CLINICAL STUDY PROTOCOL

A 6-Week, Randomized, Evaluator Blinded, in vivo within Subject Repeat Test to Evaluate the Irritation and Sensitization Potential of OmezaTM Collagen Matrix in Healthy Volunteers

PCR Number: OMZRIP1F

Document Dates

Final Protocol: 29 October 2019

Sponsor

Omeza

[redacted]

Conducted By:

Princeton Consumer Research Corp.
Baypoint Commerce Center
9600 Koger Blvd. Suite 120
St. Petersburg, FL 33702

PRINCIPAL INVESTIGATOR SIGNATURE SHEET

A 6-Week, Randomized, Evaluator Blinded, in vivo within Subject Repeat Test to Evaluate the Irritation and Sensitization Potential of OmezaTM Collagen Matrix in Healthy Volunteers

Protocol Number: OMZRIP1F

By my signature below, I attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). I understand that any changes in the protocol must be approved in writing by Omeza and Princeton Consumer Research before they can be implemented, except where necessary to eliminate immediate hazards to the subject.

Approval Signature

Principal Investigator: _____ Date _____
Signature

Lynne Ellis, M.D.
Princeton Consumer Research
Baypoint Commerce Center
9600 Koger Blvd, Suite 120
St. Petersburg, FL 33702

SPONSOR COMPANY SIGNATURE SHEET

A 6-Week, Randomized, Evaluator Blinded, in vivo within Subject Repeat Test to Evaluate the Irritation and Sensitization Potential of OmezaTM Collagen Matrix in Healthy Volunteers

Protocol Number: OMZRIP1F

By my signature below, I reviewed and approved this protocol (including appendices).

Reviewer Signature

Sponsor: _____ Date _____

Signature
Thomas Gardner
Omeza
[redacted]

PROTOCOL SYNOPSIS

TITLE:

A 6-Week, Randomized, Evaluator Blinded, in vivo within Subject Repeat Test to Evaluate the Irritation and Sensitization Potential of OmezaTM Collagen Matrix in Healthy Volunteers

PROTOCOL NUMBER:

OMZRIP1F

OBJECTIVES:

To assess the sensitization potential of OmezaTM Collagen Matrix compared to that of a negative control (0.9% sodium chloride, NaCl) using 9 consecutive continuous applications on the back area over a 3-week induction period, a 10-17-day rest period, and a challenge phase of approximately 48 hours exposure with evaluations over 72 (±2) hours.

The secondary objective is to assess the safety of OmezaTM Collagen Matrix by monitoring adverse events throughout the study.

POPULATION:

A sufficient number of subjects will be qualified for the study to randomize approximately 60 subjects with the intention that a minimum of 50 subjects will complete the challenge phase.

STUDY DESIGN AND DURATION:

The study design is based on a Modified Draize Human Repeat Insult Patch Test. This is a single site, evaluator-blinded study using a within-subject randomized design. Each subject will receive all investigational products at the same time. The trained skin evaluator and Investigator will be blinded to the identity of the test materials. The investigational products will be OmezaTM Collagen Matrix and a negative control (0.9% aqueous sodium chloride). The study will involve repetitive and continuous patch applications of all investigational products to the same test sites on the back approximately 48 hours on weekdays and for approximately 72-hour periods over weekends over 3 weeks, for a total of 9 induction applications. Sites on the back area will be evaluated by the blinded trained evaluator after each patch removal. Subjects will have a rest period of 10 – 17 days, followed by challenged applications of each investigational product to naïve sites for approximately 48 hours. Evaluations of the challenge sites will be made at approximately 30 minutes, 24 (±1), 48 (±2), and 72 (±2) hours post removal. The study will require 15 visits to the testing facility. Total study duration after screening will be approximately 5-6 weeks for each subject.

INCLUSION CRITERIA:

Subjects who have provided written informed consent and an authorization for disclosure of protected health information must meet the following criteria:

a. Males and Females, age 18 to 65 years;

b. Good general health, as assessed by medical history and brief dermal skin examination

of the application sites (back);

c. Fully informed of the risks of entering the study and willing to provide written consent to enter the study;

d. Willing to follow study rules, which include: no sun exposure (for example; no swimming, sunbathing, or tanning beds), avoid activities that would cause excessive sweating, abstain from use of lotions, creams, or oils on the back area;

e. Must be willing to not change current brand of personal care products such as soaps, body washes, laundry detergents, body sprays, body spritzes, etc. while participating on the study;

f. Willing and able to practice an acceptable measure of contraception (i.e. birth control medication for at least 3 months prior, condom with spermicide or birth control injections,) during the study, if female of childbearing potential. To be considered female of non-childbearing potential, subject must of have had a hysterectomy, tubal ligation, or have been post-menopausal for at least 1 year.

