Ablative Fractional Laser Treatment for the Clinical Improvement of Acne Vulgaris: A Self-Controlled Trial

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I. Objective

The objective of this study is to evaluate the efficacy of fractional ablative laser treatments on active acne vulgaris.

II. Background

Acne vulgaris, typically associated with Cutibacterium acnes, is a common, inflammatory skin disease that can lead to pigmentary alterations and scarring.[1] Severe nodular acne vulgaris of the face can be psychologically distressing and can cause significant morbidity, and rarely, mortality, from concurrent scarring.[2] The current standard of care for nodular acne includes oral antibiotics plus topical therapy or oral isotretinoin.[1] However, due to increasing bacterial resistance from antibiotic use,[3] in addition to the systemic side effect profile of isotretinoin and inherent challenges with the iPledge system,[4] there may be a place for alternative, effective therapies for severe cases.

Ablative fractional carbon dioxide (CO_2) lasers are commonly used to improve the appearance of various skin conditions. Recently, light or laser-based approaches have been investigated for treatment of active acne.[5]

This study proposes the use of ablative fractional laser for the treatment of active acne vulgaris. The study will take place at the Translational Clinical Research Center in White 12 at the main campus of Massachusetts General Hospital (MGH) or Clinical Unit for Research Trials and Outcomes in Skin (CURTIS).

Study design

This study is designed to evaluate the efficacy of ablative fractional laser treatment for the clinical improvement or treatment of active acne vulgaris. We will be performing a self-controlled study, where each eligible subject will serve as their own control. Each subject will receive an ablative fractional 10,600 nm carbon dioxide laser treatment (Lumenis® Ultrapulse® C02 laser with DeepFX™ Yokneam, Israel).

There is another arm in the study. 22 subjects with acne will be selected to do the same laser treatment on a localized part of the face (1-3 inflammatory lesions and up to 5 mm adjacent area).

We plan to have 22 subjects complete the study on the first arm and 22 on the second arm. Both arms will be treated with the same device and the same energy

and density will be used. The first arm will be submitted to 3 laser treatments, with a one-month interval between each treatment appointment and their full face will be treated. The second arm will have only one treatment and only 1-3 lesions will be submitted to the laser treatment.

Subjects must be 18-40 years of age but may be any gender or Fitzpatrick skin type. They must have moderate to severe active acne vulgaris, scored based on Physician's Global Assessment (PGA) of Acne severity (Tan et al. and Pascoe et al.)[6,7]. A score of 3 is given for moderate acne and is characterized by the presence of acne on more than half of the face, with many comedones, papules and pustules, and one nodule may be present. A score of 4 is given for severe acne and is characterized by the presence of acne on the entire face, covered with comedones, numerous papules and pustule, and a few nodules and cysts. Subjects may not have undergone oral isotretinoin therapy within 12 months, have current oral antibiotic or oral therapy for acne, have a history of keloidal or hypertrophic scarring, or have had laser treatment in the past six months.

Clinical Assessment

Subjects will undergo a clinical assessment performed by a study physician. Severity of acne will be determined by a lesion count, and based on Physician's Global Assessment (PGA), with a potential score of 0 to 4. Additionally, we plan to take digital photos of subjects' face, as well as use a Cherry 3D imaging device to take 3-dimensional images of each subject's face. These photos will be subjectively reviewed by physicians who were not present for the initial assessment.

I. Aims

The aims of this study are:

- To determine the efficacy of ablative fractional carbon dioxide treatment on moderate to severe active nodular acne vulgaris.
- To determine the efficacy of ablative fractional carbon dioxide treatment on a focal acne lesion treatment during a short time frame.
- To evaluate the utility of a non-selective laser on inflammatory skin disease.
- To analyze microbiome changes before and after laser treatment.

