

**University Hospitals Case Medical Center**  
**Department of Dermatology**  
**Protocol**

**Protocol Title:** Effects of UVB Excimer Laser on Serum Inflammatory Markers in Patients with Psoriasis

**Principal Investigator:** Margaret Bobonich, NP

**Co-Principal Investigator:** Elma D. Baron, MD

## **1. BACKGROUND/RATIONALE**

Psoriasis is a prevalent global skin disease (1). Psoriasis is not simply an inflammatory disease of the skin but also a systemic inflammatory condition that carries a higher risk for cardiovascular disease and other systemic comorbidities. Certain inflammatory markers are known to be elevated in the serum of patients with psoriasis. Some of these markers may correlate with severity and extent of skin lesions (i.e. PASI score), while others may not (2). Therapies that decrease the inflammation present in the skin could lead to a systemic decrease in inflammatory mediators, thereby lowering the risk for developing comorbidities. UVB phototherapy has been employed in the treatment of psoriasis for decades. The UVB wavelengths most effective for psoriasis (i.e. action spectrum) falls within 308-313 nm. Narrowband UVB (311 nm) is the most popular phototherapeutic modality for full body treatment, in which unaffected normal skin is also exposed to UV light. Lesion targeted NUVB became feasible upon the introduction of 308 nm excimer lasers. This strategy not only spared normal skin from unnecessary UV, but also allowed for higher doses of UV to be delivered on lesional skin, within a reasonable amount of time. Currently, excimer laser treatment of psoriasis is an FDA-approved therapy. Whereas changes in serum resistin have been demonstrated after NUVB (3), there is no data regarding targeted UVB excimer laser treatments and serum inflammatory markers.

Hyperpigmentation is a common adverse effect reported after targeted UVB phototherapy (4,5). In our clinical experience, the Photomedex Xtrac® Velocity Excimer Laser has resulted in minimal to no hyperpigmentation after psoriasis plaque treatment. Furthermore, there is a lack of research objectively measuring hyperpigmentation and erythema after excimer laser treatment.

## **2. STUDY OBJECTIVES/HYPOTHESIS**

The overall aims for this study are to determine whether UVB excimer laser treatment of psoriasis affects serum inflammatory markers, and to assess hyperpigmentation and erythema with excimer laser treatment.

We hypothesize that treatment of psoriasis with UVB delivered via 308 nm excimer laser will decrease the levels of serum inflammatory markers. We hypothesize that treatment will decrease plaque erythema and will result in minimal hyperpigmentation

## **3. STUDY DESIGN**

We plan on enrolling 24-27 psoriasis patients for this research study.

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### **3.1 STUDY POPULATION**

#### **3.1.1 Inclusion Criteria**

- Age 18 years and older
- Male or female with diagnosis of psoriasis
- Psoriasis involvement of 5-15% BSA
- Has been off systemic psoriasis therapies (e.g. retinoids, methotrexate, biologic agents, etc) for at least 4 weeks
- Has been off topical therapies (e.g. calcipotriene, topical steroids) for at least 2 weeks
- Fitzpatrick Skin Types I-VI

#### **3.1.2 Exclusion Criteria**

- Active history of photosensitivity (e.g. xeroderma pigmentosum, lupus erythematosus, porphyria, severe polymorphous light eruption, solar urticaria)
- Any suspicion that the psoriasis is of the photosensitive variant.
- Any medical condition that could be aggravated or may cause extreme discomfort during the study period.

### **3.2 STUDY PROCEDURES**

#### **3.2.1 Dose Determination:**

The initial dose will be determined by one of the following methods:

- **Sunburn Test/Minimal Erythema Dose (MED) Test:** This test will be performed during the screening visit to determine the initial dose of the Excimer laser. This involves exposing spots on the buttock or lower back to increasing doses of UVB via the Excimer laser. The redness generated from these exposures will be evaluated at Visit 2 by visual evaluation to determine the initial laser dose. The initial dose will be anywhere from 1-4x the MED. Patients who choose this method will have to come back for Visit 2 to determine the dose.
- **Visual MED Test:** If this method is chosen, a study doctor will visually determined the MED during the screening visit based on the patient's skin type and thickness of the psoriasis plaques. Patients who choose this method will not have to come in for Visit 2.