EXCLUSION CRITERIA:

Subjects must be excluded if any of the following conditions exist:

a. Clinically significant skin disease which may contraindicate participation, including psoriasis, eczema, atopic dermatitis, and active cancer;

b. Asthma that requires medication;

c. Insulin-dependent diabetes;

d. Known immunological disorders such as HIV positive, AIDS and systemic lupus erythematosus;

e. Treatment for any type of cancer within the last six months;

f. Routine use (as defined by using more than 3 days in a week) of any anti-inflammatory drug (e.g., aspirin, ibuprofen, corticosteroids; 81 mg aspirin is acceptable), immunosuppressive drugs, antihistamine medication (steroid nose drops and/or eye drops are acceptable) or over-the-counter pain medication that is ingested in quantities exceeding label instructions;

g. Use of topical drugs at patch site;

h. Pregnancy, lactation, or planning a pregnancy (confirmed by urine pregnancy test administered to females of childbearing potential);

i. Medical condition which, in the Investigator's judgement, makes the subject ineligible or places the subject at undue risk;

j. Participation in any patch test for irritation or sensitization within the last four weeks;

k. Dermatological aberrations in or around test sites which includes sunburn, extremely deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles or other disfiguration of the test site;

l. Confirmed allergy to adhesives, bandages, or ingredients in OmezaTM Collagen Matrix;

m. History of anaphylaxis to matrix ingredients (e.g. fish, palm oil, hemp oil, beeswax).

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

- Investigational Product :

  Approximately 0.2 ml of OmezaTM Collagen Matrix – Batch no. PVP8

- Control Product:

  Approximately 0.2 ml of 0.9% aqueous NaCl

The patch system will be patch pads made from Webril® and affixed with an occlusive hypoallergenic tape, unless the skin condition becomes sufficiently irritated to require a change to a semi-occlusive tape or even an open dressing, at the discretion of the investigator. Additional tape may be used to ensure patches stay adhered to the test sites.

EVALUATION OF IRRITATION AND SENSITIZATION:
All subjects will be evaluated using the Skin Irritation Scale:

Inflammatory Responses:

0 = No visible reaction
+ = Slight, confluent or patchy erythema
1 = Mild erythema (pink)
2 = Moderate erythema (definite redness)
3 = Strong erythema (very intense redness)

Definition of letter grades appended to a numerical grade:

E = Edema - swelling, spongy feeling when palpated
P = Papule - red, solid, pinpoint elevation
V = Vesicle - small elevation containing fluid
B = Bulla reaction - fluid-filled lesion (blister)
S = Spreading - evidence of the reaction beyond the Webril pad area
W = Weeping - result of a vesicular or bulla reaction - serous exudate
I = Induration - solid, elevated, hardened, thickened skin

Superficial Effects

g = Glazing
y = Peeling
c = Scab, dried film of serous exudate of vesicular or bulla reaction
d = Hyperpigmentation (reddish-brown discoloration of test site)
h = Hypopigmentation (loss of visible pigmentation at test site)
f = Fissuring grooves in the superficial layers of the skin

All skin responses observed with the investigational products during the induction and challenge phases will be reported. Skin responses to each patch application will be examined and graded under light supplied by a 100-watt incandescent blue bulb. The evaluator and Investigator will be blinded to treatment assignment and any previous scores. The same individual will conduct all skin evaluations of the test sites, but a qualified back-up individual will be available if needed.

Individual investigational products during the induction phase will be applied to the assigned

skin site unless the site reactions become so strong as to make it inadvisable. If excessive irritation, (for example, a numerical score of 2 or greater) is noted, that site will be discontinued from further patching and a new site adjacent to the original site will be used for the remainder of the required applications. If excessive irritation occurs at the move site, a second move site may be used. Excessive irritation at the second move site would require discontinuation of that investigational product.

The challenge patches will be applied to naïve sites on the opposite side of the back for approximately 48 hours. Challenge sites will be evaluated approximately 30 minutes, 24 (±1), 48 (±2) and 72 (±2) hours after patch removal. Evaluation of the test articles for the potential to sensitize should include the site scores as well as a narrative description of any reaction and an opinion from the investigator as to whether the reaction is indicative of a contact sensitization.

Photos will be taken of any reactions of concern and will be shared with the sponsor but will not be part of the final report.

SAFETY ASSESSMENTS:

Safety will be assessed by monitoring of adverse events reported during the study.

STATISTICAL ANALYSES:

Data from the individual patch sites is presented in tabular format. No statistical analysis of the data will be performed.

SAMPLE SIZE DETERMINATION:

Based on prior experience with contact sensitization studies in humans approximately 60 subjects will be randomized to ensure 50 subjects completing the study. There is no statistical calculation of sample size for this study.

SITES:

This study will be conducted at 1 site located in the United States.