II. Subject selection

Subjects will be screened to determine if they meet all the eligibility criteria specified below.

a. Inclusion Criteria

1. Subject must be able and willing to provide written informed consent and comply with the requirements of the study protocol;
2. In good general health, based on answers provided during the screening visit;
3. Subject must be able to read and understand English;
4. Any gender and any Fitzpatrick skin type;
5. Ages 18 through 40;
6. Subjects must have moderate to severe nodular active facial acne vulgaris (PGA 3 or 4);
7. Willing to sun protect treated area for the duration of enrollment in the study and 1 year after treatment;
8. Subjects must be ineligible for or have declined standard of care treatments (e.g. oral isotretinoin therapy).

b. Exclusion Criteria

1. Participation in another investigational drug or device clinical trial in the past 30 days;
2. Are pregnant or lactating;
3. History of allergic reaction to topical anesthesia;
4. Subjects may not have undergone oral isotretinoin therapy within the past 12 months;
5. Currently take oral antibiotic or oral therapy for acne with the exception of oral contraceptives;
6. History of keloidal or hypertrophic scarring;
7. Laser treatment in past six months;
8. History of poor wound healing;
9. Clinically significant abnormal findings or conditions which might, in the opinion of the Investigator, interfere with study evaluations or pose a risk to subject safety during the study.

c. Source and Recruitment of Subjects

The study will be posted on the Partner's clinical research web page (Rally), flyers around the hospital, and outpatient clinics (general dermatology clinics) to reach an economically and socially diverse population.

V. Subject Enrollment

a. Method of Enrollment

All subjects will be subject to a telephone prescreening by study staff before scheduling the initial screening visit. All subjects who electronically or in person sign an informed consent form (ICF) and are screened will be documented on a screening log. All subjects who qualify at the screening visit and who are enrolled in the study will be documented on the enrollment log. A note will be made in the source documentation verifying that the subject has willingly signed the ICF prior to participation in any

study procedures. All subjects will receive a subject number.

b. Informed Consent Form (ICF)

A licensed physician investigator or sub-investigator will inform the potential study subject of all aspects of the study and answer their questions. If the subject agrees to be a study subject, she will document consent in electronic form by signing an online ICF via Adobe eSign. Subjects who need more time to decide whether they would like to participate will have access to the electronic consent form and will call if they are interested in participating in the study. If the quality of the call or photos is not good enough to our investigator evaluate eligibility criteria, in person consent is a possibility. The patient will be scheduled for a visit and if he does not qualify, he will not be enrolled, and a parking ticket will be provided if required.

The investigator is responsible for using a consent form that has been approved by the IRB/Partner's HRC and is the most current version. If a new version of the consent form is approved by the IRB/Partner's HRC while a subject is still participating in the study, then the Investigator will inform the subject of the changes and, if the subject agrees to continue study participation, they should sign the updated form.

Informed consent will be obtained prior to performance of any protocol-specific procedures.

c. Patient selection

22 subjects with moderate to severe active acne vulgaris will be recruited for this study.22 more subjects will be recruit for the second arm of the study. Each subject will serve as their own control. Subjects will abstain from any oral, with the exception of a non-prescription cleanser if they are already using one, and a non-comedogenic moisturizer twice daily, for one month, in order to assess baseline acne activity. Following this, the first arm will receive three serial ablative fractional 10,600 nm carbon dioxide laser treatments (Lumenis® Ultrapulse® C02 laser with DeepFX™) between 2 to 4 weeks apart. And the second arm will receive one localized treatment in 1-3 selected acne lesions.

If the subjects want to continue to use topical treatments for acne (previously prescribed by their own doctors) or if they do not the availability to continue in the study for 6 months at least they will be directed to the second arm of the study (focal treatment).

IV. Study Procedures

Screening Visit (video/phone call)- for both arms

During the screening visit, study staff will discuss with each subject the nature of the study, its requirements and its restrictions.

The following will be performed to determine eligibility:

- Review of inclusion/exclusion criteria
- Medical history and demographics
- Review of medications
- Subjects who qualify for the study will be e-consented by trained study staff and scheduled for their baseline visit. Subjects who fulfill all inclusion and exclusion criteria may enroll and begin the Visit 1 procedures that same day.
- Subjects will be advised to not wear any makeup or products on their face before all study visits.
- Subjects will be asked to send 3 photos from your face (front, right and left profile)
- If the quality of the call or photos is not good enough to our investigator evaluate eligibility criteria, in person consent is a possibility. The patient will be scheduled for a visit for clinical assessment and if he does not qualify, he will not be enrolled, and a parking ticket will be provided if required. If he qualifies and signs the consent form, he starts the visit #1 procedures.

First arm :

Visit #1 (Baseline Visit)

At the first visit, eligibility criteria, including a review of medical history and medications, and detailed information about the study will be reviewed.