#### **3.2.2 Excimer Laser Irradiation:** This is a standard clinical procedure approved for the treatment of psoriasis. Initial laser dose will be anywhere from 1-4x the MED,

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depending on thickness of the plaque. Escalation will be 25-50% increase in dose per treatment if there is no residual erythema, 25% increase per treatment if there is mild residual erythema, and 0% increase per treatment if there is moderate residual erythema. Investigator also has the option to skip a treatment, if there is above moderate erythema, or significant patient discomfort exists. Patients will receive treatment twice a week until one of the following:

- PASI 75 Improvement
- Patient reaches a maximum of 20 treatments

**3.2.3 Optional Punch Biopsy:** Up to 8mm punch biopsies may be taken at the screening visit and final visit from a psoriasis lesion. The tissue samples will be used for histology and undergo standard H&E staining to evaluate the differences before and after Excimer laser treatment. Patients may still participate in this study if they choose to not donate punch biopsies. This procedure involves the removal of a small circle of skin (pencil eraser-sized) using a cookie cutter-like instrument. Lidocaine is used to numb the area to be removed before obtaining the biopsy and then 1-2 stitches are used per biopsy site to prevent bleeding, speed healing and improve the appearance. This procedure may last up to an hour depending on the number of biopsy sites. The stitches are then removed 7-14 days later.

**3.2.4 PASI Scoring:** PASI will be determined for all subject at the Screening Visit, Visit 8, Visit 16, at Visit 23 Final/Termination Visit and, if applicable, the 3 month follow-up visit. The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The PASI is a validated instrument that has become standard in clinical trials for psoriasis. Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score.

**3.2.5 Physician Global Assessment (PGA):** PGA skin evaluation will be performed at the Screening visit, Visit 8, Visit 16, Visit 23 Final/Early Termination Visit, and, if applicable, the optional 3 month follow-up visit. This assessment is a scale from 0 (clear) to 5 (severe). It is a global assessment of the subject's psoriasis based on the severity of induration, scaling and erythema.

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**3.2.6 Chromameter Assessment:** Treated plaques will be evaluated using a chromameter as an objective measure of hyperpigmentation and erythema at Screening Visit, Visit 8, Visit 16, Visit 23 Final/Early Termination Visit, and, if applicable, the 3 month follow-up visit. The chromameter uses the L\*a\*b\* color system. L\* measures skin reflectance or lightness, a\* measures red to green color saturation, b\* measures yellow to blue color saturation. Hyperpigmentation of treated plaques will be assessed via L\*. L\* values of treated plaques will be compared to L\* values of normal, untreated skin. Erythema of treated plaques will be assessed via a\*. a\* values of treated plaques will be compared to a\* values of normal, untreated skin. These values will also be compared from visit to visit.

**3.2.7 Limited Medical Exam:** Medical and Dermatological history, demographic information, concomitant medications, vital signs, height, weight, and BMI will be collected during Visit 1/Screening Visit.

**3.2.8 Blood Draw:** Blood will be drawn at Visit 1/Screening Visit and at Visit 23 Final/Early Termination Visit by venipuncture and will be evaluated for:

- Serum Inflammatory Markers: (e.g. Levels of CRP, resistin, MPO and S100, etc) as quantified via ELISA kits [ $\sim$ 10mL blood].
- Pro-Inflammatory Monocytes (optional): Populations of monocytes will be characterized in the blood and via flow cytometry analysis [ $\sim$ 60mL blood].

**3.2.9 Questionnaires:** Subjects will be asked to complete two questionnaires.

**3.2.5.1 Patient Satisfaction Survey:** Patients will be asked to complete a survey, scoring their satisfaction with the treatment at Visit 23 Final/Early Termination Visit.

**3.2.5.2 Nutrition Questionnaire:** Patients will be asked to complete a survey about their nutritional habits at Visit 1/Screening Visit.

**3.2.10 Photographs:** Participants will have a photographic record of their skin made throughout this study at the discretion of the study doctor to document any changes in the psoriasis from the treatment. Photographic records provide objective data on skin lesions of persons with skin disease and potential changes that may occur over time in the disease. Photography gives us a tool to compare clinical appearance with laboratory and research findings. Clinical images will be stored as digital images electronically. In the event that a photograph is taken of the patient's head or any other identifiable feature, the patient's identity may become known. Every precaution will be taken to protect the patient's identity, including blacking-out the patient's eyes on any photographs involving the face.