SPONSOR:

Omeza

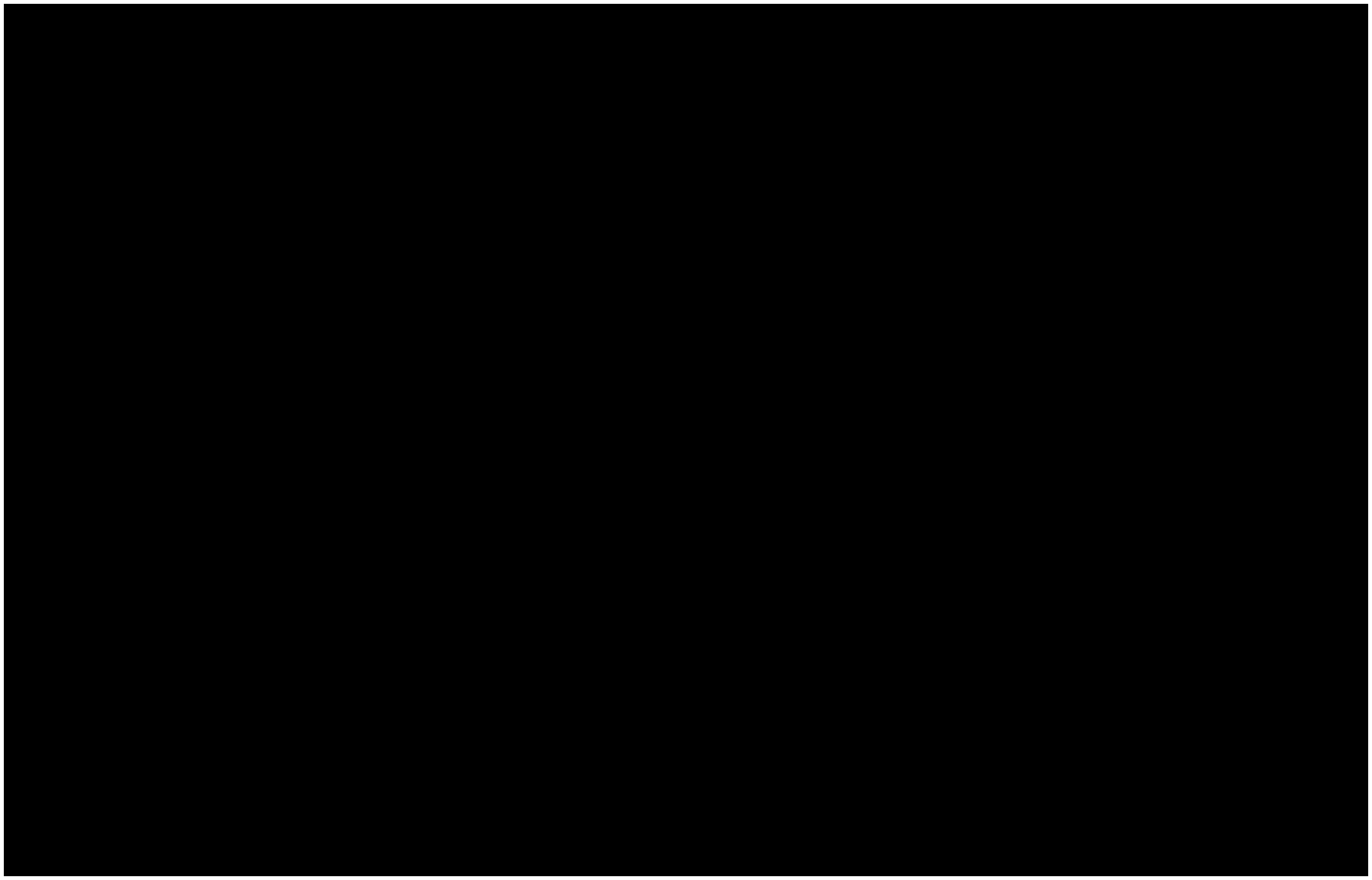
[redacted]

TABLE OF CONTENTS

TABLES

1 INTRODUCTION, RATIONALE, AND OBJECTIVES

1.1 Introduction



1.2 Rationale

This study design has been selected by the sponsor to address comments provided by the FDA in order to aid in identifying and eliminating any potential irritants or sensitization in future product development and is based on a Modified Draize Human Repeat Insult Patch Test design. The Modified Draize Procedure[1] is used as a predictive test for contact sensitization in humans. The procedure involves the application of a discontinuous series of multiple occlusive patches to human skin over a three-week induction period. Induction is followed by an approximate two-week rest period. Challenge consists of a single application to naive skin.

[1]Marzulli, F.N. and Maibach, H.I. (1977) Contact Allergy: Predictive Testing in Humans. In Advances in Modern Toxicology, Dermatotoxicology and Pharmacology. Eds. Marzulli, F.N and Maibach, H.I. 4, 353-372.

