 8-, 16, and 26-weeks (Figure 5). The digital images will be graded. Paired baseline and post-treatment photographs will be evaluated by each site study doctor (at the Week 8, 16 & 26 follow up visits) in order to provide a physician global assessment (*sPGA*) score.

In addition, the photographs will then be independently reviewed by two blinded evaluators, to evaluate the independent physician's global assessment (*iPGA*)

The PGA score used is the standardized 7-point rating scale (–3 = greatly decreased, –2 = moderately decreased, –1 = slightly decreased, 0 = no change, +1 = slightly increased, +2 = moderately increased, +3 = greatly increased).

Figure 5. Global Photography, demonstrating fixation of the participant on a brow and chin rest with the camera mounted on a rotating arm.

Participants will be asked to assess subjective scalp hair growth (SSHG). They will be provided with the following questionnaire at each follow up visit (8, 16 and 26 weeks after baseline).

Subjective Scalp Hair Growth (SSHG)

1. Since the start of the study, I can see my bald spot getting smaller

Strongly Agree	Agree	No opinion either way	Disagree	Strongly Disagree
1	2	3	4	5

2. Because of the treatment I have received since the start of the study, the appearance of my hair is:

A lot better	Somewhat better	A little better	Same	A little worse	Somewhat worse	A lot worse
1	2	3	4	5	6	7

3. Ever since the start of the study, how would you describe the growth of your hair?

Greatly increased	Moderately increased	Slightly increased	No change	Slightly decreased	Moderately decreased	Greatly decreased
1	2	3	4	5	6	7

4. Ever since the start of the study, how effective do you think the treatment has been in slowing down your hair loss

Very effective	Somewhat effective	Not very effective	Not effective at all
1	2	3	4

5. Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of:

a) The hairline front of your head?

Very satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
1	2	3	4	5

b) The hair on top of your head?

Very satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
1	2	3	4	5

c) Your hair overall?

Very satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
1	2	3	4	5

APPENDIX D: TrichoScan Procedure for Hair Counts

APPENDIX E: Informed Consent Form (ICF)

Statistical Analysis Plan

(Version 4.0)

Protocol No.: REV-01

Protocol Title:

A Prospective, Randomized, Controlled, Double-Blind Study that Evaluates the Safety and Efficacy of Three Active *REVIAN* Caps versus a Non-Active *REVIAN* Cap (Sham) in Participants with Pattern Hair Loss (Androgenic Alopecia)

TABLE OF CONTENTS

Page

Abbreviations and Definitions:

AE	Adverse event
AGA	Androgenic alopecia
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic class
cm	Centimetre
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic case report form
FPC	Flexible printed circuit board
ICH	International Conference on Harmonisation
LED	Light emitting diode
MedDRA	Medical Dictionary for Regulatory Activities
MLT	Modulated light therapy
PCBA	Printed circuit board assembly
PDF	Portable document format
SAE	Serious Adverse Event
SAS	Statistical Analysis Software, Inc
SOC	System Organ Classification
TEAE	Treatment Emergent Adverse Events
WHO	World Health Organization

1. PREFACE

This document describes in detail the methods that will be used to summarize and analyze the efficacy and safety data from protocol REV-01 (V6; August 22, 2018).

2. STUDY OBJECTIVES AND ENDPOINTS

The *REVIAN* device is a soft dome-shaped cap that contains integrated electronics and battery technology to control delivery of modulated light therapy (MLT™) for a daily 10 minute treatment to treat androgenic alopecia (AGA) and promote hair growth in men and women. The cap contains a flexible printed circuit board (FPC), LEDs, printed circuit board assembly (PCBA), lithium-polymer battery, elastic fabric and foam fitting pieces. The cap is controlled and operated by a mobile app.

The primary objective of this study is to collect data on the safety and effectiveness of *REVIAN* in male and female participants with AGA through 26-weeks of treatment.

