A PHASE 1, STUDY OF THE IMMUNE REPONSE TO HERPES SIMPLEX VIRUS TYPE 1 (HSV-1) AND GENERAL IMMUNE HEALTH IN SUBJECTS INFECTED WITH HSV-1

Detailed Protocol

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I. Objectives

Primary Objective: To compare the immune response to herpes simplex virus type 1 (HSV-1) and general immune health in subjects if three groups, all of whom are infected with HSV-1, as shown by having IgG against HSV-1:

- A. Six (6) or more herpes labialis outbreaks in the past 12 months
- B. One (1) to two (2) outbreaks in the past 12 months
- C. Zero (0) outbreaks in the past 12 months

Secondary Objective: To determine if and in what ways topical application of SADBE to the inner aspect of the upper arm in the group having 6 or more herpes labialis outbreaks in the past 12 months changes the immune response to HSV-1 and general immune health.

II. Background

Primary oral infection with the herpes simplex virus (HSV) typically occurs at a young age, is asymptomatic, and is not associated with significant morbidity. After primary oral infection, HSV may persist in a latent state in the trigeminal ganglion and later reactivate as the more common herpes labialis, or “cold sores.” Common triggers for reactivation are well known and include ultraviolet light, trauma, fatigue, stress, fever, inflammation, and menstruation. These lesions affect up to 45 percent of the U.S. population. They classically manifest as a well-localized cluster of small vesicles along the vermilion border of the lip or adjacent skin. The vesicles subsequently rupture, ulcerate, and crust within 24 to 48 hours. Spontaneous healing occurs over seven to 10 days.

In immunocompetent patients, herpes labialis usually is mild and self-limited. However, pain, swelling, and cosmetic concerns may prompt physician consultation. Orally administered antiviral agents, such as acyclovir (Zovirax) or valacyclovir (Valtrex), have a modest clinical benefit if initiated during the prodrome. Topical treatment with 1% penciclovir cream (Denavir) may reduce healing time and pain slightly, even if initiated after the prodrome. However, reduction in healing time with systemic or topical agents is modest.

Squaric acid dibutyl ester (SADBE) is a topical immunotherapeutic agent used in the treatment of verruca vulgaris and alopecia areata. During a recent FDA Compounding Advisory Committee Meeting, it was recommended that squaric acid dibutylester be included on the list of bulk drug substances allowed for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act. And SADBE has now been so listed under section 503A.

A study completed by Lee et al of 29 patients with recalcitrant warts demonstrated complete clearance in 69% of patients with application every 2-4 weeks. Silverberg et al showed a complete clearance in 58% of patients (n=61) when SADBE was applied 3 times weekly.

SADBE has also been used with some success in the treatment of alopecia areata. In a review of the literature, Rokhsar et al noted a 50% to 60% success rate of SADBE in use for hair re-growth in this population.

SADBE has been reported to cause eczema, lymphadenopathy, blistering, allergic contact dermatitis, skin hypopigmentation, a burning sensation after application, and systemic reactions including fever and arthralgias. A study completed by Oglio et al of eight patients treated with SADBE for warts noted only mild and well tolerated side effects of erythema, desquamation, cutaneous edema, pruritus, burning, and pain.

SADBE induces a delayed-type hypersensitivity response which in warts, is believed to induce the killing of virally infected cells by cytotoxic lymphocytes. This influx of lymphocytes into lesional

tissue may also enhance the recognition and processing of viral antigens, leading to clonal expansion of effector cells. It is hoped that SADBE will offer subjects a safe and effective therapeutic option to decrease the frequency and severity of future herpes labialis outbreaks through these mechanisms.

A placebo-controlled clinical study completed at Massachusetts General Hospital showed that squaric acid prevented recurrence of herpetic lesions. The effect of SADBE of delaying new herpes labialis outbreaks was highly significant ($p<0.01$) as compared to placebo. (Throughout this document, where the term "squaric acid" is used, it refers to squaric acid dibutyl ester (SADBE).)

III. Outcomes

Primary Outcome Measure:
Tests:

- Lymphocyte, T cell, B cell, CD4, CD8, natural killer cells counts
- Serum cytokine levels (IL2R, IL12, INFG, IL4, IL5, IL10, IL13, IL1B, IL6, IL8, TNFA, IL2, IL17)
- Peripheral blood mononuclear cells (PBMC) proliferation to
    - CANDIN
    - negative control
    - heat inactivated HSV-1
    - cell extracts of HSV-1-infected cells
    - positive control (concanavalin A)
- RNA gene expression arrays for 42 cytokine and immune related genes assayed on RNA isolated from PBMCs 2 days after stimulation in vitro in the first 4 conditions above for PBMC proliferation.