Once consented, the subjects will be asked to wash their face with gentle cleanser 3 hours before their appointments. The investigator takes skin swab samples at 5 separate areas from the subjects' face (right cheek, left cheek, nose, chin , forehead), and medical photography of the lesions will be obtained. After this, 3D images will be obtained using the Cherry Imaging system. Finally, a clinical assessment, including a PGA score and lesion count will be determined. Included in the lesion count will be papules, defined as an elevated, solid, palpable lesion that is ≤ 1 cm in diameter, and nodules, defined as an elevated, solid, palpable lesion > 1 cm usually located primarily in the dermis and/or subcutis. The greatest portion of the lesion may be exophytic or beneath the skin surface. This will be repeated for every visit for each subject. For one month following the baseline visit and the remainder of the study thereafter, the subject will not use any topical or prescription acne medications except a non-

prescription cleanser, if they are already using one, and a non-comedogenic moisturizer twice daily. In consultation with their current provider, the subject must be willing to stop using prescription topical medication for acne if they are using one. Subjects will be asked to wash their face and wear no make-up prior to all study visits.

Treatment #1 (second visit)

One month following the baseline visit, optional medical photography and 3D images of the lesions may be obtained. The patient will be asked to wash their face with gentle cleanser 3 hours before their appointments. The investigator will take swab samples at 5 separate areas from the subjects' face (right cheek, left cheek, nose, chin , forehead). The patient will be anesthetized with 23% lidocaine, 7% tetracaine topical numbing for one hour, which is standard of care in laser clinic. Once the subject has been anesthetized, they will be asked to wash their face before undergoing laser treatment with Ultrapulse CO_2 laser DeepFX 10-20 mJ, 10% density, 1 pass to the face. Subjects will then be instructed to perform post-procedural care with warm soaks and a non-comedogenic moisturizer as needed to keep face very moist for 2 weeks. Urine pregnancy tests, for female participants of childbearing potential, will be performed before treatment.

Third Visit

This visit will happen 15 days after the first treatment. Optional medical photography and 3D images of the lesions may be obtained. The patient will be asked to wash their face with gentle cleanser 3 hours before their appointments Skin swab samples taking swab samples at 5 separate areas from the subjects'face (right cheek, left cheek, nose, chin , forehead).

Treatment #2 (fourth visit)

This visit will be identical to Treatment #1, 3-4 weeks after visit 2. Optional medical photography and 3D images of the lesions may be obtained. The patient will be asked to wash their face with gentle cleanser 3 h before their appointment swab samples will be taken at 5 separate treatment areas from the subjects' face (right cheek, left cheek, nose, chin and forehead). The patient will be anesthetized with 23% lidocaine, 7% tetracaine topical numbing for one hour, which is standard of care in laser clinic. Once the subject has been anesthetized, they will be asked to wash their face before undergoing laser treatment with Ultrapulse CO_2 laser DeepFX 10-20 mJ, 10% density, 1 pass to the face. Subjects will then be instructed to perform post-procedural care with warm soaks and a non-comedogenic moisturizer as needed to keep face very moist for 2 weeks. Urine pregnancy tests, for female participants of childbearing potential, will be performed before treatment.

Treatment #3 (fifth visit)

This visit will be identical to Treatments 1 and 2, 3-4 weeks after visit 3 but there will be no skin swabs. Optional medical photography and 3D images of the lesions may be obtained.
The patient will be anesthetized with 23% lidocaine, 7% tetracaine topical numbing for one hour, which is standard of care in laser clinic. Once the subject has been anesthetized, they will be asked to wash their face before undergoing laser treatment with Ultrapulse CO_2 laser DeepFX 10-20 mJ, 10% density, 1 pass to the face. Subjects will then be instructed to perform post-procedural care with warm soaks and a non-comedogenic moisturizer as needed to keep face very moist for 2 weeks. Urine pregnancy tests, for female participants of childbearing potential, will be performed before treatment.

Post-procedural visits

Subjects will be followed up for two visits as early as 2 (sixth visit) and up to 12 weeks(seventh visit) after the last treatment (Treatment #3). During these follow-up visits, clinical photos and Cherry images will be obtained, and a clinical assessment may be performed (PGA, lesion count). Also, there will be 2 optional similar visits ,6 and 12 months after the end of the treatment. On the last 3 study visits a questionnaire (FACEQ Aesthetics - Satisfaction) will be applied to evaluate subjects' satisfaction with the treatment.