1.3 Objective

To assess the sensitization potential of OmezaTM Collagen Matrix compared to that of a negative control (0.9% sodium chloride, NaCl) using 9 consecutive continuous applications on the back area over a 3-week induction period, a 10-17-day rest period, and a challenge phase of approximately 48 hours exposure followed by evaluations over 72 (±2) hours.

The secondary objective is to assess the safety of OmezaTM Collagen Matrix by monitoring adverse events throughout the study.

2 INVESTIGATIONAL PLAN

2.1 Overall Study Design

This is an evaluator-blinded study using a within-subject randomized design. Each subject will receive all investigational products at the same time. The trained skin evaluator and Investigator will be blinded to the identity of the test materials. The investigational products will be OmezaTM Collagen Matrix liquid and a negative control (0.9% aqueous sodium chloride). The study will involve repetitive and continuous patch applications of all investigational products approximately 48 hours on weekdays and for approximately 72-hour periods over weekends over 3 weeks, for a total of 9 induction applications. Sites on the back area will be evaluated by the blinded trained evaluator after each patch removal. Subjects will have a rest period of 10 – 17 days, followed by challenged applications of each investigational product to naïve sites for approximately 48 hours. Evaluations of the challenge sites will be made approximately 30 minutes, 24 ($\pm$1), 48 ($\pm$2) and 72 ($\pm$2) hours post removal. Total study duration after screening will be approximately 5-6 weeks for each subject.

2.2 Randomization and Blinding Procedure

To eliminate skin evaluator bias, the assignment of the test product codes to the subject's test sites will be randomized among the subjects so that each test product code (see section 5.1) occupies individual skin sites within the panel of test subjects with equal frequency. The randomization scheme will be provided by the site.

3 SELECTION AND WITHDRAWAL OF SUBJECTS

The study will enroll approximately 60 subjects to complete approximately 50 subjects.

Subjects will be healthy volunteers drawn from the general population following the inclusion and exclusion outlined below. Subjects withdrawn from the study before completion will not be replaced.

3.1 Inclusion Criteria

1. Males and Females, age 18 to 65 years;
2. Good general health, as assessed by medical history and brief dermal skin examination of the application site (back);
3. Fully informed of the risks of entering the study and willing to provide written consent to enter the study;
4. Willing to follow study rules, which include: no sun exposure (for example; no swimming, sunbathing, or tanning beds), avoid activities that would cause excessive sweating, abstain from use of lotions, creams, or oils on the back area;
5. Must be willing to not change current brand of personal care products such as soaps, body washes, laundry detergents, body sprays, body spritzes, etc. while participating on the study;
6. Willing and able to practice an acceptable measure of contraception (i.e. birth control

medication for at least 3 months prior, condom with spermicide or birth control injections,) during the study, if female of childbearing potential. To be considered female of non-childbearing potential, subject must of have had a hysterectomy, tubal ligation, or have been post-menopausal for at least 1 year.

3.2 Exclusion Criteria

1. Clinically significant skin disease which may contraindicate participation, including psoriasis, eczema, atopic dermatitis, and active cancer;
2. Asthma that requires medication;
3. Insulin-dependent diabetes;
4. Known immunological disorders such as HIV positive, AIDS and systemic lupus erythematosus;
5. Treatment for any type of cancer within the last six months;
6. Routine use (as defined by using more than 3 days in a week) of any anti-inflammatory drug (e.g., aspirin, ibuprofen, corticosteroids; 81 mg aspirin is acceptable), immunosuppressive drugs, antihistamine medication (steroid nose drops and/or eye drops are acceptable) or over-the-counter pain medication that is ingested in quantities exceeding label instructions;
7. Use of topical drugs at patch site;
8. Pregnancy, lactation, or planning a pregnancy (confirmed by a urine pregnancy test administered to females of childbearing potential);
9. Medical condition which, in the Investigator's judgement, makes the subject ineligible or places the subject at undue risk;
10. Participation in any patch test for irritation or sensitization within the last four weeks;
11. Dermatological aberrations in or around test sites which includes sunburn, extremely deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or any other disfiguration of the test site;
12. Confirmed allergy to adhesives, bandages, or ingredients in OmezaTM Collagen Matrix;
13. History of anaphylaxis to matrix ingredients (e.g. fish, palm oil, hemp oil, beeswax).

3.3 Subject Withdrawal Criteria

Subjects may be removed from the study for reasons including the following:

1. Intolerance to a required study procedure at any time point.
2. Noncompliance with protocol restrictions and requirements (e.g., failure to remain at the test facility for the duration of the evaluation period) at any time point.
3. The occurrence of a serious adverse experience at any time point.
4. Subject withdrawal of consent at any time point.
5. Investigator considers it advisable or in the subject's best interest.