The first part of the study would test for what parameters differ between subjects with no cold sores, infrequent, or frequent cold sores, and the second part of the study would test whether and SADBE affects the same parameters in subjects with frequent cold sores.

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IV. Subject Selection

Subjects will be recruited from Prism Research database, advertisements in local newspapers and social media.

A. Inclusion criteria

1. Age ≥18 and <65
2. Positive test for IgG against herpes simplex virus type 1 (HSV-1).
3. Groups A and B only: Clinical diagnosis of herpes labialis, which may be made at the screening visit based on the patient's self-reported history of symptoms. An active herpes labialis outbreak at the time of entry into the clinical trial will neither be required nor will be an exclusion criteria.
4. Group A only: Self report having six or more episodes of herpes labialis in the past 12 months.
   Subjects will NOT be told that six-or-more episodes in the previous 12 months is the entry criterion. Subjects will be asked "How many separate episodes of cold sores have you had in the previous 12 months?" They will be included if they give an answer of six or more and excluded from Group A if they give an answer of five or fewer.
5. Group A only: At least half of the subject's episodes of the previous 12 months should be vesicular in nature and at least half preceded by prodromal symptoms.

6. Group B only: Self report having exactly 1 or 2 episodes of herpes labialis in the past 12 months.
   Subjects will NOT be told that one or two episodes in the previous 12 months is the entry criterion. Subjects will be asked "How many separate episodes of cold sores have you had in the previous 12 months?" They will be included if they give an answer of one or two and excluded from Group B if they give a different answer.
7. Group C only: Self report having zero episodes of herpes labialis in the past 12 months.
   Subjects will NOT be told that zero episodes in the previous 12 months is the entry criterion. Subjects will be asked "How many separate episodes of cold sores have you had in the previous 12 months?" They will be included if they give an answer of zero and excluded from Group C if they give an answer of one or more.

B. Exclusion criteria

1. Pregnant or lactating females.
2. Current or recurrent non-herpetic infection or any underlying condition that may predispose to infection or anyone who has been admitted to the hospital due to bacteremia, pneumonia or any other serious infection in the last 12 months.
3. Therapy with glucocorticoid or immunosuppressants at time of recruitment or within past 4 weeks prior to the screening visit (including inhaled corticosteroids for asthma), except for topical steroids in sites other than face.
4. History of malignancy (except patients with surgically cured basal cell or squamous cell skin cancers).
5. History of organ transplantation.
6. HIV-positive status determined by history at screening or known history of any other immunosuppressive disease.
7. Severe co-morbidities (diabetes mellitus requiring insulin, CHF (NYHA class II or worse) MI, CVA or TIA within 3 months of screening visit, unstable angina pectoris, oxygen-dependent severe pulmonary disease
8. Known hypersensitivity to Dimethyl sulfoxide (DMSO).
9. Any condition judged by the investigator to cause this clinical trial to be detrimental to the patient.
10. Subject is currently enrolled in another investigational device or drug trial(s), or subject has received other investigational agent(s) within 28 days of baseline visit.
11. Previous exposure to SADBE (squaric acid or squaric acid dibutyl ester).
12. Subject has an abnormal skin condition (e.g., acne, eczema, rosacea, psoriasis, albinism, or chronic visiculo-bullous disorder) that occurs in the area ordinarily affected by herpes labialis.
13. Subject has had a vaccine for either HSV-1 or HSV-2.
14. Group A only: People that have had treatment with anti viral therapy within 2 weeks before sensitization dose of SADBE.
15. Groups B and C only: People that have had treatment with anti-viral therapy any time in the past 12 months.

C. **Subject Selection**

Subjects will be recruited in three groups, all of whom are infected with HSV-1, as shown by having IgG against HSV-1:

- Group A: 12 subjects with 6 or more herpes labialis outbreaks in the past 12 months
- Group B: 12 subjects with 1 to 2 outbreaks in the past 12 months
- Group C: 12 subjects with zero outbreaks in the past 12 months

Subjects in group A will receive 2% SADBE dose on the arm after their initial blood samples are obtained. Group A subjects will have blood collected and tests repeated 2 and 8 weeks later.

Subjects in Groups B and C will be matched to the subjects in Group A so that demographic characteristics (i.e., gender distribution, age and weight) are within broadly similar ranges.