3. STUDY DESIGN

This study is designed as a prospective, randomized, controlled, double-blind, four-arm study. Up to 3 clinical sites will enroll up to 200 participants over an approximate 6-month duration. Eligible participants with AGA meeting all inclusion and exclusion criteria will be enrolled and randomized to one of four study arms in a 1:1:1:1 ratio:

- Arm 1: Active *REVIAN* 101 (___mW/cm^2 of 625 nm and 660 nm)
- Arm 2: Active *REVIAN* 102 (___ mW/cm^2 of 425 nm)
- Arm 3: Active *REVIAN* 103 (___ mW/cm^2 of 425 nm + ___ mW/cm2 of 625 nm and 660 nm)
- Arm 4: Non-Active *REVIAN* Cap 100 (SHAM)

Male and female participants will be randomized from separate randomization schedules to ensure balance among treatment arms in each gender.

All data except for Global Assessment Photography and Macrophotography will be captured in an electronic clinical report form (eCRF). Global Assessment Photography and Macrophotography data will be imported from external vendor. Demographic, baseline characteristics, efficacy and safety data will be collected at regularly scheduled visits according to the planned schedule of procedures (Table 1).

Screening procedures will be performed at Visit 1.

Participants who are eligible to enroll will return within 7 days for Visit 2 to obtain baseline data and to be randomized to one of the treatment arms. The first treatment will be performed in the clinic on Visit 2.

Visit 3 will occur approximately 7 days later via telephone interviews to assess treatment compliance, to report use of concomitant medications and to report any adverse events.

Visits 4 and 5 will occur approximately 8 and 16 weeks, respectively, after Visit 1. Participants will return to the investigation centers for efficacy assessments and questionnaires.

The final visit (Visit 6) will occur approximately 10 weeks after Visit 5. Participants will undergo a final assessment of efficacy and safety at Visit 6. Participants will return the caps at Visit 6. If there are no adverse events requiring follow-up, participants will not need to return for any follow up assessments.

Any participant who competes the Week 16 efficacy assessments (at Visit 5) will be considered a completer.

Table 1: Planned Visits and Procedures.

PROCEDURES	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening (Day -7)	Baseline (Day 0)	Phone Call (7 ±3 Days)	Week 8[1,2] (56 ±5 Days)	Week 16[1,2] (112 ±10 Days)	Week 26[1,2] (182 ±10 Days)
Informed Consent	X	X				
Demographics	X	X				
Medical History	X	X				
Medication History	X	X				
Inclusion/Exclusion Criteria	X	X				
Pregnancy Test (As required)	X	X				
Brief Physical Examination		X				X
Instruction on Device and 1st Application		X				
Shave and Tattoo Scalp		X		X[3]	X[3]	X[3]
Hair Count - Macrophotography (1cm^2 Area)		X		X	X	X
Follow-up on Compliance and Use of *REVIAN*		X	X	X	X	X
Growth Assessment and Questionnaires:						
Subjective Scalp Hair Growth (SHG) score[4]				X	X	X
Physician's Global Assessment (PGA) score[4]				X	X	X
Hair Specific Skindex-29 Questionnaire		X		X	X	X
Global Assessment Photography (superior and vertex scalp)		X		X	X	X
Blinded Review of Global Photographs		X		X	X	X
Participant Compliance Review			X	X	X	X
Concomitant Medications		X	X	X	X	X
Adverse Events		X	X	X	X	X
End of Study / Early Termination / Return Device						X

[1] All visit dates are in reference to Baseline, i.e., Visit 4 occurs about eight weeks (56 days) after the Baseline Visit.
[2] Participants will continue treatments throughout the 26-weeks with a daily 10-minute treatment for a total of 56 treatments over 8 weeks, 112 treatments over 16-weeks, and 182 treatments over 26-weeks.
[3] Participants may have tattoo ink reapplied to original site of ink dot application at these time periods.
[4] SHG & PGA is not taken at baseline. These are assessed only at the follow up visits

4. SEQUENCE OF PLANNED ANALYSES

All analyses outlined in this document will be carried out after:

- The study database has been authorized by the PhotonMD Review team as complete and final;
- Protocol deviations that warrant exclusion from the per protocol analyses have been identified.