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### **3.3 STUDY VISITS**

#### **3.3.1 Visit 1: Screening Visit (estimated time: ~ 90 minutes)**

- Subjects will review the Institutional Review Board (IRB) approved Informed Consent Form (ICF) with the study staff. After all study procedures have been discussed and all questions have been answered, subjects will affirm participation by signing and dating the consent form.
- Inclusion/exclusion criteria will be reviewed and subject eligibility confirmed.
- Study staff will review concomitant medications and procedures with each subject.
- Medical and Dermatological History information will be collected.
- Vital signs, height, weight and BMI will be collected and recorded.
- Subjects will have their psoriasis clinically evaluated through PASI scoring and PGA.
- A chromameter will be used to evaluate pigmentation before treatment.
- Subjects will have plaque/body photographs taken
- Subjects will undergo a Sunburn MED Test or Visual MED Test.
- Subjects will complete a dietary/nutrition questionnaire.
- Subjects will undergo a pre-treatment blood draw.
- An optional, pre-treatment punch biopsy may be taken from a psoriasis lesion.

#### **3.3.2 Visit 2 (estimated time: up to 15 minutes)**

*\*\*This visit will only be scheduled for patients undergoing the Sunburn MED Test\*\**

- Study staff will review concomitant medications, any AEs since the previous visit, and procedures with each subject.
- Study staff will determine the MED through visual evaluation.
- Patient may begin first treatment/Visit 3 during this visit.

#### **3.3.3 Treatment Visits (Visits 3-22) (estimated time: up to 1 hour):**

***\*Patients will undergo Treatment twice a week until they reach a PASI 75 improvement, or until they reach the maximum of 20 total treatments\****

- Study staff will review concomitant medications, any AEs since the previous visit, and procedures with each subject.
- Subjects will have their psoriasis clinically evaluated through PASI scoring and PGA every four weeks during Visit 8 and Visit 16.
- During Visit 8 and Visit 16, treated plaques will be evaluated using a chromameter to measure hyperpigmentation and erythema that may be caused by the laser.
- Subjects will have plaque/body photographs throughout this study.
- Subjects will undergo standard clinical treatment with an Excimer Laser.

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**3.3.4 Visit 23: Final Visit/Early Termination Visit [2 days-2 weeks after last treatment]  
(estimated time: up to 1 hour )**

- Subjects will have their psoriasis clinically evaluated through PASI scoring and PGA.
- Treated plaques will be evaluated using a chromameter to measure hyperpigmentation and erythema that may be caused by the laser.
- Subjects may have plaque/body photographs taken.
- Subjects will undergo a post-treatment blood draw.
- Optional, post-treatment punch biopsies may be taken from a psoriasis lesion.
- Subjects will fill out the Patient Satisfaction Survey.

**3.3.5 \*\*Optional 3 Month Follow-Up Visit (estimated time: approximately 30 minutes):**

- Subjects will have their psoriasis clinically evaluated through PASI scoring and PGA.
- Treated plaques will be evaluated using a chromameter to measure hyperpigmentation and erythema that may be caused by the laser.
- Subjects may have plaque/body photographs taken.

**3.4 Schedule of Events**

	Visit 1: Screening	Visit 2 (Only if Sunburn/MED was done)	All Treatment Visits (Visits 3-22)	Treatment Visit 8 and Visit 16	Visit 23: Final Visit/Early Termination Visit	**Optional 3 Month Follow- Up Visit
Informed Consent	X					
Limited Medical Exam	X					
PASI & PGA	X			X	X	X
Photographs*	X	X	X	X	X	X
Chromameter	X			X	X	X
Blood Draw	X				X	
Concomitant Med Assessment	X	X	X	X	X	X
Optional Sunburn/MED Test	X					
Optional Sunburn/MED assessment		X				
Excimer Laser Treatment			X	X		
Nutrition Questionnaire	X					
Patient Satisfaction Questionnaire					X	
Adverse Event Assessment	X	X	X	X	X	X
Optional Sub-Study: Additional Blood	X				X	
Optional Sub-Study: Punch Biopsy	X				X	

*\*Photographs will be taken throughout this study at the discretion of the study doctor to document any changes in the psoriasis from the laser treatment.*

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#### **4. RISKS AND DISCOMFORTS AND HOW MINIMIZED**