V. Subject Enrollment

Preliminary eligibility will be determined based on study staff interviews of interested subjects over the phone. Eligible subjects will then be scheduled for a screening visit. Approximately fifteen subjects will be recruited for Group A, approximately 30 subjects will be recruited for Group B and approximately 60 subjects will be recruited for Group C.

A. Methods of Enrollment

All subjects who sign an informed consent form (ICF) and are screened will be documented on the enrollment log. A note will be made in the source documentation verifying that the subject has willingly signed the ICF prior to participation in any study procedures. All enrolled subjects will receive a subject number to ensure their protected health information (PHI) and subject anonymity. Adult men and women of any race or and ethnic group may participate in this study. Women of childbearing potential must agree to use adequate birth control while in the study and for a period of one month after use of the study medication**.** No minors (i.e., <18 years of age) will be included in this study.

B. Informed Consent

The Investigator or sub-investigator will inform the potential study subject of all aspects of the study and answer all their questions. If the subject agrees to be a study subject, they will document their consent in writing by signing an ICF. If a subject needs more time to think about study participation, they will be given a copy of the consent and sign it upon return if they elect to participate. The investigator is responsible for using a consent form that has been approved by the IRB and is the most current version. If a new version of the consent form is approved by the IRB while a subject is in the treatment portion of the study, then the investigator or designee will inform the subject of the changes and, if the subject agrees to continue treatment, both the investigator and subject should sign the updated form.

VI. Study Procedures

Screening Visit (Day -28 to -1) (Groups A, B and C)

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

The following will be performed:

- Review and sign ICF
- Medical history and demographics
- Physical examination (targeted skin examination) and vital signs (oral temp, blood pressure, heart rate, respiration rate after resting supine for 5 minutes)
- Blood collection for
  - anti-HSV-1 IgG
- Urine pregnancy test (for female participants of childbearing potential)
- Review of concomitant medications
- Review of inclusion/exclusion criteria
- Adverse events collection

Group A:

Day 0

The following procedures will be performed during this visit.

- Blood collection
    - 5 ml plasma collected for cytokine level testing (MD Biosciences, Inc. Cytokine Panel, test 0051394)
    - 5 ml EDTA whole blood collected for counting lymphocytes, T cells, B cells, CD4, CD8, and natural killer cells (MD Biosciences, Inc. test TBBS)
    - 30 ml EDTA whole blood collected for PBMC isolation and PBMC in vitro proliferation and mRNA expression array testing (IGF Oncology, LLC)
    - 5 ml serum collected for anti-HSV-1 IgG (MD Biosciences, Inc.)
- Urine pregnancy test (for female participants of childbearing potential)
- Query subject if the subject is currently having a herpes labialis (cold sore) outbreak
- Targeted skin exam (at drug application site)
- Vital Signs
- Review of concomitant medications
- Adverse events collection

After this blood collection, 2% squaric acid dibutyl ester (SADBE) (Supplied by Squarex) is topically applied to the inner aspect of the upper arm of the subject and covered with Tegaderm. Subject is advised to wash it off after 3 hours.

2 weeks (Day 14 ±2)

The following procedures will be performed during this visit.

- Blood collection:
    - 5 ml plasma collected for cytokine level testing (MD Biosciences, Inc. Cytokine Panel, test 0051394)
    - 5 ml EDTA whole blood collected for counting CD4, CD8, and natural killer cells (MD Biosciences, Inc. test TBBS)
    - 30 ml EDTA whole blood collected for PBMC isolation and PBMC in vitro proliferation and mRNA expression array testing (IGF Oncology, LLC)
    - 5 ml serum collected for anti-HSV-1 IgG (MD Biosciences, Inc.)
- Query subject if the subject is currently having a herpes labialis (cold sore) outbreak
- Targeted skin exam (at drug application site)
- Vital Signs
- Urine pregnancy test (for female participants of childbearing potential)
- Review of concomitant medications
- Adverse events collection

8 weeks (Day 56 ±7)

The following procedures will be performed during this visit.

- Blood collection:
    - 5 ml plasma collected for cytokine level testing (MD Biosciences, Inc. Cytokine Panel, test 0051394)

    - 5 ml EDTA whole blood collected for counting CD4, CD8, and natural killer cells (MD Biosciences, Inc. test TBBS)
    - 30 ml EDTA whole blood collected for PBMC isolation and PBMC in vitro proliferation and mRNA expression array testing (IGF Oncology, LLC)
    - 5 ml serum collected for anti-HSV-1 IgG (MD Biosciences, Inc.)
- Query subject if the subject is currently having a herpes labialis (cold sore) outbreak
- Targeted skin exam (at drug application site)
- Vital Signs
- Urine pregnancy test (for female participants of childbearing potential)
- Review of concomitant medications
- Adverse events collection

Group B:

After Day 0 for group A is completed, the sex and age distribution of Group A will be determined.