5. SAMPLE SIZE CONSIDERATIONS

Prior hair growth studies, regardless of potential efficacy of the Sham device, showed the delta between active treatments and control treatments was consistently at around 15-22 hairs/cm^2 which appears to be the expected level of improvement. It is estimated that participants in the active group will have increases of 15 hairs/cm^2 by 16-weeks. Assumptions are 15 hair count difference between treatments, standard deviation (SD)=20, 10% drop-out rate, 5% alpha level, 90% power and 2-sided t-test. Based on these assumptions, the study requires a minimum of 40 evaluable participants per arm.

The study will accrue a maximum of 200 participants (50 per each Active Study Arm and 50 control participants) to target, after lost to follow-up, a minimum of 160 evaluable (40 per arm) participants.

6. ANALYSIS POPULATIONS

Participants receive either an active *REVIAN* Cap or a non-active *REVIAN* Cap (three versions of an active *REVIAN* Cap and one non-active *REVIAN* Cap). The following participant groups or analysis populations will be used to complete the analysis of data:

Intent-to-Treat participant population (ITT): The ITT participant population will include all participants that started a treatment at Baseline. All baseline characteristics, demographics and primary efficacy analyses will be performed on the ITT population.

Per-Protocol participant population (PP): The PP participant population will include all participants in the ITT population with 16-week follow-up data, with no major protocol deviations and at least 80% compliance. The primary and secondary efficacy analyses also will be performed on the PP population.

Safety participant population (SAF): The SAF is the same as the ITT population. All safety summaries will be performed on the SAF population.

7. INTERIM ANALYSES

No interim analyses are planned for this study.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The purpose of the study is to collect data on the safety and effectiveness of *REVIAN* in participants with AGA. In general, for continuous variables, the sample size, mean, standard deviation, minimum and maximum will be presented. For categorical variables, the number and percentage in each category will be presented. All statistical analyses will be performed using SAS version 9.4 for PC. Unless otherwise specified, statistical significance will be determined using $p \leq 0.05$.

All outcomes will be provided in listings by participant and treatment group. In addition, some endpoints will be summarized in tables by treatment group.

Primary Efficacy Endpoint: The primary efficacy endpoint of this study is the change in hair count from baseline to 16-weeks following the initial application (CFB_HC16).

Primary Safety Endpoint: The primary safety outcome will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 16-week period for all participants.

Secondary Efficacy Endpoints:

Change from Baseline Hair Count: Like the primary endpoint, change from baseline hair count, will also be assessed at 8 (CFB_HC08) and 26 (CFB_HC26) weeks.

Rate of Change in Hair Growth: The rate of change in hair growth at 8, 16, and 26 weeks will be calculated as a ratio of change from baseline to baseline.

Independent Physician's Global Assessment (iPGA): Two independent reviewers will assess overall hair growth from photographs, using PGA scores at weeks 8, 16 and 26. The PGA score hair growth as: -3=greatly decreased, -2=moderately decreased, -1=slightly decreased, 0=no change, 1=slightly increased, 2=moderately increased and 3=greatly increased. In the event the two independent reviewers do not agree, a third assessment will be made by the PI. The PI's score will superceed the two other independent reviewers' score.

Site Physician's Global Assessment (sPGA): The site investigator will assess overall hair growth using the PGA scores at weeks 8, 16 and 26.

