

**UCSD Human Research Protections Program**  
**New Biomedical Application**  
**RESEARCH PLAN**  
**Last Updated 11/06/2020**

**1. PROJECT TITLE**

A single site evaluation of the inhibitory effects of topical ivermectin on serine protease activity and production of LL-37 cathelicidin peptide, biochemical markers of rosacea-specific inflammation and on the skin microbiome in rosacea (NCT02806414)

**2. PRINCIPAL INVESTIGATOR**

Tissa Hata, MD

**3. FACILITIES**

UCSD Dermatology Outpatient Clinic (University Pacific Center in La Jolla, CA)

**4. ESTIMATED DURATION OF THE STUDY**

2 years

**5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)**

This study will assess the role of topical Ivermectin 1% cream and its effect on protease and antimicrobial peptide expression and on the skin microbiome (the microorganisms that live on the skin) in rosacea. This is a single-site 16-week open-label study at University of California, San Diego. We will do this by first measuring serine protease activity and cathelicidin and skin microbiome of all subjects. All subjects will receive Ivermectin topical cream and will be instructed on how to apply it daily for 12 weeks. Participants will return for monthly visits during which their clinical symptoms of facial redness and number of facial papules will be scored, and they will have repeat tape stripping and/or skin swabs. At the end of the study, tape strips and skin swabs will be analyzed to determine serine protease activity and skin microbiome of participants at each of their visits and expression of cathelicidin (LL-37) mRNA. We will then look at changes in serine protease activity and LL-37 expression and skin microbiome over time, and we will also determine whether or not these changes correlate with disease severity.

**6. SPECIFIC AIMS**

1. To determine if 12 weeks of topical ivermectin to affected areas of facial skin can decrease biochemical markers of rosacea-specific inflammation and/or change the skin microbiome composition of rosacea patients
2. To validate and correlate the efficacy of topical ivermectin on rosacea and biochemical markers of rosacea.

**7. BACKGROUND AND SIGNIFICANCE**

Recent observations have shown that facial skin from patients with rosacea produce excess amounts of the serine protease kallikrein 5 (KLK5), and abnormal forms of the antimicrobial peptide cathelicidin (CAMP). In mice, abnormal CAMP and KLK5 expression influences inflammation, and administration of the forms of human CAMP found in rosacea results in inflammation, angiogenesis and vascular ectasia. In this study, we sought to further confirm the critical role of KLK5 and CAMP in rosacea by examining if the effects of a current human beneficial therapy correlated with changes in the expression of these genes. We measured KLK5 in cultured normal human epidermal keratinocytes (NHEKs), and found that differentiated keratinocytes in high calcium media (1.6 mM) greatly increased both KLK5 mRNA and protein compared to undifferentiated cells. Addition of Azelaic acid (Aza, 10<sup>-8</sup> to 10<sup>-9</sup> M) to differentiated NHEKs significantly decreased KLK5 in media (vehicle; 91.26 ± 22.58 ng/ml, 10<sup>-8</sup> M Aza; 41.69 ± 15.08 ng/ml). Total protease activity was also significantly less in media recovered from keratinocytes treated with 10<sup>-8</sup> M Aza. Furthermore, mice treated once a day for 9 d with topical application of Aza gel (15%, Finacea™) showed significantly less KLK5 and Camp mRNA compared with mouse skin treated with the vehicle alone (relative expression of KLK5 and camp was 55% and 32% of control, respectively). In conclusion, since an excess of KLK5 and cathelicidin has been hypothesized to contribute to the development of rosacea, finding that an effective treatment for rosacea can decrease expression of these molecules further supports the involvement of KLK5 and cathelicidin in the pathogenesis

of this disease.

Individuals with rosacea show high Cathelicidin antimicrobial peptide (CAMP) expression in lesional skin. High CAMP expression in rosacea is accompanied by an increase of its processing enzyme kallikrein 5 (KLK5), a major serine protease in skin epidermis. Combination of high CAMP and high protease activity by KLK5 increase makes CAMP in active form LL-37, which is not seen in normal skin. Persistent abundance of LL-37 induces inflammatory reactions in skin. Therefore, imbalance of CAMP and protease KLK5 is a key factor in rosacea pathogenesis.