4 STUDY TREATMENTS

4.1 Identity of Test Products

The following test products will be used on this study. Test product Code A will be provided by the Sponsor. Test product Code B (negative control) will be provided by Princeton Consumer Research.

Princeton Code	Sponsor Code	Patch Type	Concentration	Method and Quantity of Application to Patch
A	[redacted]	Occlusive	Neat	Quantity sufficient to saturate the Webril patch pad ~0.2 mL squeezed out from the 2.5 mL squeeze vial
B	0.9% aqueous sodium chloride	Occlusive	Neat	0.2 ml via Pipette onto Webril patch pad

Both PCR Codes A and B will be placed onto the patch pads at the quantities listed above. These patch pads will be adhered to the application sites located on the back and marked with a skin marker. Additional adhesive tape may be used to ensure patch contact with the skin.

4.2 Test Product Storage and Accountability

Upon receipt, the test products will be inventoried and stored at room temperature (about 15-30°C).

Physiological saline (0.9% Aqueous Sodium Chloride) will serve as a negative control.

Both products will be placed on patches no more than 30 minutes before application.

All application and removal of test materials will be recorded for each subject.

All unused test products (excluding the negative control) will be returned to or destroyed following Sponsor instruction after completion of the study.

4.3 Methods of Assigning Subjects to Treatment Groups

At the testing facility, a unique 3-digit screening number will be assigned to each subject after written Informed Consent is obtained. Subject screening numbers will be assigned sequentially at the testing facility. Princeton Consumer Research will develop the randomization scheme. At Visit 2, a 2-digit randomization number will be assigned by Princeton Consumer Research to each subject in a sequential manner as they become eligible for randomization. To eliminate any position bias, the assignment of the test product codes to the test sites will be randomized among the subjects so that each test product code occupies individual skin sites within panel of test subjects with equal frequency. The randomization number will correspond to a predetermined assignment design. Randomization numbers must not be re-used once assigned, even if the subject is not administered the test products. There will be no replacement of subjects who are withdrawn prior to completion of the study.

4.4 Administration of Test Products

For all subjects, the test products will be placed, on Webril patch pads (2 x 2 cm) adhered to occlusive tape (approximately 4 x 4 cm) and will be applied as per study design and randomization scheme onto designated sites located on the back of each subject unless the skin condition becomes sufficiently irritated to require a change to a semi-occlusive tape or even an open dressing, at the discretion of the investigator.

The patches will be reinforced with additional non-irritating tape as deemed necessary by the patch applicator. Subjects will be instructed to keep all patches dry during showering so that the test sites are protected from accidental water exposure for the duration of the study.

Two test sites located on one side of the paraspinal region of the back will be utilized for application. The assignment of the test product codes to individual skin sites will be randomized so that each test product code occupies individual skin sites within the panel of test subjects, with approximately equal frequency, in order to eliminate any position bias. The sites of patch/test product application will be marked by a skin marker so that the location of the patch pad/application site is clearly indicated for evaluations.

The test products will be applied and removed by study personnel. The study will involve repetitive and continuous patch applications of all investigational products, Codes A and B, approximately 48 hours on weekdays and for approximately 72-hour periods over weekends over 3 weeks, for a total of 9 induction applications. All applications for individual test products will be made to the same site unless reactions become so strong as to make this inadvisable. If excessive irritation, (for example, a numerical score of 2 or greater) is noted, that site will be discontinued from further patching and a new site adjacent to the original site will be used for the remainder of the required applications (move site 1). If excessive irritation occurs at the move site, a second move site may be used. Excessive irritation at the second move site would require discontinuation of that patch. Residue on the skin from any test patch will be removed by study staff prior to skin evaluation (if observed) by gently wiping the patch application site with a moistened gauze pad.

Photos will be taken of any reactions of concern and will be shared with the sponsor but will not be part of the final report.

4.5 Treatment Accountability and Compliance

Since all test products are to be administered in-clinic, 100% compliance is anticipated. Subjects are required to attend all visits.

4.6 Blinding and Unblinding Method

Study products will be administered in a single-blinded fashion, i.e., the treatment assignment will not be known to the skin evaluator.

5 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Table 6-1 represents the schedule of procedures and assessments at each of the scheduled visits. Details of each visit are provided in Sections 6.1 through 6.4.