Identify 15 or so among those who reported one or two herpes labialis outbreaks in the previous 12 months, who are positive for IgG against HSV-1, and as a group have the same demographics as group A regarding sex and age distribution. Invite these back for a further blood draw on Day 0 (Goal 12 matched subjects).

Day 0:

The following procedures will be performed during this visit.

- Urine pregnancy test (for female participants of childbearing potential)
- Blood collection:
    - 5 ml plasma collected for cytokine level testing (MD Biosciences, Inc. Cytokine Panel, test 0051394)
    - 5 ml EDTA whole blood collected for counting CD4, CD8, and natural killer cells (MD Biosciences, Inc. test TBBS)
    - 30 ml EDTA whole blood collected for PBMC isolation and PBMC in vitro proliferation and mRNA expression array testing (IGF Oncology, LLC)
    - 5 ml serum collected for anti-HSV-1 IgG (MD Biosciences, Inc.)
- Query subject if the subject is currently having a herpes labialis (cold sore) outbreak
- Review of concomitant medications
- Adverse events collection

Group C:

After Day 0 for group A is completed, the sex and age distribution of Group A will be determined.

Identify 15 or so among those who reported zero herpes labialis outbreaks in the previous 12 months, who are positive for IgG against HSV-1, and as a group have the same demographics as group A regarding sex and age distribution. Invite these back for a further blood draw on Day 0 (Goal 12 matched subjects).

Day 0:

The following procedures will be performed during this visit.

- Urine pregnancy test (for female participants of childbearing potential)

- Blood collection:
    - 5 ml plasma collected for cytokine level testing (MD Biosciences, Inc. Cytokine Panel, test 0051394)

    - 5 ml EDTA whole blood collected for counting CD4, CD8, and natural killer cells (MD Biosciences, Inc. test TBBS)
    - 30 ml EDTA whole blood collected for PBMC isolation and PBMC in vitro proliferation and mRNA expression array testing (IGF Oncology, LLC)
    - 5 ml serum collected for anti-HSV-1 IgG (MD Biosciences, Inc.)
- Query subject if the subject is currently having a herpes labialis (cold sore) outbreak
- Review of concomitant medications
- Adverse events collection

VII. Risks and discomforts

Possible side effects of Squaric Acid dibutyl ester include:

1. Localized erythema
2. Increasing lesional inflammation.
3. Pruritis
4. Contact dermatitis
5. Lymphadenopathy
6. Vitiligo or leukoderma
7. Generalized allergic reaction
8. Blistering
9. Burning sensation with application
10. Fever
11. Arthralgias

VIII. Potential Benefits

A. Potential benefits to participating individuals

Subjects may or may not benefit from participating in the study.

B. Potential benefits to society

Information gathered from this study may help other people in the future with herpes labialis.

IX. Monitoring and Quality Assurance

Written informed consent will be obtained from each subject at the initiation of the screening visit. In all cases, the consent will be witnessed by an appropriate health care professional. A copy of the signed consent form will be given to the subject to keep. All efforts will be made to insure the privacy rights of the study subject.

A. Study Drug Management

Study medication will be provided by Squarex and shipped directly to Prism Research.

All study medications will be retained in secure and restricted access storage by the Investigator's designee for the duration of the study. All study medication will be stored at room temperature and conditions (59-77ºF or 15-25ºC). Controlled access to study medications will be maintained until Squarex, Inc. has completed final drug accountability and provided instructions for drug return and destruction.

B. Data and Safety Monitoring Plan

This study is considered to be moderate risk to human subjects as the study drug is not FDA approved, but is commonly used for treatment of warts and alopecia areata.

C. Data and Drug Handling Guidelines

Data will be transcribed on case report forms and will be complete and accurate based on available source documentation. Corrections of data will be made in a manner that allows Squarex to track changes according to FDA regulations. The investigator will respond to inquiries regarding data errors, inconsistencies, and missing data in a timely fashion.

The study site will keep all study records, including source docs, CRFs, signed ICFs, regulatory papers, patient logs, drug accountability logs, etc. until Squarex determines that they can be returned or destroyed. The investigator will follow the procedures outlined in the protocol and discuss any deviations with Squarex.