On the last post procedural visit (visit number 7) subjects will be asked to wash their face with gentle cleanser 3 hours before their appointments. The investigator will take swab samples at 5 separate areas on subject' face from the subjects' face (right cheek , left cheek , nose, chin , forehead).

Clinical assessment

Clinical assessments will occur at each visit by a study investigator. Medical and three-dimensional photographs taken pre-treatment and post-treatment will be complied and scored at first by the dermatologist present, and later compared to scores given in blinded fashion by at least one additional dermatologist using the Physician's Global Assessment (PGA) of acne severity, a widely used scale from the existing literature to determine clinical change from baseline, in addition to acne lesion count.

Acne Microbiome Swab

Swab samples will be collected from subjects' face in 5 separate areas (i.e. cheek and chin) and labeled with the coded subject ID. The samples will be stored at -20°C for DNAShield or equivalent buffers, and/or frozen at -80°C in PBS with glycerol (to a final concentration of 25%). De-identified samples and

photos (i.e., blacking out eyes and eyebrows) will be sent to the Lieberman Lab at MIT for analysis. Samples will be taken both before and after treatment.

A member of the research team will either process samples or maintain them frozen for later processing and/or cultivation. Members of the research team will use de-identified data to compare results from different participants and to analyze both intrapersonal and interpersonal variation.

Samples will be cultured for bacteria. Microbes will be cultured in the laboratory and preserved for future processing and/or cultivation. Microbes will be characterized in various ways (e.g. growth assays, metabolomics, and analysis of nucleic acids).

DNA from uncultured extracts will also be analyzed for community composition. Samples will be used to collect microbial nucleic acids to characterize the microbial community (e.g., by amplicon-based surveys using 16S or clade-specific marker genes; or by shotgun metagenomic sequencing). In the process of shotgun metagenomic sequencing of swab samples human DNA will also be sequenced. However, no human tissue will be cultured during the course of this work, and no human DNA will be analyzed (any sequences aligning to the human genome will be discarded). As explained above, bacterial samples and DNA sequences from these samples may be stored indefinitely, but no identifying information will be stored long-term. Only the anonymous subject code will be connected to the data/samples.

Second arm:

Visit #1 (Baseline Visit+ treatment)

At the first visit, eligibility criteria, including a review of medical history and medications, and detailed information about the study will be reviewed.

Medical photography of the lesions will be obtained. After this, 3D images will be obtained using the Cherry Imaging system. Finally, a clinical assessment, including a PGA score and lesion count will be determined. Included in the lesion count will be papules, defined as an elevated, solid, palpable lesion that is ≤ 1 cm in diameter, and nodules, defined as an elevated, solid, palpable lesion > 1 cm usually located primarily in the dermis and/or subcutis.

During the clinical assessment 1-3 inflammatory acne lesions (papules or nodules) will be selected by the investigator (trained dermatologist). This area will be anesthetized with 23% lidocaine, 7% tetracaine topical numbing for one hour, which is standard of care in laser clinic. Once the subject has been anesthetized, they will be asked to wash their face before undergoing laser treatment with Ultrapulse CO_2 laser DeepFX 10-20 mJ, 10% density, 1 pass to the 1-3 inflammatory- acne lesions previously selected. Subjects will then be instructed

to perform post-procedural care with warm soaks and a non-comedogenic moisturizer as needed to keep face very moist for 2 weeks.

Urine pregnancy tests, for female participants of childbearing potential, will be performed before treatment.

After the visit and the remainder of the study thereafter, the subject will not use any topical or prescription acne medications on the treated area except a non-prescription cleanser, if they are already using one, and a non-comedogenic moisturizer twice daily.

Subjects will be asked to wash their face and wear no make-up prior to all study visits.

Visit #2

Visit 2 will happen 1 week after visit 1. Medical photography of the lesions will be obtained. After this, 3D images will be obtained using the Cherry Imaging system. Finally, a clinical assessment, including a PGA score and lesion count will be determined. Included in the lesion count will be papules, defined as an elevated, solid, palpable lesion that is ≤ 1 cm in diameter, and nodules, defined as an elevated, solid, palpable lesion > 1 cm usually located primarily in the dermis and/or subcutis. More detailed clinical photos from the treated area (1-3 inflammatory acne lesions previously selected) will also be taken.