- 4.1. Sunburn Test/Minimum Erythema Dose (MED) Testing:** A sunburn reaction may result from the MED testing. The degree of sunburn that the participant experiences should be light to moderate redness (sometimes no redness occurs). It may result in some tenderness and possibly some mild dryness and itching and may change into a tan color, with the degree of darkness and the time it takes to fade being dependent upon the light dose and participant skin type. In the most extreme circumstance, to achieve a completely even color of light-exposed and adjacent unexposed skin can take over one year, and in most cases, will result in no long-term effects from this type of exposure. Some sunburns will not be visible, so the area will be marked with a black pen to facilitate evaluation.
- 4.2. Excimer Laser Irradiation:** Similar to a sunburn, there could be redness, scaling, occasionally blistering of the skin lesion treated. These are considered expected reactions to the ultraviolet light. As this is a therapeutic, clinical intervention that is known to reduce the inflammation in psoriasis, the benefits outweigh the risks and discomforts. Long-term risks of UVB Excimer laser have not been reported in the literature.
- 4.3. Chromameter Assessment:** The chromameter poses minimal risk, as this is a non-invasive instrument that is used to measure pigmentation and redness.
- 4.4. Optional Punch Biopsies:** Punch biopsies will be up to 8mm in diameter. Lidocaine, which is used to numb the skin prior to biopsy, may cause a tingling or burning sensation when injected into the skin. Potential risks of the biopsy include bleeding or oozing from the biopsy wound, discomfort at the site, or infection. One to two sutures will be utilized to close the biopsy site. These will be removed 14 days after the biopsy occurs. Suture removal is generally painless, but may involve a scant amount of bleeding and some pinching or pulling of the skin. The biopsy site will heal with a small, flat scar, which may be red for several months. The scar may be lighter or darker than the surrounding area.
- 4.5. Blood Draw:** The risks of simple blood drawing may commonly include the occurrence of discomfort and/or bruise at the site of the puncture and, less commonly, the formation of a small clot, swelling of the vein, or bleeding from the puncture site.
- 4.6. Questionnaires:** There are no known risks to filling out questionnaires. However, in rare instances some participants may feel uncomfortable with answering or applying responses to some questions.
- 4.7. Photographs:** There are no known risks to taking photographs. In the event a photograph is taken of the face or any other identifiable feature, the patient's identity may be known. Every precaution will be taken to protect the patient's identity. In the event a photograph is taken of

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the patient's head or face, the patient's eyes will be blacked out.

**5. COMPENSATION FOR INJURIES**

Every effort to avoid side-effects of participating in this research study will be made, but there can be no guarantee that study subjects will not experience some physical damage. As there is no automatic compensation available for physical injury for a research study, study subjects will not be automatically reimbursed for the costs of time lost from work or the costs of extra hospital days, doctor's fees, and medicine.

**6. BENEFITS TO SUBJECT**

No direct benefit can be guaranteed as a result of participation in this research study, however, because UVB Excimer laser is an established therapy for psoriasis, it is anticipated that some participants may see an improvement of their disease. Participation in this study will help aid in the understanding of Excimer lasers and the effects they have on serum inflammatory markers in the body.

**7. COSTS TO THE SUBJECT**

There is no cost to the participant for research-specific procedures. Standard of care procedures will be billed to the subject's insurance.

**8. ALTERNATIVES TO PARTICIPATION**

Alternative treatments available to patients who decide not to participate or who may withdraw early from the study are:

- Topical creams/ointments
- Methotrexate
- Oral retinoids
- Cyclosporine
- Full body narrowband UVB
- Biologics

**9. WITHDRAWAL FROM STUDY PARTICIPATION**

The participants are entitled to withdraw from the study at any time and for whatever reason without this having an effect on their access to the treatment via the investigator.

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## **10. PAYMENT TO THE SUBJECTS (REIMBURSEMENT AND INCENTIVES)**

The participant will be compensated for study parking costs (if any); parking validated for study-related visits. Subjects will be compensated \$50 at the screening visit and \$50 at the final visit to cover study-related procedures. All Excimer laser treatment visits will be billable to the patient's insurance company, per standard of care. Participants to choose to participate in the optional sub-study will receive \$20 for each additional blood draw and \$25 for each punch biopsy.

## **11. PLAN FOR OBTAINING INFORMED CONSENT (INFORMED CONSENT PROCESS)**

Potential subjects recruited for study participation will be seen by a member of the study staff in a private exam room for the formal consent process. Each participant will have the study explained in its entirety with special attention to the length of the study, the actual study procedures, financial obligations, risks, benefits and alternatives to participation. Participants will be given ample time to consider study participation and encouraged to discuss with significant others, have any questions answered by the study staff. Only participants willing to undergo all study procedures will be asked to affirm participation by signing the consent form. Only study staff that have been trained on the study and having IRB required Human Subject Protection Training and authorized by the investigator will obtain consent. Subjects will be reminded the importance of adhering to all study requirements and their right to withdrawal at any time without affecting the quality of their individual medical care.