Subjective Scalp Hair Growth Score (SHG): Beginning at Week 8, participants will complete a subjective hair growth questionnaire. The participants choose the answer that best fits the following statements:

1) Since the start of the study, I can see my bald spot getting smaller. (1="strongly agree" to 5="strongly disagree")

2) Because of the treatment, I have received since the starts if the study, the appearance of my hair is: (1="a lot better" to 5="a lot worse")

3) Ever since the start of the study, how would you describe the growth of your hair? (1="greatly increased" to 7="Greatly decreased")

4) Ever since the start of the study, how effective do you think the treatment has been in slowing down your hair loss? (1="Very effective" to 4="Not effective at all")

5) Compared to the beginning of the study, which statement best describes your satisfaction with your appearance of:

    a. The hairline in front of your head? (1="very satisfied" to 5="very dissatisfied")

    b. The hair on top of your head? (1="very satisfied" to 5="very dissatisfied")

    c. Your hair overall? (1="very satisfied" to 5="very dissatisfied")

SHG will be administered at 8 weeks, 16 weeks and 26 weeks

Hair Specific Skindex-29 Quality of Life Questionnaire (HSSQOL): The hair specific skindex-29 QOL questionnaire is a 29-item questionnaire with 3 domains: 7 questions for symptoms domain, 10 questions for emotion domain and 12 questions for function domain. Participants score each question on a scale from 1 (never) to 5 (all the time). Total scores will be summed at Week 8, 16 and 26. HSSQOL will be administered at baseline, 8, 16 and 26 weeks.

Secondary Safety Endpoint: The secondary safety outcome will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 26-week period for all participants.

8.1. Missing and Imputed Data

Every effort will be undertaken to fulfill all the requirements of the protocol concerning the collection of data. If participants refuse to return for data collection, but agree to continue in the study, questionnaire data and safety data will be collected over the telephone or at a home visit, if necessary.

The primary analysis will be performed on the ITT group. Those participants who withdraw or who are lost to follow up (LTFU) after enrollment will be included in the primary analysis using a last observation carried forward (LOCF) approach where the outcome at the most recent visit will be carried forward to all subsequent missing assessment times. Since all post-baseline efficacy assessments are first assessed at approximately Week 8, participants without an 8-week visit will have their baseline observation carried forward (BOCF) for the primary and secondary efficacy analyses. Analyses will also be performed on all available data with no imputations.

8.2. Hypothesis Testing

The treatment consists of 3 active caps and one Sham cap. Each active cap group will be compared to the same Sham group using 1 degree of freedom contrasts in general linear models analysis of covariance (ANCOVA). Comparisons will be adjusted for multiple comparisons to the same Sham group using Dunnett's correction.

The primary outcome is the change from baseline in hair count after 16 weeks of treatment with a cap. The null hypothesis is there is no difference in outcome between an active cap compared to a Sham cap, while the alternative hypothesis is there is a difference outcome between active compared Sham cap:

$$H_{null}: \quad D_{active} = D_{Sham}$$

$$H_{alternative}: D_{active} \neq D_{Sham}$$

The null hypothesis will be rejected in favor of the alternative hypothesis for each active cap if the Dunnett's corrected p-value for the contrast ≤ 0.05. Treatment superiority will be

demonstrated if the significant difference is in favor of the active cap (e.g., greater increase in hair count for the active cap. No comparisons between active caps will be performed.

Secondary outcomes will the same hypotheses testing process as the primary outcome, but with statistical methods appropriate for the type of endpoints to be tested. For example, continuous outcomes will be analysed by parametric methods, such as ANCOVA, while categorical outcomes will be analysed by non-parametric methods, such as Cochran-Mantel-Haenszel (CMH) test. Details of analyses by outcomes are provided in Section 10.

8.3. Covariates

Demographic and baseline characteristics, such, but not limited to age, gender, race and baseline hair count, will be consider as covariates in the ANCOVA. Any covariate that significantly accounts for variability ($p<0.10$) in the ANOVA model or Chi-Square test will be retained for the hypothesis testing.

8.4. Examination of Subgroups

There are no specific plans to perform any subgroup analyses. However, subgroup analyses may be performed for categories of gender, age, race or other baseline characteristics as deemed clinically relevant and appropriate in further characterizing treatment effects.