Table 5-1 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Period	Baseline	Induction Phase										Rest Phase	Challenge Phase				
Day	**1**	**3**	**5**	**8**	**10**	**12**	**15**	**17**	**19**	**22**		**23-35**	**36**	**38**	**39**	**40**	**41**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			**11**	**12**	**13**	**14**	**15**
Informed Consent/HIPAA	X																
Demographics	X																
Back check for excessive hair, moles, tattoos, dermatological conditions	X																
Inclusion/Exclusion Criteria review	X																
Urine Pregnancy Test	X																
Patch Application	X	X	X	X	X	X	X	X	X				X				
AE/Con Med Review		X	X	X	X	X	X	X	X	X				X	X	X	X
Patch Removal		X	X	X	X	X	X	X	X	X				X			
15 Minute Minimal Wait		X	X	X	X	X	X	X	X	X				X			
Irritation Evaluation		X	X	X	X	X	X	X	X	X				X[1]	X	X	X

[1]Evaluations to occur approximately 30 minutes after patch removal and 24 (±1), 48 (± 2) and 72 (± 2) hours post challenge patch removal.

5.1 Qualifying Visit – First Application (Visit 1)

- Written Informed Consent
- Medical history
- Current medications (past 30 days)
- Brief dermal skin examination of the back
- Pregnancy Status confirmed by urine pregnancy test if applicable
- Eligibility review of Inclusion/Exclusion criteria
- Mark test sites/patch application

5.2 Induction Phase (Visits 2 – 9)

- Adverse event, concomitant medication review
- Patch removal
- Note: Approximate 15-minute wait time from removal to evaluation
- Skin Evaluation
- Mark test sites/patch application
- Photograph(s) if applicable

5.3 Induction Phase (Visit 10)

- Adverse event, concomitant medication review
- Patch removal
- Note: Approximate 15-minute wait time from removal to evaluation
- Skin evaluation
- Photograph(s) of sites if applicable

5.4 Rest Phase

- Subjects will have a rest period of 10-17 days

5.5 Challenge Phase (Visit 11)

- Adverse event, concomitant medication review
- Eligibility review
- Patch application

5.6 Challenge Phase (Visit 12)

- Adverse event, concomitant medication review
- Patch removal
- Note: Approximate 30-minute wait time from removal to evaluation
- Skin evaluation
- Photograph(s) of sites if applicable

5.7 Challenge Phase (Visit 13-15)

- Adverse event, concomitant medication review
- Skin evaluation
- Photograph(s) of sites if applicable

5.8 Protocol Deviations

This study is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Principal Investigator must determine whether the subject should continue in the study.

6 DETAILED DESCRIPTION OF ASSESSMENTS

6.1 Informed Consent

Written Informed Consent will be obtained from each subject before any study procedures are performed. All potentially eligible subjects for the study will be given a copy of the informed consent form to read. The protocol will be discussed in detail with each potentially eligible subject. The study subject must sign the Informed Consent form if he/she decides to participate in the study. No study procedures will be performed, or study products applied to any subject who has not signed the Informed Consent form.

6.2 Eligibility Review

Princeton Consumer Research (PCR) staff under the oversight of the Principal Investigator reviews eligibility criteria at Visit 1. Each subject's eligibility will also be reviewed prior to randomization.

Screen Failure: A screen failure is defined as a subject who was consented but who was not randomized. Screen failures may not re-screen for the study.

6.3 Brief Examination of the Back

A brief dermal examination of the subject's back will be conducted by a trained associate and will consist of an evaluation of the dermal acceptability of the skin for patching after consent and preferably prior to moving to the interview. Exclusive conditions would include excessive hair, moles, tattoos, dermatological conditions, etc.

6.4 Pregnancy Tests

Urine pregnancy tests will be conducted at the testing facility on women of childbearing potential to confirm pregnancy status.

6.5 Patch Application and Removal

PCR staff will apply the patches according to the predetermined randomization schedule. Each test product will remain on the skin for approximately 48 hours on the week days and 72-hour periods over the weekend for the Induction phase of the study for a total of 9 induction applications. Application 1 will occur at Visit 1. At Visit 2 and every day of patch removal, there should be an approximate 15-minute waiting period to let any erythema from patch removal subside prior to the skin evaluation. All remaining patch applications will occur following the same randomization scheme as on Visit 1.

For the Challenge Phase of the study, patches will be applied once and be worn for approximately 48 hours. There will be an approximate 30-minute waiting period from patch removal prior to the first evaluation. Subsequent evaluations will take place 24 (±1), 48 (±2) and 72 (±2) hours post challenge patch removal.

All patch preparation, application, removal, and evaluation times will be recorded on source documents.