## Microbiome

Although the demodex mite has been described in the microbiome of rosacea, a specific driver of disease still remains to be found and the microbiome yet unidentified. In preliminary studies, our lab identified an increase in both the commensal organisms *Cutibacterium acnes* and *Staphylococcus epidermidis* after treatment with topical ivermectin. These findings correlated with a decrease in erythema and for *Staphylococcus epidermidis*, also a decrease in papule count. As different strains of these microorganisms have been associated with both a healthy microbiome and a diseased state of the microbiome, we hope to be able to expand on these early findings, and better identify the role of *Cutibacterium acnes* and *Staphylococcus epidermidis* in rosacea in hopes of establishing alternative treatments for patients with rosacea.

In this study, we will assess topical Ivermectin, which is FDA-approved in the treatment of rosacea, to enable us 1) to test if Ivermectin changes LL-37 mRNA and serine protease expression and skin microbiome composition in rosacea patients, and 2) to assess if improvement of rosacea symptoms is associated with a decrease in LL-37 and serine protease activity and related microbial changes.

## 8. PROGRESS REPORT

None

## 9. RESEARCH DESIGN AND METHODS

This trial is designed as a pilot study to determine the range and mechanism of monitoring biochemical surrogates of rosacea after daily topical Ivermectin 1% cream treatment. This is a single-site 16-week open label study at University of California, San Diego. Up to 25 subjects (age 18+) with at least one inflammatory papule (IGA>1) and at least mild erythema (see Clinical Assessment for Inclusion Criteria) will all be treated with topical ivermectin daily for up to 12 weeks with 4 in-office visits (screening, then monthly follow-ups for 3 months and one follow-up telephone visit one month after study medication completion). Twenty tape strip samples (similar to the tape strip method described in Dyjack, et. al. 2018) from each of the four sites will be obtained at each visit to determine KLK activity and LL-37 expression and/or up to twelve skin swabs to assess skin microbiome. Safety monitoring has been established based on both the most likely reactions and the most serious though extremely rare events. At each visit, in addition to one planned phone call, the subject will be queried tolerance of therapy and Adverse Events. . The study will end with the last subject completing the telephone visit (Visit 5/week 16). If a patient does not return for a follow up visit after baseline, a replacement patient will be added.

The biochemical analysis of protease activity and LL-37 cathelicidin expression obtained by tape strip analysis at each time point and compared to baseline. Analysis of the tape strips will compare baseline to week 12 and also be correlated to the trends assessed in the tape strip analysis. The skin microbiome obtained by skin swab will also be analyzed at each time point and compared to baseline.

Ivermectin 1% cream is lawfully marketed in the U.S. as a topical treatment for inflammatory lesions of rosacea. Subjects will be instructed on the proper application of Ivermectin topical cream in accordance with the package insert, and they will apply a pea-sized amount for each area of the face that is affected daily. This research proposal therefore does not involve a route of administration, dose, or patient population that significantly affects the risk to benefit ratio associated with the use of the drug product. Furthermore, this is a proof of concept study, and therefore, this investigation is not intended to support a

change in advertising of the drug, in labeling, nor in promoting the drug product.

**Table of Events**

Visit number	Screening /Baseline Visit 1*	2	3	4	5 (Phone Visit)
Time of Visit	Day -31 to Day 0	Week 4	Week 8	Week 12	Week 16
Demographic Information	x				
Inclusion/Exclusion criteria	x				
Informed consent	x				
Physical examination	x				
Rosacea Severity Score (IGA & CEA)	x	x	x	x	
Medical History	x				
Subject Satisfaction Assessment					
Tape strip	x	x	x	x	
Skin swabs	X	X	X	X	
Weigh/dispense study medication as needed	x	x	x	x	
Weigh and return study medication		x	x	x	
Adverse events	x	x	x	x	x

\*Patients who require washout may be re-screened

### **VISIT 1 (Day 0)**

Prior to beginning any study procedures, subjects will first be asked to review and sign the informed consent form. After obtaining informed consent, the inclusion/exclusion criteria will be reviewed. A brief medical history and physical exam will be performed in helping to assess whether the subject meets the required criteria for the study. Female subjects of child-bearing potential will complete a urine pregnancy test while in our office to ensure that they are not pregnant. Patients who meet the inclusion and exclusion criteria will then have their rosacea severity scored by two different standardized grading scales: IGA and erythema scale. At the screening visit may occur at the same time as your screening visit if none of your medications are excluded. Tape strips and/or skin swabs will be collected from 4 areas of involved rosacea facial skin. Subjects will then be given a pre-weighed tube of study medication and instructed to apply the medication daily. Subjects will also be instructed not to apply the study drug on the morning before the tape strip samples are collected on return visits. The total time for this visit will be approximately 1 hour.