8.5. Study Centers

The clinical study will be conducted under a common protocol for each of 4 investigational sites with the intention of pooling the data over all sites for analysis. Every effort will be made to promote consistency in study execution at each investigational site. Assuming there is not a high degree of imbalance in the number of participants from each site an initial analysis will be performed with Site as a blocking factor and accounting for site by treatment interaction. If there is no site by treatment interaction, the factor will be dropped from subsequent analyses. If site is deemed to significantly account for outcome variability, then subgroup analyses by site will be performed.

8.6. Data Review

Prior to unblinding of the study database, the data will be reviewed by the Clinical Project Manager. The investigational sites will be queried about any discrepancies or unclear data and, if necessary, these will be corrected in the database.

8.7. Derived Data

No variables will be derived.

8.8. Transformed Data

No data transformations are planned.

9. STUDY POPULATION

9.1. Participant Accountability

The number of participants in the study will be summarized by treatment and overall. The number of participants who were screened, the number who were randomized, the number in the SAF population, the number in the ITT population, and the number in the PP population will be summarized by treatment and overall.

9.2. Protocol Deviations

Participant data will be reviewed for major protocol violations by a qualified clinical reviewer prior to database lock and unblinding. Participants with any major protocol violations will be excluded from the Per Protocol Population. The major protocol deviation is defined as:

- Outside the age window
- Deleterious concomitant medications
- Compliance < 80%
- Tattoo outside the specified location

All other protocol deviations will be considered as minor. The major protocol deviations and the descriptions will be listed by participants.

9.3. Treatment Compliance

A review of treatment compliance will begin with a telephone interview at Visit 3 (approximately 7 days after baseline). Participants are expected to use the use the caps for 10 minutes every day. The percent compliance will be based on the actual number of days used divided by the expected number of days available to use. For example, if a participant uses the cap 50 times over the course of 56 days, compliance will be 89.3%. The number of days of participation and percent compliance by will be summarized by treatment group.

9.4. Other Descriptions of Study Population

Demographics data will be summarized by treatment group and overall. Demographics will include age, gender, baseline height and baseline weight.

Baseline characteristics will be summarized by treatment group and overall. Baseline characteristics include hair count, responses to Hair Specific Skindex-29 questionnaire, and blinded reviewer Physician's Global Assessments from photographs.

Medical history, physical exam and vital signs findings will be summarized by treatment group and overall.

Prior medications are any medications taken and stopped prior to initiating treatment with a Revain cap. Prior medications will be collected as part of the medication history. These will be coded to Anatomical Therapeutic Classification (ATC) and by the preferred medication

names using WHO-Drug dictionary (WHODrug Mar-15) Incidence of participants having taken prior medications will be summarized by treatment group and overall.

Concomitant medications are defined as any medication that started prior to treatment initiation and is ongoing, or any medication that starts after the initiation of treatment. These will be handled as part of the safety assessments.

10. EFFICACY ANALYSES

10.1. Primary Endpoint

The primary efficacy endpoint is the change from baseline in hair count, over a pre-specified 1 cm^2 area of scalp after 16 weeks of treatment (CFB_HC16).

As specified in Section 9.2, each active cap will be compared to the same Sham treatment using 1 degree of freedom contrasts in an analysis of covariance (ANCOVA). Analyses will be adjusted for multiple comparisons using Dunnett's correction. An example of SAS code to be used for the primary analysis is as follows:

```
PROC MIXED;
CLASS SITE ARM;
MODEL CFB_HC16 = SITE ARM SITE*ARM <covariates>;
LSMEANS ARM /ADJUST=DUNNETT DIFF=CONTROL('SHAM');
RUN;
```

If the SITE*ARM interaction is not significant (p>0.05), this interaction will be dropped from the subsequent model. SITE will remain in the model if it significantly attributes to variability of the outcome. All subsequent analyses of secondary endpoints will retain the same factors and covariates as the primary outcome analysis.