The subjects will be instructed to send photos from the treated area 2 weeks and 4 weeks after the procedure.

a. Devices to Be Used

Lumenis® Ultrapulse® CO2 laser with DeepFX™

This Ultrapulse CO2 laser with DeepFX is an FDA-cleared device used for skin resurfacing. The lesion(s) will be treated with the laser at an energy level of 10-20 mJ, 10% density, 4 passes to the face. Protective eyewear will be worn by subjects and study staff in accordance with standard laser safety procedures. Subjects will then be instructed to perform post-procedural care with warm soaks and a non-comedogenic moisturizer as needed to keep face very moist for 2 weeks.
Both arms will use the same laser device and the same energy level and density will be applied.

Cherry Imaging Photography

The Cherry Imaging system is a 3-dimensional photographic imaging system

designed to accurately measure aesthetic treatments to deliver objective patient data before and after aesthetic treatments. The handheld camera captures thousands of three-dimensional images of the face and/or body from multiple field views and angles that are analyzed to provide 100-micron accuracy level data of the body and/or face for real-time evaluation of treatment results and traceability over time. The Cherry Imaging device will be used to take images of the face before the laser treatment takes place and during the last visit. No special lighting is needed for the imaging device, so the images will be taken and processed directly in the room where the laser procedure will take place.
The Cherry software creator (Vardit Eckhouse) will analyze the 3D images created by study staff from subject's face (eyes closed) during appointments. The images are coded (only subjects' study number will be sent).She will have access to those images using Team Viewer that will allow her to connect the computer where Cherry Imaging Software is.

b. Remuneration

For the first arm: Subjects will receive $50 for completing each of Visits 1- 5 and optional visits. $75 per visit for completing Visits 6-7.

For the second arm: Subjects will receive $50 for completing Visits 1and optional visits. $75 for completing Visits 2.

We will provide a parking voucher at MGH main campus for each visit upon request.

We will be using an approved, outside vendor (Forte Research) to make remuneration payments via a reloadable credit card-based system called Forte Payments. This secure system is similar to a gift card or credit card.

Subjects will be given a Forte Payments Visa card (which is just like a debit card) when they enroll in the study. Once the card is activated, the study team will add a payment after each paid visit completed by the subjects. The payment should be available within one (1) business day. Research staff will not know where subjects spend the money. Subjects may use the card anywhere Visa cards are accepted, such as at a grocery store.

We will need to collects subjects' Social Security number in order to make remuneration payments, and it will be shared securely with the company that runs the card-based system. Payments like this are considered taxable income. If subjects receive more than $600, the payment will be reported to the IRS as income by the hospital.

VII. Biostatistical Analysis

In order to achieve a power of 0.95 with a p-value < 0.01, a sample size of 22 subjects is needed, assuming a standard deviation of 1 on the Physician's Global

Assessment (PGA) scale (a numerical scale from 0-4), which will be used as the primary clinical outcome measure. A two-sided, one sample, paired t-test will be used to determine if any significant statistical difference is present between the clinical response of each treatment arm using the absolute difference between the pre- and post-experimental PGA.

VIII. Risks and Discomforts

There is a potential risk of loss of privacy. We will protect privacy by labeling samples and information only with a code and keeping the key to the code in a password protected database.

Possible risks of fractional laser surgery include pain, scarring, infection, abnormal wound healing, hyper or hypopigmentation, pinpoint bleeding, or swelling.

Possible side effects of topical 23% lidocaine, 7% tetracaine include redness, mild burning sensation, tingling, itching or swelling. Rare side effects include an allergic reaction, which may manifest as dizziness or drowsiness.

IX. Potential Benefits

a. Potential Benefits to subjects

Subjects who participate in this study may benefit by having improvement in the appearance of their skin lesions.

b. Potential Benefits to Society

Information gathered from this study may improve the understanding of acne and laser treatment for inflammatory skin conditions.

X. Monitoring and Quality Assurance

a. Independent monitoring of source data

Experienced study personnel (study monitor) who are not assigned to complete procedures of this study will conduct monitoring after the first subject is enrolled and periodically thereafter. The monitor will be responsible for confirming the completion and correctness of the study procedures as well as record collection and keeping.

b. Safety monitoring

Prior to enrollment, subjects will be screened for eligibility; at which time a complete medical history, including a baseline assessment of the subject's skin in the area of interest will be done. Evaluations will be ongoing throughout the study to detect adverse events and changes in existing medical conditions.