**VISIT 2 Week 4 (+/- 4 days)**

On Visit 2, rosacea severity will again be evaluated. Tape strips and/or skin swabs will be collected from the same sites as in the initial collection. Patients will be instructed not to apply the study drug on the morning before the tape strip samples are collected on return visits. Study drug will be weighed, and additional drug will be provided as needed. The total time for this visit will be approximately 1 hour.

**VISIT 3 Week 8 (+/- 4 days)**

On Visit 3, rosacea severity will again be evaluated. Tape strips and/or skin swabs will be collected from the same sites as in the initial collection. Patients will be instructed not to apply the study drug on the morning before the tape strip samples are collected on return visits. Study drug will be weighed, and additional drug will be provided as needed. The total time for this visit will be approximately 1 hour.

**VISIT 4 Week 12 (+/- 4 days)**

On Visit 4, rosacea severity will again be evaluated. Tape strips and/or skin swabs will be collected from the same sites as in the initial collection. Patients will be instructed not to apply the study drug on the morning before the tape strip samples are collected on return visits. Study drug will be weighed, and additional drug will be provided as needed. The total time for this visit will be approximately 1 hour.

**Visit 5 Week 16 (+/- 4 days) (phone follow-up)**

Subjects will be contacted via phone to inquire about any adverse events experienced since the last in clinic visit. This phone call will take approximately 5 minutes.

**Clinical assessments for inclusionary criteria:**

IGA scale, a subjective 5-point measure of overall disease severity. IGA scores range from 0 to 4: 0 = no signs or symptoms present (clear); 1 = 1 to 2 small, noninflammatory papules (near clear); 2 = 3 to 10 papules/pustules (mild); 3 = 11 to 19 papules/ pustules (moderate); and 4 = 20 or more papules/pustules and nodules (severe).

Erythema scale: Scores range from 0-4: 0=none (no redness present); 1= mild (slight pinkness); 2= moderate (definite redness); 3=significant (marked erythema); and 4=severe (fiery redness). For inclusion criteria subjects will require at least mild erythema.

**Lesional site identification and sample collection:**

At Visit 1, Four ~20x20mm areas will be identified as clinically involved. These sites will be recorded to ensure subsequent sampling is from the same area during follow up visits (Visits 2-4).

**Standard Tape stripping**-Four sites will be selected, ideally two on the right cheek, and two on the left cheek. Commercially available stratum corneum sampling tape (such as D-Squame) will be used for 20 repeated tapings. To ensure consistent sampling methods, a pressure instrument (D500–D-squame® pressure instrument, CuDerm, Dallas, TX, USA) will be applied to the tape of the tape strip for uniform pressure. The tape is placed on the skin and removed and placed into an Eppendorf tube. This will be repeated 20 times. Tape stripping is a well-accepted less invasive method in dermatologic research that is now becoming an alternative to skin biopsy for certain assays. As we are doing here, we hope to validate this sampling method for use in larger studies and transition its use into clinical practice. In summary, 20 tape strips from each of the four sites, for a total of 80 tape strips will be collected at each visit for biochemical evaluation. They will be stored at -80°C until processing.

### Standard Skin Swabs

Skin swabs will be done to collect bacteria from participants' skin. Swabs are then analyzed for the amount of bacteria and the presence of different bacterial species picked up by the swab. After swabbing, the swab are placed into either an empty Eppendorf tube (if analyzing the DNA of the bacteria present on the skin surface) or into a liquid medium such as tryptic soy broth (if analyzing the amount of bacteria present on the swabbed skin surface). These tubes are then stored at -80 degrees Celsius until analyzed for the data previously mentioned. The exact location of all swabbings, including whether the swabbing was taken from lesional or non-lesional skin in a patient with an inflammatory skin condition, will be recorded in the participant's file.

### **Laboratory Assessments**

#### **Processing of Tape-strips:**

The tape strips from the same visit from the same patient will be combined and processed together. Tapes will be immersed in 1 ml of 10mM Tris-HCl (pH 7.8) + 0.1% TritonX and vortexed. Protein extracts will be completely lyophilized and the pellet dissolved in 40 µl of PBS pH 7.4.