6.6 Skin Assessments and Procedures

All subjects will be evaluated using the Skin Irritation Scale:

Inflammatory Responses:

0 = No visible reaction
+ = Slight, confluent or patchy erythema
1 = Mild erythema (pink)
2 = Moderate erythema (definite redness)
3 = Strong erythema (very intense redness)

Definition of letter grades appended to a numerical grade:

E = Edema - swelling, spongy feeling when palpated
P = Papule - red, solid, pinpoint elevation
V = Vesicle - small elevation containing fluid
B = Bulla reaction - fluid-filled lesion (blister)
S = Spreading - evidence of the reaction beyond the Webril pad area
W = Weeping - result of a vesicular or bulla reaction - serous exudate
I = Induration - solid, elevated, hardened, thickened skin

Superficial Effects

g = Glazing
y = Peeling
c = Scab, dried film of serous exudate of vesicular or bulla reaction
d = Hyperpigmentation (reddish-brown discoloration of test site)
h = Hypopigmentation (loss of visible pigmentation at test site)
f = Fissuring grooves in the superficial layers of the skin

All skin responses observed during the induction and challenge phases will be reported. Skin responses to each patch application will be examined and graded under light supplied by a 100-watt incandescent blue bulb. The evaluator and Investigator will be blinded to treatment assignment and any previous scores. The same individual will conduct all skin evaluations of the test sites, but a qualified back-up individual will be available if needed.

Individual investigational products during the induction phase will be applied to the assigned skin site unless the site reactions become so strong as to make it inadvisable. If excessive irritation, (for example, a numerical score of 2 or greater or any grade(even 0) if appended with a letter grade of E, P, V or B) is noted, that site will be discontinued from further patching and a new site adjacent to the original site will be used for the remainder of the required applications. If excessive irritation occurs at the move site, a second move site may be used. Excessive irritation at the second move site would require discontinuation of that patch material.

The challenge patches will be applied to naïve sites on the opposite side of the back for approximately 48 hours. Challenge sites will be evaluated approximately 30 minutes, 24 (±1), 48 (±2) and 72 (±2) hours after patch removal. Evaluation of the test articles for the potential to sensitize should include a review of the induction site scores as well as the challenge site scores and a narrative description of any reaction observed at challenge will be recorded. The opinion from the investigator as to whether the reaction is indicative of contact sensitization will be documented in the study records and reported in the final report.

Photos will be taken of any reactions of concern and will be shared with the sponsor but will not be part of the final report.

6.7 Randomization and/or Treatment Assignment

To eliminate any position bias, the assignment of the test product code to the test sites will be randomized among the subjects so that each test product code occupies individual skin sites within the panel of test subjects with equal frequency.

6.8 Assessment of Sensitization

Subjects who had all 9 induction patches and completed the challenge phase (at least the 24-hour post challenge skin assessment) will be considered evaluable subjects for the study. The Principal Investigator in consultation with the irritation grader will review all induction and challenge scores recorded for all evaluable subjects. The induction of dermal sensitization is determined by enhancement of the skin reaction observed at Challenge greater than that observed during Induction. Low grade reactions observed during Induction, but which are not observed at Challenge are considered to be irritant in nature.

An erythematous and edematous reaction to the test article (and none to the negative control) during Challenge is indicative of dermal sensitization. Usually the skin irritation score response is greater than scores observed during induction phase and often spreads outside of the patch site. If sensitization is suspected, a full description of the skin responses observed will be documented and reported in the final report.

7 STATISTICAL METHODS

7.1 Randomization

A computer-generated randomization scheme will be used to obtain a balanced allocation of each test code to each treatment site.

7.2 Statistical Analysis

Data from the individual patch sites will be presented tabular format. No statistical analysis of the data will be performed.

8 ADVERSE EVENT/EXPERIENCE MONITORING

8.1 Definition

An **Adverse Event/Experience** is any unexpected or undesirable experience occurring to a subject during a study, which may or may not be related to the test device. All adverse events will be recorded and reported according to the Standard Operating Procedures of Princeton Consumer Research.

Events should be considered AEs if they:

- result in discontinuation from the study,
- require treatment or any other therapeutic intervention,
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality),
- are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

An Adverse Event is not:

- A surgical procedure
- A situation where an untoward event did not occur, (e.g. a social hospitalization)
- Baseline conditions that have not worsened in severity or frequency

Skin irritation is expected and graded at Visits 3 – 23 and will not be reported as an adverse event unless it leads to withdrawal from the study.

A **Serious Adverse Event/Experience** is any adverse experience occurring that results in any of the following outcomes:

* death;
* a life-threatening adverse experience;
* inpatient hospitalization or prolongation of existing hospitalization;
* a persistent or significant disability/incapacity;
* a congenital anomaly/birth defect

Important medical event/experiences that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An **Unexpected Adverse Event/Experience** is any adverse event/experience not listed in the current labeling for the test device.

8.2 Follow-up

Investigators should follow AEs until the event has resolved, the condition has stabilized, is well characterized, or referred for appropriate medical management, whichever comes first. Events and follow-up information occurring after the last visit should be recorded in the source documentation. Investigators are not obliged to solicit adverse events after a subject's final visit, however, if an investigator learns of an SAE that is believed to be possibly related to the study products, an SAE report form should be submitted.

8.3 Notification

The Sponsor will be notified of all adverse event/experiences. Any Serious or Unexpected Adverse Event/Experience which occurs during the study must be reported promptly by the Investigator to the Sponsor and the reviewing IRB, as applicable, within 24 hours of the information being reported to Princeton Consumer Research.