## **12. PROVISIONS FOR SUBJECTS FROM VULNERABLE POPULATIONS**

No special subject populations are targeted for inclusion in this protocol however if subjects from vulnerable populations noted below are eligible, additional procedures will be followed.

In the event that an illiterate person who understands English presents themselves as a potential study participant and they meet all of the inclusion/exclusion criteria, the consent form will be read to that individual in the presence of a witness. The study participant will sign the consent document by "making their mark" in the signature space; the witness must also sign and date the consent form, noting that the informed consent process has taken place.

House staff and students, medical students on a clerkship, and employees of Case Western Reserve University (CWRU) or UHC are not excluded from the study, but their participation will be entirely voluntary. Their scholastic or employment evaluations will be conducted by a rater uninvolved with, and most likely totally unaware of, the study. Members of the study team are not eligible to participate in this study as a subject. Subject participation is kept confidential by the entire study team, and will not be divulged to supervisors, evaluators, or others, unless under the unlikely condition where it becomes medically necessary information, with the subject's consent.

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### **13. SUBJECT PRIVACY AND DATA CONFIDENTIALITY**

Study participant information collected in the research process may include; contact information, consent documentation, demographics, social security number (necessary for reimbursement), and personal medical history. All data will be stored on the secure UH or REDCap<sup>©</sup> server or as paper records stored in a locked cabinet. Data collected in this study will include: Patient records collected electronically and on paper, consent forms, and blood samples. Each class of data will be handled in the following manner:

**13.1 Patient Records and Consent Forms:** Patients enrolled into the study will complete informed consent and provide medical history. All patients upon entering the study will be assigned a unique identifier by REDCap<sup>©</sup> that will be used throughout the study to de-identify their information. Consent forms and paper records will be filed in study binders, stored in a locked room within the Department of Dermatology. Only authorized research personnel will have access to these records.

Patient records will be created and stored electronically on both the secure and encrypted University Hospitals server and the secure REDCap<sup>©</sup> server. REDCap serves as the main computerized data management system for this study.

The PI will ensure protocol adherence, proper protocol conduct, data quality, and subject safety and efficacy by conducting regular meetings with the entire study staff. The adverse events submitted by subject phone inquiry or email will be reviewed and adjudicated with all research team members. In addition, any adverse events or deviations to the protocol or other issues will be discussed at the Regulatory Meeting held monthly in the department of Dermatology.

**13.2 Blood Samples:** Study personnel will acquire the specimen from each patient via needlestick, de-identify the specimen using a code specific for this trial before sending it to the lab for processing.

**13.3 Photographs:** All photographs will be de-identified and stored on the secure UH server, only accessible to authorized study personnel. In the event a photograph is taken of the face or any other identifiable feature, the patient's identity may become known.

**13.4 Data Transfer/Transmission:** Research data will be sent to Pingfu Fu, PhD, Biostatistical Core, CWRU after finishing the clinical trial; however, all of the data will be stripped of patient identifiers prior to transfer.

In order to comply with federal regulations, records identifying participants in this study may be reviewed authorized representatives of the Institutional Review Board or other federal regulatory officials responsible for oversight of human subject protection. Any data

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linking participants to their sample will be de-identified. A code will be used to link participants to identifying information and only the investigators and the research study coordinators will have access to this information, which will be stored on a server at University Hospitals Case Medical Center with a separate encryption code. Upon enrollment, each patient record will be stripped of all identifying information and assigned a unique numerical identifier that has no reference to any identifiable patient information.