#### **Cathelicidin LL-37 protein analysis (tape strips)**

For quantification of cathelicidin, 2 µl of each sample or serially diluted synthetic LL-37 peptide as a standard will be dotted onto a nitrocellulose membrane. The membrane will be blocked with 5% non-fat dry milk in PBS for 1 h, incubated overnight with rabbit antibody to LL-37 at 4°C followed by incubation for 1 h with HRP-conjugated goat antibody to rabbit IgG. The immunoreactions will be visualized by Western Lighting chemiluminescence reagent plus and the density of each blot measured with NIH Image and compared with standard controls. Alternatively, SELDI-TOF-MS (surface enhanced laser desorption/ionization, time of flight, mass spectrometry) can be used to determine the cathelicidin peptide size. These procedures are developed in our laboratory to determine cathelicidin peptides from skin tape strip samples. Since the recovery of material from tape stripping may be variable, not all patients may have sufficient material for these studies.

### Skin Swabs

Samples will be analysed for the bacterial composition of the skin either by amplicon sequencing utilizing 16S ribosomal RNA amplification, quantitative polymerase chain reaction (qPCR), whole genome shotgun metagenomics or other next generation sequencing method.

### **Statistical Methods**

#### *Demographics, Population, and Baseline Characteristics*

Background and baseline demographic data and subject disposition data will be tabulated and presented for all enrolled participants. Subjects will be classified by severity of disease. The background and baseline characteristics will consist of age, race, sex, past and current medical conditions, and results from the physical examination. Continuous data (i.e., age) will be summarized descriptively by mean, standard deviation, median, and range. Categorical data (i.e., sex, race, and severity of disease) will be presented as enumerations and percentages. T-test will be used to evaluate continuous data and chi-squared test for categorical data.

#### *Primary and Secondary Analysis*

All information required will be entered into the Case Report Forms (CRFs). The objective of this trial is to determine if 12 weeks of topical ivermectin to affected areas of facial skin can decrease biochemical markers of rosacea-specific inflammation and affect the skin microbiome. Changes in lab measures before and after treatment will be compared pre and post ivermectin treatment using paired sample t-tests. Variables with right-skewed distributions will be log transformed at each time (pre and post treatment) before analysis. If log transformations do not provide distributions suitable for 2-sample t-tests (based on violation to the normality assumption), the Wilcoxon Rank-Sum test will be employed.

#### *Sample Size Calculation*

Given this is a proof of concept study, no sample size calculation will be performed.

#### *Safety Data*

All AEs, including SAEs, occurring during the course of this study will be listed for all subjects. Adverse events resulting in discontinuation from the study will be listed separately. Other information collected about AEs (e.g., severity or relationship to study procedures) will be listed as appropriate.

## **10. HUMAN SUBJECTS**

Up to 25 adult subjects (age 18+) will be enrolled with a diagnosis of rosacea and at least mild erythema and one inflammatory papule. The specific criteria for subjects will be discussed below. Each subject must be capable of providing informed consent.

Inclusion:

- Subject is male or non-pregnant female, 18+years of age.
- Subjects willing and able to give informed consent.
- Subjects willing and able to comply with the requirements of the study.
- Subject has the clinical diagnosis of rosacea with at least one inflammatory papule and at least mild erythema.
- Subject has been on a stable dose for greater than 3 months of medications for treatment of concurrent medical condition (including oral contraceptive pills, vasodilators, adrenergic blocking agents) OR the investigator has determined that the medications are unlikely to affect the patient's rosacea and/or treatment during the study
- Subject is in general good health in the opinion of the investigator.
- .
- Exclusion: Subject has a diagnosis of Steroid Rosacea or Pyoderma Faciale (rosacea fulminans).
- Subject has used facial topical therapies (OTC drug products or prescription products) for any reason within the prior 7 days
- Subject has used oral ivermectin within the prior 28 days.
- Subject has used systemic corticosteroid or systemic antibiotics (especially doxycycline, minocycline, tetracycline, metronidazole) within the prior 28 days.
- Subject has had laser or light-based treatment for rosacea within the prior 3 months.
- Subject has had systemic retinoids and retinoid derivatives over the past 6 months
- Subject has a known hypersensitivity or allergy to topical ivermectin or components of the vehicle.
- Subject is pregnant or lactating or planning a pregnancy during the duration of the study
- Subject has been treated with another investigational device or drug within 28 days prior to study enrollment or intends to participate in a clinical trial concurrent with this study
- Subject has clinically significant findings, medical history or conditions (other than rosacea), which in the opinion of the Investigator may compromise the study, treatment protocol, or safety of the patient or treatment allocation

## **11. RECRUITMENT**

Patients will be recruited online through advertisements placed on Craigslist and through fliers posted around the



UCSD campus. Recruitment will be performed by investigators and study coordinators. All recruitment materials will receive approval from the IRB before utilization. Involvement will be completely voluntary (no coercion) and all risks will be clearly outlined and explained prior to enrollment. Involvement will not lead to promotion or any salary compensation.

## 12. INFORMED CONSENT

Informed consent is an ongoing process that includes the signing of an informed consent form. Subjects will be required to sign an informed consent form prior to being screened and before undergoing any study procedures or assessments, in accordance with ICH E6; 4.8, "Informed Consent of Trial Subjects". Subjects will be provided with a copy of the informed consent form and printed materials that explain the purpose of the study, procedures, and assessments. Subjects will also be provided with the telephone numbers of the investigator and qualified personnel who can assist with their questions and concerns. Participants will sign the informed consent form at the Outpatient Dermatology Clinic in La Jolla at the time of their screening visit prior to any study-related procedures occurring. The study procedures, as well as the risks and benefits, will be discussed with prospective participants during the recruitment process prior to scheduling their screening visit, giving participants a minimum of 2 days to consider whether or not they are interested in participating. The procedures, risk and benefits will be discussed with patients again verbally at their visit prior to providing them with and having them sign the informed consent form. Members of the research team listed below will be involved in the consenting procedure.

Please see attached consent form.

## 13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to participating in the study would be to not participate in the study.

## 14. POTENTIAL RISKS

Summary of the known and potential risks and benefits to human subjects:

**Tape stripping:** The risk associated with tape stripping theoretically includes only the rare possibility of allergic reaction to the tape. Since the tape is immediately removed after application, the risk of reaction is extremely low. However, in previous and ongoing studies involving tape stripping, it has been noted that a very mild erythema may develop immediately after a series of tape strippings on one localized area of skin, presumably due to the mild mechanical disturbance. The erythema is expected to resolve within 12hrs without sequelae.

**Skin swabbing:** Risks from swabbing procedure during visits include discomfort and irritation during the procedure, which will promptly subside following cessation of swabbing with the cotton swab.

**Risks of Medication Withdrawal:** Stopping use of certain excluded medications may result in worsening of the patient's rosacea. Subjects whose rosacea will be severely exacerbated by withholding use of their normal drug regimen will be excluded.

**Risk of Loss of Confidentiality:** Samples will be labeled with the subject identification number prior to storage and only study investigators and study coordinators will have access to the patients' identifying information. The patients name and sample/test results will be stored separately and securely, but the principal investigator and site study staff will know which sample belongs to which patient until one year following the end of this study. At that time, the link between the subject and their sample will be destroyed and it will not be possible to determine which sample belongs to a particular patient. A patient may withdraw their sample from the study any time before the link between the patient and the sample is broken. Study participants will not be identified by name on any study documents. The study-related records will be maintained by the investigator. All study-related records (patient charts and other study records) must be retained no sooner than 2 years after data analysis is complete. Patients will be reassured that PHI will not be re-used or disclosed for other purposes.

**Risks of Topical Ivermectin cream:**

Although this drug was approved by the FDA for the treatment of rosacea, it does carry some risks. Hypersensitivity to topical ivermectin cream or any components of the cream is possible. Also, the study sponsor reports that the medication may cause sensations of burning/stinging/redness/itching at local sites of application. There have also been rare reports of burning, dry, itching eyes as well as redness, pain, excessive tearing or discharge, swelling of the eye if contact occurs with the eyes. This research plan does not utilize a route, dose, or patient population that differs from its lawfully marketed purpose.

**Topical Ivermectin Pregnancy Category: C**

There are no adequate and well-controlled studies in pregnant women.

**Effect on lactation:** Following oral administration, ivermectin is excreted in human milk in low concentrations; excretion following topical administration has not been evaluated

**15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES****SERIOUS ADVERSE EVENT REPORTING****Serious Adverse Events**

Serious adverse events will be collected throughout the study period, beginning with the signing of the informed consent through seven days post the last tape stripping. Serious adverse events also will be collected if they occur > 30 days after the end of the study and is thought to be possibly related to investigational product.

An adverse event is any undesirable sign, symptom, or medical condition occurring after starting the study drug (or therapy). Medical conditions / diseases present before starting the study treatment are only considered adverse events if they worsen after starting study treatment.

A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or adverse event, regardless of the investigator or sponsor's opinion on the relationship to investigational product. This includes, but may not be limited to, any event that (at any dose):

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any event that does not exactly meet this definition, but in the investigator's opinion represents a significant hazard (eg, emergency room visit or outpatient surgery), can be assigned the "other significant hazard" in regards to reporting serious criteria.

Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

**Reporting Procedures for All Adverse Events**

The investigator is responsible for ensuring that all adverse events are properly recorded in the subjects' records. After signing of the informed consent form, all adverse events observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be recorded in the case report form.



The following attributes must be assigned by the investigator: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The investigator may need to provide follow-up information, medical records, and extracts from medical records.

### **Adverse Events Standard Grading Score**

Clinical investigators will “grade” the severity of all AEs using the following scale; the results will be reported on the SAE form, if necessary.

1 = MILD – aware of sign or symptom, but easily tolerated

2 = MODERATE – discomfort enough to cause interference with usual activity

3 = SEVERE – incapacitating with inability to work or do usual activity

4 = LIFE-THREATENING – refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

5 = FATAL

### **Recording and Reporting Obligations for SAEs**

The investigator will provide the IRB appropriate information concerning any findings that suggest there has been an SAE related to the study. Any adverse event that is considered serious must be reported within one working day by the investigator to Galderma and to the IRB as required.

The investigator will notify the UCSD Human Research Protections Program of any unexpected, fatal or life-threatening experiences in writing no later than 10 working days of the event, according to standard IRB procedures. All serious and medically significant adverse events considered related to the product by the investigator will be followed until resolved or considered stable.

Unexpected and related fatal or life-threatening events will be reported to FDA by phone or FAX within 7-calendar day.

A written report will be sent to FDA within 15 calendar days for any serious unexpected adverse event considered related to study drug (including those which have already been reported under the 7 day rule).

Additionally, any pregnancies reported during this study will be reported to Galderma.

**Withdrawal from Medications:** Adverse events associated with stopping the use of protocol-prohibited medications may result in worsening of the condition being treated.

**Irritation from tape strips:** It is possible but unlikely that patient's may have some irritation due to the application of tape strips. Patient will be instructed to inform study doctor if irritation occurs.

**Irritation from skin swabs:** It is possible but unlikely that patient's may have some irritation due to the skin swabs. Patient will be instructed to inform study doctor if irritation persists.

**Confidentiality:** Subject confidentiality will be maintained by the investigator, the investigator's associates and co-workers, and by all administrators who are part of the ADVN project. Confidentiality will be maintained according to ICH E6; 4.8.10, part O: “Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.”

**Treatment and Monitoring:** If a subject has experienced an adverse event from use of topical Ivermectin or otherwise, the subject will be asked to return to the site. Actions taken in response to an AE will be recorded in the subject's medical record in accordance with the site's procedures. Any treatment administered for the AE

must be recorded in the subject's source document.

All subjects will receive verbal and written instructions with site contact information for whom to contact if they experience an AE associated with study procedures performed for this protocol or if the subject resumes their protocol-prohibited medication during the washout period.

Medically significant adverse events considered related to the study by the investigator will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment whether or not an adverse event is related and of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occur, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If the subject was permanently withdrawn from the study or investigational product due to a serious adverse event, this information must be included in either the initial or follow-up Serious Adverse Event Report Form.

## **16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT**

Personal information will be kept confidential and will be maintained at the Institution receiving the samples. The research records will be labeled with a code number. The list that matches the patients name with the code number will be kept in a locked file at the UCSD Dermatology Clinic on the 3<sup>rd</sup> floor of University Pacific Center in La Jolla. The research records will be kept only as paper records in a secure location, or as files behind the secure computer firewall. Any presentations or publications from this information will not identify any personal information. Identifying information will only be available to the doctor obtaining the samples from the patient. De-identified information will be available to all other persons involved with the research study. Study data will be combined for analysis at Dr. Gallo's laboratory at 3525 John Hopkins Court in La Jolla. No personal or confidential information will be provided to the trial's sponsor.

## **17. POTENTIAL BENEFITS**

A potential benefit to rosacea patients is a possible improvement in their disease. Benefits to the population include a better understanding of the immune modulating effects of topical Ivermectin.

## **18. RISK/BENEFIT RATIO**

The risks involved in this study are small and include the risks of medication withdrawal, irritation from tape strips and skin swabs, and loss of confidentiality. There is some risk that the study drug could cause local irritation. All attempts will be made to minimize these risks, as outlined in Item 14. These risks seem reasonable in relation to the benefits of the study, which would be to potentially better understand of the immunomodulation of topical Ivermectin and its effect on the skin microbiome.

## **19. EXPENSE TO PARTICIPANT**

The participant is not expected to incur any expenses. Since there are no lab draws or biopsies associated with this study aside from a pregnancy test for females of child-bearing potential, which we will do in our outpatient dermatology clinic, there will not be any study-related charges to either the patient or his/her insurance.

## **20. COMPENSATION FOR PARTICIPATION**

Participants will receive \$50 per in-office visit completed, and up to \$200 for completion of all study-related procedures for the study (for 4 in-office visits). No compensation will be provided for the screening visit. Therefore, subjects who are ineligible for the study based on the results of their screening visit will not be compensated for the screening visit. Compensation will be provided to participants in the form of a check that will be mailed to them from UCSD using UCSD's payment authorization system. Payment authorization will be submitted after the completion of all study procedures.

## 21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

The below members of the research team are certified, privileged and licensed to perform the duties as outlined in the protocol. These duties include discussion of the informed consent with the patient; physical exam; skin evaluation; placement of tape strips; and adverse and serious adverse events assessment and relationship to protocol. All these procedures are performed at UCSD's Outpatient Dermatology Clinic in La Jolla. Copies of CVs and licenses will be kept on file and regularly updated.

Tissa Hata, MD, Principal Investigator will be primarily responsible for the clinical aspects of the study, which will include patient screening, physical exams, and clinical assessments. Dr. Hata is a board certified dermatologist and is a Professor in Dermatology at UCSD.

Richard Gallo MD, PhD, Co-Investigator, will be primarily responsible for overseeing the basic science portion of the study. Dr. Gallo currently is Professor and Chair of Dermatology at UCSD.

Joyce Cheng, MD, clinical research fellow in the Department of Dermatology, will also be responsible in overseeing the coordination of the study, as well as informed consent discussions and enrollment interview. She will also be performing medical histories, physical exams, clinical assessment, and tape stripping/skin swabs.

Faiza Shafiq, MBBS, staff research associate in the Department of Dermatology, will be assisting in study visits. She will be scheduling patient visits and performing tape stripping procedures/skin swabs.

## 22. BIBLIOGRAPHY

Dyjack N, Goleva E, Rios C, Kim BE, Bin L, Taylor P, et al. Minimally invasive skin tape strip RNA sequencing identifies novel characteristics of the type 2-high atopic dermatitis disease endotype. Journal of Allergy and Clinical Immunology [Internet]. 2018 Jan 6; Available from: <http://www.sciencedirect.com/science/article/pii/S0091674918300010>

Yamasaki K, Di Nardo A, Bardan A, Murakami M, Ohtake T, Coda A, Dorschner RA, Bonnart C, Descargues P, Hovnanian A, Morhenn VB, Gallo RL. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. Nat Med. 2007 Aug;13(8):975-80. Epub 2007 Aug 5.

Yamasaki K, Gallo RL. The molecular pathology of rosacea. J Dermatol Sci. 2009 Aug;55(2):77-81. Epub 2009 May 29.

## 23. FUNDING SUPPORT FOR THIS STUDY

National Rosacea Society

## 24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

## 25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Ivermectin cream is not an investigational drug.

## 26. IMPACT ON STAFF

None

## 27. CONFLICT OF INTEREST

None

<b>28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES</b>
N/A
<b>29. OTHER APPROVALS/REGULATED MATERIALS</b>
N/A
<b>30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT</b>
N/A

Version date: May 11, 2011