10.2. Secondary Analyses

Secondary efficacy endpoints will be analysed as follows:

Change from Baseline Hair Count: the change from baseline hair count at 8 (CFB_HC08) and 26 (CFB_HC26) weeks will be analyzed in the same manner as the primary endpoint.

Rate of Change in Hair Growth: The rate of change in hair growth at 8, 16 and 26 weeks will be analyzed in the same manner as the primary endpoint.

Independent Physician's Global Assessment (iPGA): The percentage of participants with each score will be summarized by treatment group and by week. The active cap groups will be compared to the Sham group using Cochran-Mantel Haenszel (CMH) chi-squared method for detecting shifts in distribution of answers. The modified RIDIT scores will be used to take into account the ordered nature of the categorical responses. An example of SAS code for this analysis is as follows:

```
IF ARM IN ('SHAM', 'CAP101');
PROC FREQ;
```

```
TABLE ARM*(iPGA08 iPGA16 iPGA26)
        /CMH SCORE=MODRIDIT;
RUN;
```

Site Physician's Global Assessment (sPGA): The site investigator will assess over hair growth using the PGA scores at weeks 8, 16 and 26. These outcomes will be summarized and analysed in the same manner as the iPGA, above.

Subjective Scalp Hair Growth Score (SHG): The percentage of participants with each score in for each question will be summarized by week and by treatment group. The active cap groups will be compared to the Sham group using Cochran-Mantel Haenszel (CMH) chi-squared method for detecting shifts in distribution of answers. The modified RIDIT scores will be used to take into account the ordered nature of the categorical responses. An example of SAS code for this analysis is as follows:

```
IF ARM IN ('SHAM', 'CAP101');
PROC FREQ;
TABLE ARM*(SHG1 SHG2 SHG3 SHG4 SHG5A SHG5B SHG5C)
        /CMH SCORE=MODRIDIT;
RUN;
```

Hair Specific Skindex-29 Quality of Life Questionnaire (HSSQOL): The sum of scores for overall will be summarized by treatment group for each visit. These outcomes will be summarized and analysed in the same manner as the SHG above.

11. SAFETY ANALYSES

11.1. Concomitant Medications

Concomitant medications are defined as any medication that started prior to treatment initiation and is ongoing during treatment, or any medication that starts after the initiation of treatment. These will be coded to Anatomical Therapeutic Classification (ATC) and by the preferred medication names using WHO-Drug dictionary (WHODrug Mar-15). Incidence of participants taking concomitant medications will be summarized by treatment group.

11.2. Adverse Events

All treatment emergent Adverse events (TEAEs) will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology (Version 20.0). TEAEs will be defined as AEs reported after the first treamtment into the study.

TEAEs will be summarized by the number of participants reporting a TEAE, SOC, preferred term, severity, relationship to treatment (causality), and seriousness. When summarizing AEs by severity and relationship, each participant will be counted only once, within a system organ class or a preferred term, by using the event with the highest severity and greatest relationship within each classification.

In addition, a summary table of participants who prematurely discontinue treatment due to an AE will be provided.

12. REPORTING CONVENTIONS

Reporting conventions will adhere when possible to the International Conference on Harmonization (ICH) Guidance document E3, "Structure and Content of Clinical Study Reports". Some specific conventions are outlined below:

1. All tables and listings will be in landscape format.
2. All SAS output for tables and listings will be distributed in PDF files.

LIST OF TABLES

Table Number	Title	Population Summarized
14.3.1.5	Summary of Serious Treatment Emergent Adverse Events	(SAF Population)
14.3.1.6	Summary of Treatment Emergent Adverse Events Resulting in Discontinuation	(SAF Population)
14.3.2	Concomitant Medications	(SAF Population)
14.3.3	Physical Examination Findings	(SAF Population)
14.4	Device Issues at Disposition	(ITT Population)
14.5	Treatment Compliance	(ITT Population)

LIST OF LISTINGS