8.4 Severity

Adverse events are first graded according to seriousness and then severity.

The Investigator will evaluate the severity of each AE. Adverse events will be graded as

Mild: Awareness of symptoms but easily tolerated

Moderate: Discomfort enough to interfere with but not prevent daily activity

Severe: Unable to perform usual activity

8.5 Relationship

The Investigator will judge the likelihood that the AE was related to the study products according to the following criteria

Not related: There is no temporal or causal relationship to the study products.

Related: There is a possible temporal or causal relationship to the study products.

8.6 Action Taken and Outcome

The Action Taken with study products for every AE will be reported as either: Dose Not Changed, Dose Interrupted, or Dose Withdrawn. Other actions taken can include none, medication required, or other intervention documented on the AE. The Outcome of each AE will be entered as either: Recovered/Resolved, Recovered/Resolved with Sequelae, Not Recovered/Not Resolved, Fatal, or Unknown.

9 INVESTIGATOR OBLIGATIONS

9.1 Ethical and Regulatory Considerations

This study will be conducted in accordance with GCP, Title 21 of the Code of Federal Regulations (CFR), Part 50, Subparts A and B; Part 56, and the Standard Operating Procedures (SOPs) of Princeton Consumer Research and the study protocol and protocol amendment(s) if any.

9.2 Institutional Review Board

The Principal Investigator will ensure that an appropriately constituted Institutional Review Board (IRB), in compliance with the requirements of 21 CFR 56, reviews and approves the clinical study before the study is initiated. IRB approval must refer to the study by exact protocol title, number, and amendment number, (if applicable), identify the documents reviewed, and state the date of review.

The Principal Investigator will ensure that Omeza approves any changes to the Informed Consent (IC) form prior to submission to the IRB.

Should changes to the IC form become necessary during the study, the Principal Investigator will ensure that the protocol amendment and IC is approved by the IRB prior to implementation. The Principal Investigator will ensure that protocol administrative changes have been reviewed by the IRB.

9.3 Informed Consent

A properly executed and written IC, in compliance with 21 CFR Part 50 and HIPAA authorization, will be obtained from each subject prior to enrollment and the initiation of

screening evaluations required by this protocol. Consent forms will be written in language fully comprehensible to the prospective subject. Consent for photographs of test sites will be obtained.

9.4 Subject Confidentiality

All communications, reports, and subject scores will be identified only by a coded number and/or initials to maintain subject confidentiality. All records will be kept confidential to the extent permitted by law. If a waiver or authorization separate from the statement in the IC is required for permitting access to a subject's medical records (e.g. HIPAA), the investigator will obtain such authorization prior to enrolling a subject in the study. The Principal Investigator should keep a separate log of subjects, codes, names, and addresses. Documents which identify the subject by name (for example, the IC form) should be kept in strict confidence.

Princeton Consumer Research and its business associates agree to keep all subject information confidential. Only coded, blinded data will be released. Data resulting from analyses will be entered into a database that is not accessible to the public. Subject data will be identified only by the subject screen number, randomization number and initials, not by any other annotation or identifying information. Princeton Consumer Research and its business associates will take every possible step to reduce the risk of releasing information to the public that would enable subjects to be personally identified.

10 STUDY MONITORING

Monitoring visits may be made during the study. The Principal Investigator will make a reasonable amount of time available to the sponsor monitor on reasonable notice to assist with monitoring.

11 CHANGES TO THE PROTOCOL AND STUDY TERMINATION

11.1 Protocol Amendment and Administrative Change

All changes to the protocol must be documented by amendments, or administrative changes where applicable, and the amended protocol must be signed by the Principal Investigator.

11.2 Termination of the Study

The Principal Investigator reserves the right to terminate the study at any time. In terminating the study, the Principal Investigator will ensure that adequate consideration is given to the protection of each subject's interest.

12 SOURCE DOCUMENTS AND RECORD RETENTION

12.1 Source Documents

The Investigator will complete and maintain relevant source documents for each subject participating in the study.

Record Retention

Record Retention - The Principal Investigator will maintain adequate records so that the conduct of the study can be documented appropriately. Copies of protocols, originals, all study product accountability records, subject IC forms, and any other documents relevant to

the conduct of the study will be kept on file for a minimum of five years from completion of the study.

12.2 Data Collection/Tabulation

Skin irritation evaluation scores will be entered into an excel spreadsheet and sent to the statistician to provide tables and frequency of scores.

13 REPORT

13.1 Final Report

The final report will summarize the method and adverse events relative to the test product and the subjects. A determination of the test product's potential for sensitization, including any necessary discussion, will be included in the report. A demographics table with subject numbers, age, race and gender will be provided as an Appendix in the report.