D. Site Monitoring of Source Data

The principal investigator and members of the study staff not directly involved in clinical assessments or clinical study procedures will monitor the study. All data relevant to the assessments outlined in this protocol will be recorded in the case report form (CRF) and the subject's sourcebook.

The original case report form for each subject will be audited to source documents at the study site by the study monitor. The study staff monitor will review the progress of the study to ensure proper study conduct and accurate data collections through ongoing reviews of Case Report Forms, clinical records, and administrative documents. Reviews will be made at least once a month.

E. Sponsor Monitoring of Study Data

Representatives of Squarex will also monitor this study's data regularly via scheduled monitoring visits. Monitoring procedures include pre-study preparations, site initiation visit, interim monitoring visits, and study close-out preparations and visits. During sponsor's visits, the Investigator will provide Squarex's monitors with access to all protocol regulatory documents, all medical data collected on the participating subjects, screening logs, enrollment logs, drug accountability logs and the drug supply, case report forms, signed informed consent forms, and any other information that Squarex may consider to be necessary to evaluate the safety of the investigational product and patient safety. Both the monitors and study staff will review the accuracy and completeness of case report form entries, all log entries, source documents, and informed consent documents.

F. Adverse event reporting guidelines

Definitions

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

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

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

Reporting and Documenting Adverse Events

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

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

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

All SAEs will be reported to the IRB according to the IRB's requirements. They will also be reported to the study sponsor and FDA according to regulatory guidelines.

Study Discontinuation

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

- Subject is found to be intolerant to a required study procedure at any time point
- Subject experiences a serious adverse experience at any time point.
- Subject develops an inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject begins a medication that, in the judgment of the investigator, may affect assessments of clinical status to a significant degree.
- Subject becomes pregnant while participating in the study
- Subject enrolls in another investigational study
- Subject requests to withdraw from the study
- The study sponsor decides to suspend or terminate the study.

X. STATISTICAL METHODS

Statistical analyses will be performed using SAS software. Default estimation methods in version 9.4 of SAS are always used unless an alternative is specified below. In general, data summaries will include the mean, standard deviation, median, minimum and maximum values for continuous data; the median, 25th and 75th percentiles, minimum and maximum values for time-to-event endpoints (if any); and the number and percentage of patients in each category for categorical data. Pointwise 95% confidence intervals (CI) will also be estimated for the mean (continuous data), median (time-to-event endpoints) or percentage of patients (categorical data). A series of power transformations (including the log transformation) may be applied to observed values of continuous outcome measures if the distribution of raw (i.e., untransformed) data to not appear to follow a normal distribution.

There is no plan for case-control matching that would permit pairing of subjects in Group A with patient in Groups B and C. Therefore, unpaired data analyses will be performed on screening data across the three groups. Analysis of variance (ANOVA) models will be fit to numeric outcome measures such as serum cytokine levels. Any categorical outcome measures will be summarized using within-group frequency tables.

Longitudinal data from patients in Group A (screening to Weeks 3 and 8) will be analyzed using statistical techniques appropriate for paired observations such as 95% confidence intervals for the difference between screening and follow-up values.

No interim data analyses are planned.

Sample Size

The primary and secondary objectives of this study will be addressed with descriptive statistics and subjective comparisons of outcome measures between the three groups and within Group A from screening to Weeks 3 and 8. Although statistical methods will be employed to estimate means, variances and confidence intervals, no formal statistical hypotheses will be tested. Therefore the sample size of 12 subjects per group (36 subjects total) was selected purely based on clinical judgement.

Safety Analyses

Reported adverse event (AE) terms will be mapped to MedDRA preferred terminology. All reported events will appear in AE listings, however only treatment-emergent adverse events will be summarized. A treatment-emergent adverse event (TEAE) is an AE that starts or increases in severity any time after the first application of any study drug up to 30 days following the last application of any study drug. Therefore, by definition and study design, only patients in Group A can experience TEAEs.

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Appendix A. Study Schema

	Screening Day -28 to -1	Week 1; Day 0	Week 2; Day 14*	Week 8; Day 56*
			+2 Days	±7 Days
Informed Consent	X			
Inclusion/Exclusion	X			
History/Demographics	X			
Urine Pregnancy Test	X	X	X	X
Vital Signs	X	X	X	X
Squaric acid application*		X*		
Blood Collection (Processing, storing, shipping, dry ice)		X	X	X
HSV-1	X			
Concomitant medications/Adverse event collection	X	X	X	X

*Group A Only