## **14. DATA ANALYSIS PLAN**

- 14.1 Clinical Outcome:** Clinical evaluation through PASI scoring and PGA will be performed, supported by photographic documentation. Percent change in PASI and number of treatments to obtain PASI 75 improvement will be calculated for each patient and results summarized as descriptive statistics using means and standard deviations.
- 14.2 Serum inflammatory markers:** Levels of inflammatory markers in the serum e.g. CRP, resistin, MPO and S100. will be quantified pre and post treatment via ELISA kits and correlated with PASI score, total number of treatments received, BMI and nutrition data, using multivariate regression analyses.
- 14.3 Optional flow cytometry analysis:** Populations of monocytes will be characterized in the blood and response to excimer laser expressed in improvement in PASI scores will be correlated with levels of specific pro-inflammatory monocytes using Pearson correlation coefficient. Level of pro-inflammatory monocytes will also be correlated with levels of CRP, resistin, MPO, S100.
- 14.4 Chromameter Assessment:** Hyperpigmentation of treated plaques will be assessed via  $L^*$ .  $L^*$  values of treated plaques will be compared to  $L^*$  values of normal, untreated skin. Erythema of treated plaques will be assessed via  $a^*$ .  $a^*$  values of treated plaques will be compared to  $a^*$  values of normal, untreated skin. These values will also be compared from visit to visit. They will also be correlated with response to treatment.
- 14.5 Patient Satisfaction Questionnaire:** Each item in the survey will be scored from 1-5. Scores will be summarized and descriptive statistics will be used. Satisfaction scores will also be correlated with PASI improvement.

## **15. DATA AND SAFETY MONITORING PLAN**

### **15.1 Procedures for analysis and interpretation of data**

The PI or co-investigator holds meetings with the staff performing both the clinical and laboratory based assessments. These meetings occur on a minimum of a monthly basis, but

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often occur more frequently. These meetings are held for two primary functions: to discuss primary data and progress of the study. Data include both clinical observation and laboratory measurements. The secondary function of these meetings is to monitor clinical outcomes for potential adverse events associated with the study. The PI has put into place an action plan should adverse events occur during the course of the study. Adverse events that could be envisioned are outlined below:

- A. Responsible party for safety monitoring:** In addition to the PI, safety monitoring will also be performed by the designated medical study coordinator.
- B. Safety Monitoring Methods and Intervals:** Grading method and attribution for adverse event reporting AE will be graded according to the following 0-5 scale:

<b>Score</b>	<b>Description</b>
0	No Adverse Event or within normal limits or not clinically significant
1	Mild AE did not require treatment
2	Moderate AE resolved with treatment
3	Severe AE resulted in inability to carry on normal activities and required medical attention
4	Life threatening or disabling AE
5	Fatal AE

The PI will determine the relationship of AE's to the test procedure/agent/device as; not related, possibly related, or definitely related, using standard criteria for clinical trials.

- All reported AEs will be followed until the event resolves or stabilizes OR
- The event returns to baseline OR
- The event can be attributed to agents other than the study agent(s) OR
- The subject withdraws informed consent OR
- The subject is lost to follow up.

- C. Implementation of the data and safety monitoring plan:** Adverse event reports for this protocol will be submitted to the approved IRB. Adverse Event Report Form sent in a timely manner consistent with the approved IRB policy.

In addition, any serious adverse event (grade 3 or greater), with the exception of those reported in the protocol, must be reported to the sponsor by the investigator by telephone, fax or email within 24 hours. A notification form will then be sent to the sponsor by fax or email with acknowledgement of receipt within 48 hours of the event.

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The investigator will also inform the sponsor of adverse events and abnormal results of the analysis, which are defined as decisive for the evaluation of safety of persons taking part in biomedical research.

#### **16. PLANS FOR THE SUBJECTS AT THE END OF THE PROTOCOL**

At the last visit, patients will be advised that lesions that do not demonstrate improvement should be treated using other established therapies (e.g. topical steroids, retinoids, phototherapy, etc), and appropriate referrals will be made.

#### **16. REFERENCES**

- 1) Parisi R et al. Global Epidemiology of Psoriasis: A Systemic Review of Incidence and Prevalence. *J Invest Dermatol* 2013; 133(2): 377-85.
- 2) Nakajima et al. Clear association between serum levels of adipokines and T-helper 17-related cytokines in patients with psoriasis. *Clin exp Dermatol* 2013; 38(1):66-70.
- 3) Kawashima et al. Phototherapy reduces serum resistin levels in psoriasis patients. *Photoderm Photoimmunol Photomed* 2011, 27(3);152-55.
- 4) Mudigonda et al. A review of targeted ultraviolet B phototherapy of psoriasis. *J Am Acad Dermatol* 2012, 66; 664-72.
- 5) Taibjee et al. Controlled study of excimer and pulsed dye lasers in the treatment of psoriasis. *Br J Dermatol* 2005, 153; 960-966.