At any time after enrollment, a subject may be discontinued. Reasons for discontinuation of a subject from the study will include, but may not be limited to, the following:

1. Subject is found to be intolerant to a required study procedure at any time point.
2. Subject is noncompliant with protocol restrictions and requirements.
3. Subject develops an intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
4. Subject becomes pregnant while participating in the study.
5. Subject enrolls in another investigational study.
6. Subject requests to withdraw from the study.
7. The study Sponsor decides to suspend or terminate the study.

If possible, a final set of assessments will be performed on all subjects who end their participation prior to study completion.

d. Outcome monitoring

The study will be conducted in accordance with applicable regulations and Good Clinical Practice Guidelines. Keeping files locked with access limited to study staff will ensure confidentiality and data integrity.

e. Adverse Event Reporting

Definition

Adverse Event (AE) is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is another medically important condition

Reporting and Documenting Adverse Events

All untoward medical occurrences that occur after the subject signs a consent form will be documented as an AE. The Investigator will ensure that all events that occur during the study period are recorded. All AEs will be followed until resolution or until, in the Investigator's judgment, they are chronic and stable. If an emergency situation should occur, appropriate medical measures should be taken to stabilize the subject.

Documentation of AEs includes: date and time of onset and resolution of AE, intensity, frequency, seriousness, related interventions and outcome. The Investigator will also evaluate the probability of a causal relationship of the AE to the study treatment as being: "definite, probable, possible, unlikely, or unrelated." Intensity of adverse events will be graded as mild, moderate, or severe according to the following criteria:

- Mild: symptoms that are easily tolerated and transient in nature with minimal or no impairment of normal activity
- Moderate: symptoms that are poorly tolerated, are sustained, and interfere with normal activity
- Severe: symptoms that are incapacitating and render the subject unable to work or participate in many or all usual activities

All SAEs will be reported to the IRB according to the IRB's requirements. They will also be reported to the study Sponsor.

XII. Data Management

a. Data collection

Study data will be collected during all study visits. Study data to be collected includes clinical photography, Cherry images, results from microbiome culturing, DNA testing of microbiome and qualitative patient responses to treatment. Clinical assessments (all visits), pregnancy test results (visit 2,4 and 5), and adverse events (all visits) will be recorded. All physical documentation and IRB correspondence will be stored in study binders maintained in restricted lab space only accessible by study staff and members of the Manstein Lab. Digital data including photographs will deidentified and stored on Partners computers and EPIC. Any identifiable information in photographs such as eyes and tattoos will be blacked out and deidentified. All study documents containing PHI will be password encrypted, including the enrollment log and identification key. An encrypted external hard drive will be used to store the data as a backup.

b. Data sharing

De-identified information (i.e. blacking out eyes and eyebrows) will be shared with Lieberman Lab at MIT, but no information linking subjects to their data/samples will be shared. De-identified data, including subject ID, location of swab, and treatment status will be shared. Subjects can withdraw consent at any time by notifying a study team member and their data and samples will be pulled and destroyed including any analysis already conducted.

The Cherry software creator (Vardit Eckhouse) will analyze the 3D images created by study staff from subject's face (eyes closed) during appointments. The images are coded (only subjects' study number will be sent).She will have access to those images using Team Viewer that will allow her to connect the computer where Cherry Imaging Software is.

c. Record retention

The Investigator or designees will retain all study records in accordance with MGB Human Subject Research Recordkeeping and Record Retention Requirements Policy and clinical trial regulations.

XIII. IRB Review and Approval

The study will not begin prior to the receipt of written confirmation of approval by the IRB and any relevant regulatory authority. It is the responsibility of the Investigator to obtain the IRB approval (per the U.S. Code of Federal Regulations, Title 21, Part 56 and applicable ICH guidelines) for the protocol, amendments,

informed consent, subject information sheet, questionnaires, and advertising materials used to recruit study subjects, if appropriate.

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Appendix 1: Physician's Global Assessment (PGA) of Acne Severity

Physician's Global Assessment (PGA) of acne severity		
0	'Clear'	Residual hyperpigmentation and erythema may be present
1	'Almost clear'	A few scattered comedones and a few small papules

2	'Mild'	Easily recognizable; less than half the face is involved.
3	'Moderate'	More than half the face is involved. Many comedones, papules and pustules. One nodule may be present
4	'Severe'	Entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts