UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Version Date: 03/20/2017

1. PROJECT TITLE

Evaluation of the effect of subcutaneous hyaluronidase administration on psoriatic plaques

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

UCSD Dermatology Outpatient Clinic (University Center Lane, La Jolla)

4. ESTIMATED DURATION OF THE STUDY

3 years

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

Dendritic cells are a key component of the inflammatory response seen in psoriasis. Several current psoriasis therapies have been shown to reduce the number of dendritic cells in patients with psoriasis, leading researchers to believe that therapies specifically targeting dendritic cells may lead to improvement in psoriaisis. Research recently conducted in Dr. Gallo's lab has shown that transgenic mice overexpressing the enzyme hyaluronidase have a significant decrease in the number of dendritic cells in the dermal component of their skin compared to wild type mice. If hyaluronidase overexpression in humans also decreases the number of dendritic cells in the dermis, then hyaluronidase therapy may improve the clinical presentation of psoriasis. In order to test this hypothesis, we plan to inject recombinant human hyaluronidase (Hylenex®) subcutaneously below a psoriatic plaque in human psoriasis patients every week for a total of 4 weeks. Each week we will measure the clinical appearance of the plaque. At visit 5we will also take skin biopsies of the treated plaque to visualize the histology of the plaque and look for changes in expression of different inflammatory markers.

6. SPECIFIC AIMS

- To determine whether administration of subcutaneous hyaluronidase (Hylenex®) into a psoriasis plaque is able to improve its clinical appearance
- To determine whether administration of subcutaneous hyaluronidase (Hylenex®) into a psoriasis plaque is able to change its histologic appearance

If there appears to be either a clinical or histologic change in the psoriatic plaque after subcutaneous hyaluronidase (Hylenex®) administration, we will also attempt the following aim:

- To determine whether administration of subcutaneous hyaluronidase (Hylenex®) into a psoriasis plaque down-regulates the expression of inflammatory markers interferon α (INFα), tumor necrosis factor α (TNFα), Toll-like receptor (TLR) 7, TLR 8, or TLR 9

7. BACKGROUND AND SIGNIFICANCE

Psoriasis is a chronic inflammatory skin condition affecting approximately 2% of the population[1]. Affected patients experience raised, well-demarcated, erythematous plaques with an overlying silvery scale on various parts of their skin. These lesions are associated with significant morbidity. Patients are embarrassed by the appearance of their skin; the lesions can be extremely itchy, causing distraction and difficulty sleeping; and most medications have significant side effects. In addition, patients with psoriasis, like those with other major medical disorders, have reduced levels of employment and income as well as a decreased quality of life[2,3].

The pathogenesis of psoriasis is thought to be initiated by triggers such as physical trauma or bacterial products that start a cascade of events, including the formation of self-DNA/LL-37 complexes. These complexes are recognized by Toll-like receptors on dendritic cells, activating the dendritic cells and causing them to secrete IFN-α. Activated dendritic cells then migrate into draining lymph nodes and induce the differentiation of naive T cells into effector cells such as type 17 helper T cells (Th17) or type 17 cytotoxic T cells (Tc17) and type 1 helper T cells (Th1) or type 1 cytotoxic T cells (Tc1). Effector cells continue to recirculate, and immune cells expressing the chemokine receptors CCR6, CCR4, and CXCR3 emigrate into skin tissue along chemokine

gradients.

Current therapeutic options for psoriasis target different points in the psoriatic cascade described above, including cytokines secretion and T cell activation and differentiation. Another therapeutic option, psoralen and ultraviolet A (PUVA), has been shown to reduce the number of dendritic cells in patients with psoriasis, providing key support for the role of these cells in the psoriatic cascade. Furthermore, A functional and potentially therapeutic role of dendritic cells as potential drug targets has also been shown in models of psoriasis[50]. In this study we hope to confirm the role of dendritic cells as a therapeutic target in psoriasis by injecting psoriatic plaques with an enzyme shown to decrease dendritic cell abundance in the animal model described below.

Hyaluronan is a major component of the dermal and epidermal extracellular matrix. An extraordinarily wide variety of biological functions have been attributed to HA including roles as a space-filling molecule maintaining hydration, lubrication of joints and actions in angiogenesis (19), and immune regulation (21, 22). Although the nascent size of hyaluronan is typically very large, large molecular weight hyaluronan undergoes breakdown after wounding into small fragments. These hyaluronan fragments can then interact with endothelial cells, macrophages and dendritic cells. Dr. Gallo's lab recently set out to investigate the role of hyaluronan breakdown *in vivo* using a transgenic mouse model overexpressing hyaluronidase, the enzyme responsible for breaking larger molecular weight hyaluronan into fragments. Results from these studies showed that hyaluronidase over-expressing mice had a significantly lower number of dendritic cells in the dermal compartment of the skin compared to wild type mice. The mice were otherwise morphologically normal compared to wild type mice and had no significant laboratory abnormalities during a hematologic survey that included a complete blood count, blood chemistry, coagulation and bleeding time except for a slight but significant increase in LDL. Since dendritic cells also play a role in mounting an inflammatory response to contact allergens, the ability of the hyaluronidase over-expressing mice were also tested to determine whether or not they were able to mount an allergic response. The transgenic mice were sensitized with the hapten eFluor670, which is known to cause a contact hypersensitivity reaction in wild type mice. Cutaneous inflammation was neither observed visually nor detected biochemically in the transgenic mice after application of this agent, suggesting that these mice were unable to mount an immune response to the agent because they lacked a sufficient number of dermal dendritic cells to mount an allergic response to this agent. Taken together, these results in these mice suggest that hyaluronidase overexpression, which causes breakdown of high molecular weight hyaluronan into small fragments, lack dendritic cells in their dermis that can prevent antigen presentation and reduce the resulting inflammatory cascade usually caused by exogenous stimuli.

In this study, we propose a plan that would allow us to test our hypothesize that hyaluronidase may have a role in treating psoriasis by reducing the number of dendritic cells in the dermis. Since dendritic cells play a key role in the inflammatory cascade of psoriasis, reducing their expression in the dermis could prevent the propagation of this inflammatory cascade.

Hylenex® is a recombinant form of human hyaluronidase that is FDA- approved for subcutaneous administration as an adjuvant for subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in subcutaneous urography for improving resorption of radiopaque agents. In this study we will inject Hylenex® subcutaneously beneath a psoriatic plaque every week for 4 weeks. Over the course of those 4 weeks we will observe the plaque for clinical changes. After the last administration of the drug, we will also do a skin biopsy of the treated plaque to determine whether any histologic changes have occurred. If there do appear to be histologic signs of psoriasis improvement, we will run RT-PCR of a second biopsy taken at the same time as the first biopsy to determine the expression levels of inflammatory cytokines such as IFN-α and receptors of inflammatory signals such as Toll-like receptors (TLR) 7-9 are different in these psoriatic plaques.

8. PROGRESS REPORT

None.

9. RESEARCH DESIGN AND METHODS

Participation in this study will consist of a total of 5 visits (plus 2 optional visits for a total of 7 visits) to the UCSD Dermatology Clinic over approximately a three-month period. At the first visit, two psoriatic plaques between 2-cm and 5-cm in diameter to be studied in this trial will be agreed upon by the patient as well as the blinded and unblinded investigators. Preference will be given to plaques on the elbows since the elbow is a common place of psoriatic plaques, and since scarring on the elbows is usually more acceptable than scarring on other parts of the skin since the skin on the elbows is naturally hyperpigmented in most people. For the remainder of the study, all grading and measurements of the psoriatic plaques will be completed by a blinded investigator who is unaware of which plaque is receiving which treatment. An unblinded investigator will complete all other portions of the study visit, including digital photography, injecting the plaques, and completing the biopsies. The patient will also be blinded as to which plaque is being injected with which treatment.

During the first 4 visits, we will be injecting the plaques with 1-mL of Hylenex® or 1-mL of sterile (pharmaceutical grade) normal saline (NS). 1-mL of Hyelenx® contains 150 Units of recombinant hyaluronidase. This is the standard dose of the drug that has been approved by the FDA, and therefore this dose is considered to be safe for use in adults. If injected subcutaneously into the center of a psoriatic plaque that is between 2 and 5 centimeters in diameter, this 1-mL dose should be able to diffuse throughout the entire area beneath the plaque. The exact pharmacokinetics of Hylenex® are difficult to study due to its rapid inactivation after intravenous injection. According to the Hylenex® package insert, though, disruptions to the dermal barrier that occur in response to subcutaneous Hyelenx® injection persist 24 hours after injection, but this barrier is completely restored after 48 hours. We expect cutaneous dendritic cells residing in the epidermis to migrate away from the epidermis through either lymphatic or vascular channels after Hylenex® is injected. This process should take only a few hours. Since cutaneous dendritic cells are thought to turnover only every 1-2 weeks, we would not expect new dendritic cells to populate the epidermis before patients receive the next injection of Hylenex®. Since dendritic cell activation initiates the inflammatory cascade thought to result in psoriasis, preventing dendritic cells from being harbored in the epidermis should essentially prevent the inflammatory cascade that results in psoriasis. Therefore, we hope that during the month-long period while patients are receiving Hylenex® injections, the inflammatory cascade triggering their psoriasis will be turned off, allowing their affected plaques to heal without further propagation of psoriasis. We therefore hope to see differences in the Hylenex®-treated versus the NS-treated plaques both morphologically and histologically when we complete our final set of biopsies on the Visit 5.

The specific procedures planned for each visit are described below:

Screening/Baseline Visit (Visit 1/Day -28 to 1)**:** After signing informed consent, participants will first be screened to ensure that they are eligible for the study. This includes undergoing any necessary wash-out period in the case that the subject has treated their psoriasis with any topical agents (topical steroids, vitamin D, or calcineurin inhibitors) within 7 days of the screening/baseline visit, or any oral or injectable treatments (cyclosporine, methotrexate, immuran, oral retinoids, chemotherapeutic agents, anti-inflammatory biologics such as alefacept, etanercept, or oral calcineurin inhibitors) within 28 days of the screening/baseline visit. If patients have taken one of these medications within the specified time and are still interested in participating in the study, they must hold that medication for a total of 7 days for topical agents and 28 days for oral/injectable agents and return for a baseline visit. For subjects who are eligible for the study, we will then take a brief

medical history and do a physical exam. Next we will choose two of their psoriasis plaques to monitor throughout the study. Both plaques must be between 2-cm and 5-cm in diameter, and must be in different locations on the body (either on different extremities or one on an extremity and the other on the trunk). One of these plaques will be treated with Hylenex® over the course of the trial, while the other will be treated with NS to use as a control plaque. First we will take pictures of the two plaques using a digital camera in order to visually compare the plaques and to use as a reference for determining the location of the plaque in future visits should the plaque(s) resolve over the course of the trial. The photographs will not contain any identifying information. They will be uploaded onto a password-protected computer and saved under the patient's unique study identification number, which will not be traceable to any identifying information about the patient on the computer. A blinded investigator will grade the severity of the plaques using known psoriatic grading scales such as the Physician's Global Assessment (PGA) and the Psoriasis Area and Severity Index (PASI) and will also take measurements of the plaque sizes. The unblinded investigator will then do one (1) 4-millimeter punch biopsies of the two plaques. These biopsies will be fixed in formalin for histologic examination (to be read by Dr. Hinds), and will be frozen for later use for RT-PCR to determine expression levels of inflammatory cytokines and receptors including TNFα, IFNα, and TLR 7, 8 and 9. There will not be any genetic testing done on this tissue, nor will it be stored for later use in other research projects. We will then inject a single dose (1 mL, or 150 units) of Hylenex® subcutaneously under the skin of the plaque designated the treatment plaque. We will next inject the control plaque with 1 mL NS subcutaneously. We will monitor the patient for thirty (30) minutes after the injection to ensure the patient does not have a reaction to the injections prior to them leaving the clinic. The total length of this visit will be approximately one hour and 15 minutes.

Visit 2 (Day 8 +/- 1): Participants will return to the clinic, where we will first record any adverse events since the last visit. We will take digital photographs of the two psoriasis plaques of interest in this study to document changes in the plaque since the last visit. The photographs will not contain any identifying information. Next the blinded investigator will grade the severity of the psoriasis plaques of interest using the PGA and PASI scores, as well as by taking measurements of the plaque sizes. The unblinded investigator will then administer a 1 mL (equivalent to 150 units) dose of Hylenex® under the skin of the same plaque injected at Visit 1. We will next administer a subcutaneous injection of 1 mL NS to the control plaque. We will monitor the patient for thirty (30) minutes after the injections to ensure the patient does not have a reaction to the injection prior to them leaving the clinic. The total length of this visit will be approximately 45 minutes.

Visit 3 (Day 15 +/- 1): The activities of Visit 3 will be identical to those of Visit 2

Visit 4 (Day 22 +/- 1): The activities of Visit 4 will be identical to those of Visit 2

Visit 5 (Day 29 +/- 1): We will first record any adverse events. We will take digital photographs of the two psoriasis plaques of interest in this study to document changes in the plaques since the last visit. The photographs will not contain any identifying information. The blinded investigator will then grade the severity of the psoriasis plaques of interest, including size measurements. Finally, the unblinded investigator will perform to one (1) 4-millimeter punch biopsies of the plaque we injected with Hylenex® during previous visits, and one (1) 4-millimeter punch biopsies of the plaque we previously injected with NS. The biopsy from both the treatment and control psoriatic plaques will be fixed in formalin for histologic examination (to be ready by Dr. Robert Lee or Dr. Casey Carlos), and will be stored at -80° Celsius for later use for RT-PCR to determine expression levels inflammatory cytokines and receptors such as TNFα, IFNα, and TLR 7, 8 and 9. The total length of this visit will be approximately 30 minutes.

Phone 1 (Day 59 +/- 7):
Subjects will be called approximately one month after Visit 5. Patients can opt for an optional in-clinic visit

instead of a phone call if so desired. During this phone call, subjects will be asked about any adverse events (including serious adverse events) since their last follow-up visit, as well as how their psoriasis is currently doing. If patients opt for an in-clinic visit, digital photographs of the two psoriasis plaques of interest will be taken to document changes in the plaques since the last visit. The photographs will not contain any identifying information.

Phone 2 (Day 109 +/- 7):
Subjects will be called approximately 2 months after Visit 5. Patients can opt for an optional in-clinic visit instead of a phone call if so desired. During this phone call, subjects will be asked about any adverse events (including serious adverse events) since their last follow-up visit, as well as how their psoriasis is currently doing. If patients opt for an in-clinic visit, digital photographs of the two psoriasis plaques of interest will be taken to document changes in the plaques since the last visit. The photographs will not contain any identifying information. Although this phone contact or in-clinic visit will be the last scheduled contact for subjects with respect to this study, any subject with an ongoing adverse event (including serious adverse event) at the time of this phone contact/clinic visit will continue to be followed by study personnel until resolution of the event.

Statistics
Sample size calculation: Since this study is a proof-of-concept pilot study, there is no sample size calculation for this study.
Comparison of psoriatic plaques:
The treated plaque for each individual will be compared at each visit to the previous visit in terms of PGA, PASI and area using a paired t-test.
Each participant's baseline biopsy for histology will be compared to the histology of the treated plaque by our dermatopathologist to determine whether there appears to be any histologic changes in the plaque treated with Hylenex® compared to the untreated plaque. These histologic changes will include the number of dendritic cells in particular slices of the biopsy, as well as histologic markers of psoriasis severity.
Each participant's baseline biopsy for expression levels of inflammatory cytokines and receptors including TNFα, IFNα, and TLR 7, 8 and 9 will be compared to the expression levels of these cytokines and receptors in the treated psoriatic plaque using a paired t-test.

10. HUMAN SUBJECTS

Ten patients with a clinical diagnosis of psoriasis on physical exam will be recruited for this study. All subjects will be between the ages of 18 and 65. Enrollment will not take race or gender into consideration. Women of child-bearing potential (pre-menopausal females who have not been surgically sterilized), children (under age 18), and unhealthy subjects with significant co-morbid conditions as determined by the PI will be excluded.

This study is planned as a single center at the University of California, San Diego.

SUBJECT ELIGIBILITY

Inclusion Criteria:
Those who meet all of the following criteria are eligible for enrollment into the study:
1. Diagnosis of plaque psoriasis for at least 6 months, with at least 2 psoriatic plaques on different parts of the body that are both between 2-cm and 5-cm in diameter at the time of screening
2. Age 18-65 years
3. Male subjects who agree to use barrier methods for contraception throughout the course of the trial if their female partners are of child-bearing potential, or female subjects not of child-bearing potential
4. Subject agrees to comply with study requirements

5. Subject is fluent in English and is able to provide written informed consent

Exclusion Criteria:

1. Subjects with severe medical condition(s) that in the view of the investigator prohibits participation in the study
2. Subject has Netherton's syndrome or other genodermatoses that result in a defective epidermal barrier
3. Subjects who have applied topical medications (prescription or over-the-counter) for the treatment of psoriasis to their body within 7 days of the baseline visit
4. Subjects who have taken cyclosporine, methotrexate, immuran, oral retinoids, chemotherapeutic agents, anti-inflammatory biologics (e.g., alefacept, etanercept, etc.), or oral calcineurin inhibitors within 28 days of the baseline visit
5. Subjects who are unable to hold their current psoriasis medications for the period of time indicated (at least 7 days for topical medications, at least 28 days for oral or injectable medications) without significant worsening of their psoriasis
6. Immunocompromised subjects (e.g., lymphoma, HIV/AIDS, Wiskott-Aldrich Syndrome), or subjects with a history of malignant disease (excluding non-melanoma skin cancer) as determined by the participant's medical history.
7. Subjects receiving phototherapy (e.g., ultraviolet light B [UVB], psoralen plus ultraviolet light A [PUVA]) within 28 days of the baseline visit
8. Subjects with a history of psychiatric disease or history of alcohol or drug abuse that would interfere with the ability to comply with the study protocol
9. Subjects with significant concurrent medical condition(s) at screening that in the view of the investigator prohibits participation in the study (e.g., severe concurrent allergic disease, condition associated with malignancy, and condition associated with immunosuppression)
10. Subjects who have used any systemic antibiotics within 28 days of the baseline visit
11. Subjects with an active bacterial, viral or fungal skin infection (excluding nail fungus)
12. Subjects currently receiving lithium or have received lithium within the last 4 weeks.
13. Ongoing participation in an investigational drug trial
14. Subjects with diabetes requiring medication
15. Presence of psoriasis with exfoliative erythroderma or presence of guttate psoriasis, primary palmoplantar psoriasis, or pustular psoriasis
16. Hypersensitivity to hyaluronidase or any other ingredient in the formulation of hyaluronidase, as well as subjects with an allergy or hypersensitivity to lidocaine
17. Subjects taking furosemide, benzodiazepines, phenytoin, salicylates, cortisone, antihistamines or estrogens

REMOVAL AND REPLACEMENT OF SUBJECTS

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at UCSD. All data generated up to the time of discontinuation from the study will be analyzed and the reason for discontinuation will be recorded.

11. RECRUITMENT

Patients will be recruited from the practice of the investigators (once the study starts, investigators will ask psoriasis patients who they see in their clinic if they are interested in participating in a clinical trial), online advertisements placed on Craigslist, and fliers. 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. The informed consent process will occur at the UCSD outpatient dermatology clinic in La Jolla. After first being told about the study and its risks and benefits, participants will be given a minimum of 3 days to fully consider their willingness to participate in the study before coming in to sign the consent form during their screening visit. Before any other procedures at the screening visit, 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. Members of the research team listed below will be involved in this consenting procedure. Once the consent form has been signed and dated, the participant can proceed with the screening procedures.

Please see attached consent form.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health. Patients may withdraw their consent at any point in the study without risk of compromising future care at UCSD.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to participating would be not to participate in the trial. Patients not wanting to enroll in the study but still wanting to treat their psoriasis will need to see a dermatologist to discuss other therapeutic options, which include topical steroids, methotrexate and biologics.

14. POTENTIAL RISKS

Risks of Hylenex®

Hylenex® has been FDA-approved as an adjuvant in subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in subcutaneous urography for improving resorption of radiopaque agents in the same dosages being used in this study. Nonetheless, the use of Hylenex® still has risks. These risks will be listed below:

1. The most frequently reported adverse reactions to Hylenex® have been local injection site reactions such as erythema and pain in response to Hylenex® injections. These reactions are self-limited and tend to resolve spontaneously over a period of a few days.
2. Hypersensitivities or allergies to hyaluronidase or any other ingredient in the formulation have been reported in less than 0.1% of patients receiving Hylenex®. Rare anaphylactic-like reactions after Hylenex® administration have occurred, but only after retrobulbar blocks or intravenous injections. Although neither of these routes of administration will be used in this study, an anaphylactic reaction is possible.
3. Hylenex® recombinant contains albumin, which is a derivative of human blood that may carry a remote risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases, CJD, or variant CJD (vCJD) have ever been identified for licensed albumin or albumin contained in other licensed products.
4. Hyaluronidase is antigenic; repeated injections of relatively large amounts of hyaluronidase preparations may result in the formation of neutralizing antibodies. Since we are only administering 4 injections of Hylenex®, each containing the dose recommended by the manufacturer, we do not anticipate antibody production to be an issue.
5. Hylenex® can enhance the spread of local infections when administered in an infected site. Psoriatic plaques do not typically get infected, however we will avoid injecting the medication into a plaque that appears to be infected or is surrounded by skin with clinical signs of infection or excoriations representing recent trauma to the skin.
6. Hylenex® is categorized as Pregnancy Class C by the FDA (Animal reproduction studies have shown

an adverse effect on the fetus and there are no adequate and well-controlled studies in humans)

For additional information on the risks of Hylenex®, please see the product insert included with this submission.

Risks of Normal Saline
Normal saline is a solution commonly used in biological research. It is a salt solution with an osmolarity that matches that of the human body (isotonic), therefore we do not expect there to be risks associated with subcutaneous administration of this medication.

Risks associated with Hylenex®/NS injections
Risks associated with injecting Hylenex®/NS include the following:

1. Pain
2. Tenderness at the injection site for a few days
3. Worsening of psoriasis at the injection site
4. Infection
5. Redness and/or swelling at the site of the injection

Risks of medication withdrawal
Discontinuation of a person's psoriasis medication prior to participating in this study may result in worsening of the patient's psoriasis. After the study, patients will be allowed to resume their standard psoriasis treatment regimens, however during the study they will not be permitted to use their regular medications or any other medications for psoriasis. Subjects' usual treatment regimens are still expected to be efficacious after participating in the study, however if the patient's psoriasis is much worse than before the study, they may need to temporarily increase the strength or dose of their regular psoriasis medications. Patients will be advised to see the dermatologist who prescribes their medications to help them in making any such medication adjustments. Similarly, if Hylenex® use improves a patient's psoriasis, discontinuation of this medication at the end of the study may cause worsening of their psoriasis. We would recommend patients resume their regular psoriasis medications at the end of the study to prevent this rebound effect from happening. We would expect the patient's psoriasis to respond to their usual medication regimen just as it did before participating in the study.

Risks of a skin biopsy
The following are potential risks of a skin biopsy:

1. Bleeding, infection, pain, and/or discomfort at the site of the biopsies.
2. The biopsied areas will be tender for a few days following the procedures.
3. The biopsy procedures will result in a small scar.
4. The skin may become temporarily inflamed (swollen) as a result of these procedures.
5. The subject may experience an allergic reaction (itchy rash on the body or fainting) to the numbing medication.
6. The biopsy site may develop an increase or decrease in the pigmentation (color) of the skin.

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 samples belongs to which patients 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 samples belong 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 at least 3 years after data analysis is complete. Patients will be reassured that PHI will not be re-used or disclosed for other purposes.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Risk management procedures related to Hylenex® were discussed above in Section 14. These procedures include:

- Avoidance of Hylenex® injections in patients with an active skin infection
- Administering Hylenex® only in the dosages recommended by the manufacturer
- Not administering Hylenex® intravenously
- Female subjects of child-bearing potential will not be enrolled in the study unless surgically sterilized, and male subjects whose partners are of child-bearing potential must agree to use barrier contraceptive methods during the course of the study.

Further risk management strategies related to Hylenex® injections include the following:
All adverse events will be seriously considered to determine whether or not they are related to the study procedures, including the administration of Hylenex®. Any participants having an adverse event related to the study procedures will be considered for withdrawal from the study. The PI will be responsible for determining whether it is in the subject's best medical interest to be removed from the study.

Risk management strategies related to drug injections:
In order to minimize the potential for an infection after drug injections, we will use a sterile need for all injections. Needles will not be re-used on the same or different people. We will also clean each plaque we are going to inject with an alcohol swab prior to doing the injection.

Risk management strategies related to skin biopsies:
To minimize potential risks, skin sites for biopsy will be cleaned. Patients will be excluded from study with known tape or anesthetic allergy. The procedure will be done under aseptic conditions, and bleeding controlled by standard dermatologic techniques of pressure of electrocautery wound care instructions will be provided to all patients. It is extremely unlikely that an adverse reaction will occur as these procedures are routinely performed at our institution with rare (less than 1/10,000) reports of adverse effects. In the event of adverse outcome, all patients are provided with wound care instructions that contain emergency contact information for the dermatology service. If the subject is injured as a result of participation in this research, treatment will be available.

Risk management strategies to avoid loss of confidentiality:
To protect patient confidentiality, all samples will be encoded and anonymous. The link between subjects and their study identifier will be stored under lock and key, only accessible to the study coordinator and the PI. Strict adherence to current HIPPA guidelines will also minimize the risk of loss of confidentiality.

Site resources:
The outpatient dermatology clinic at UCSD is fully staffed with between 5 to 7 physicians and up to 6 ancillary medical personnel (registered nurses and medical assistants) at any given time during regular business hours. In case of an emergency including a type 1 hypersensitivity reaction such as anaphylaxis, the clinic has automated machines for taking vitals; an automatic external defibrillator; and an emergency box containing needles and syringes, an epinephrine pen, a non-rebreather mask with tubing that can be connected to one of

several oxygen outlets in the clinic, and a first-aid kit. All of these emergency supplies are checked daily to ensure that they are well-stocked and functional. Furthermore, our clinic is located within 3 miles of the UCSD-affiliated Thornton Hospital. Emergency personnel will be contacted to transport subjects to this location should subjects require an escalated level of care.

The subject may call the Human Research Protections Program at (858) 246-HRPP (4777) to inquire about their rights as a research subject or to report research related problems.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Personal information will be kept confidential and will be maintained at the UCSD Dermatology Outpatient Clinic in La Jolla. All research records will be labeled with a code number so that they are de-identified. The list that matches the patient's name with their code number will be kept in a locked file at the UCSD Dermatology Clinic on the 3rd 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. Digital photographs will be identified by participants' code number, and will not contain any identifying information about the participant. Photographs will not be used in any publications or for any future uses. Any presentations or publications from this information will not identify any personal information. Identifying information will only be available to the study PI and study coordinator conducting patient visits. De-identified information will be available to all other persons involved with the research study.

17. POTENTIAL BENEFITS

Animal studies conducted in our lab on mice suggest that subcutaneous hyaluronidase may improve psoriasis plaques. If this is true, patients may experience improvement or even clearing in the psoriasis plaque that is treated. This information may be beneficial to the population of psoriasis patients in general, and may also promote further research leading to more knowledge regarding the effects of hyaluronic acid on psoriasis.

18. RISK/BENEFIT RATIO

Skin biopsies are relatively safe and well-tolerated. Hylenex® is a relatively safe drug that is generally well-tolerated with few side effects. Animal studies have suggested that administration of this drug may improve psoriasis. If so, not only will enrolled subjects benefit from improvement of their psoriasis, but also the population of patients with psoriasis could one day benefit from the findings in this study. It is also possible that a patient's psoriasis may not change with our dosing and frequency of Hylenex® administration. Alternatively, patients' psoriasis may even worsen with Hylenex®, however they may withdraw from the study if they feel that their psoriasis is worsening and they do not wish to continue in the study. Given the relatively low risk of the medication and the potential for patients to have an improvement in their psoriasis, it seems that the benefits of the study would outweigh the risks.

19. EXPENSE TO PARTICIPANT

None. Hylenex will be provided free of charge to participants.

20. COMPENSATION FOR PARTICIPATION

Participants will be compensated $50 per visit for completing Visit 1, $20 each for completing Visits 2, 3 and 4, and $50 for completing Visit 5. Payments will be issued in the form of a payment authorization through UCSD. A single payment authorization for $160 will be issued to each participant upon the participant's completion of the study. If a person withdraws from the study (voluntarily or otherwise) before completing all of the study procedures, they will be issued a payment authorization for the total sum of money owed to them based which visits they completed.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Dr. Tissa Hata will be primarily responsible for overseeing the clinical portion of this study. Dr. Hata holds a California Medical License and she is a Clinical Professor in the Department of Dermatology and Director of Clinical Trials in the Department of Dermatology.

Yun Tong, MD, is a Clinical Research Fellow who will be involved in study coordination, enrollment interviews and informed consent discussions. He will serve as the unblinded coordinator and therefore will also be responsible for administration of the study drug. He will also serve as the study pharmacist and therefore will also be responsible for the storage and proper handling of study drug. Dr. Tong is licensed to practice medicine in the State of California. He currently serves as the pharmacist for several industry-sponsored clinical trials in the Department of Dermatology.

Dr. Brian Hinds is an Assistant Clinical Professor in the Department of Dermatology. He is a board-certified Dermatologist and fellowship-trained/board-certified in Dermatopathology. Dr. Lee holds a California Medical License. He will be responsible for analyzing the skin biopsies taken in this study.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

Funding will be internal through the UCSD Department of Dermatology and through a Fellowship Grant from the National Psoriasis Foundation.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

IND# 119899

26. IMPACT ON STAFF

None.

27. CONFLICT OF INTEREST

None.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

N/A

29. OTHER APPROVALS/REGULATED MATERIALS

None.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

N/A (persons without decisional capacity or those needing a surrogate consenter will not be enrolled)