Protocol CCSTOH001689

A 28-DAY, SINGLE-CENTER, RANDOMIZED, COMPARATOR-CONTROLLED, PROOF-OF-PRINCIPLE STUDY TO ASSESS WOUND HEALING EFFICACIES OF DIFFERENT ADHESIVE BANDAGES

Statistical Analysis Plan (SAP)

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CONTENTS

1 INTRODUCTION

The primary goal in wound care is to protect the wound from further damage and to facilitate healing by providing the optimal environment that limits infection, inflammation and scarring. Appropriate wound dressings play an important role in providing this necessary protection and may promote restoration of skin barrier function compared to untreated wounds.

Wound healing is a complex process wherein the skin surface and the underlying tissue must go through an intricate process of tissue repair. The dermis of an uncovered wound is relatively more fibroplastic, fibrotic, and scarred compared to occluded wounds, and is likely to be more inflamed and necrotic in early stages of repair. Exudate, the moisture secretion from the wound site, facilitates the healing process, by providing a variety of bioactive mediators such as enzymes, growth factors and hormones. Wound exudate may also aid in limiting inflammation by providing various immune cells with an ideal medium to destroy invading pathogens such as bacteria, foreign bodies and necrotic tissues. However, exudate in an uncovered wound can lead to scab formation, with trapped inflammatory cells, wound debris, and a layer of desiccated dermal tissue. Covering a wound with an occlusive dressing reduces scab formation and may radically alter the pattern of epidermal wound healing.

Another factor that plays an important role in wound healing is the moisture in the wound environment. As early as 1962, Winter et al., provided the first evidence that keeping wounds moist helps them heal faster compared to dry wounds.

As occlusion affects both the epidermis by enhancing epithelial cell migration and the dermis by enhancing dermal collagen synthesis, maintaining a moist environment may promote the restoration of epidermal barrier function and overall wound healing while making dressing changes relatively easier. Moreover, it has been suggested that the scar left by an occlusively dressed wound is more cosmetically acceptable than that left by an uncovered wound.

1.1 Study Objectives

The objective of this study is to assess the wound healing efficacy (time to complete healing) of different adhesive bandages.

1.2 Study Design

This is a single center, randomized, comparator-controlled, proof-of-principle clinical trial. The target population is 25- to 55-year-old males and females of Fitzpatrick skin types II-III who have uniform skin color on both volar forearms. A sufficient number of subjects will be screened and enrolled to ensure completion of at least 30 subjects.

At Screening (Visit 1; 3 to 7 days prior to Baseline), subjects will be provided with an auxiliary cleanser to use on their forearms and for all body cleansing in place of their regular body cleanser for the duration of the study.

At Baseline (Visit 2, Day 0), a Sciton Er:YAG 2940 laser will be used to induce eight partial-thickness (i.e. minor) wounds on the subjects' forearms (four per arm). The wounds created by this method heal by the migration of epidermal cells from the dermal appendages located in the wound's base (dermal islands) and/or wound borders, and mimic minor wounds similar to real life scraped skin, typically healing in at less than 14 days if left untreated, based on the Site's previous experience.

Each wound site will be [redacted] and assessed at pre-specified intervals by clinical grading of wound healing parameters (until Day 16), [redacted] and Trans-Epidermal Water Loss (TEWL) (until Day 14). In addition, subjects will assess the wound sites via questionnaire from Day 0 to Day 4, [redacted]

Between Baseline and Day 16, each wound site will be subjected to one of eight randomly-assigned treatments (see section 6). Treatments include an adhesive bandage that is considered the [redacted] a marketed adhesive bandage benchmark control, a non-marketed adhesive bandage benchmark control, four non-marketed adhesive bandages, and no treatment (uncovered, negative control). [redacted]

All wound sites will be uncovered from Day 16 to Day 28, at which point subjects will return for a scar assessment of each wound site, [redacted]

2 INTERIM ANALYSES

No interim analysis is planned for this trial.

3 ANALYSIS SETS

3.1 Primary Analyses Set

The analyses will be based on the Intent-to-Treat (ITT) principle, i.e., all subjects who received laser-induced wounds and started the study treatments will be included in the analysis.

3.2 Per-Protocol Set

Not applicable.

3.3 Safety Analysis Set

The safety analysis will be based on all subjects who have IP applied at least once.

4 EFFICACY ASSESSMENTS AND ENDPOINTS

4.1 Efficacy Assessments

4.1.1 Clinical Grading of Wound Healing Parameters

- Erythema

  0 = none/absent

  1 = mild

  2 = moderate

  3 = marked

  4 = severe

- Edema

  0 = none/absent

  1 = mild

  2 = moderate

  3 = marked

  4 = severe

- Epithelial Confluence

  0 = none, no epithelial coverage

  1 = slight (up to 30%)

2 = moderate (31-60%)

3 = extensive (61-90%)

4 = almost complete or complete (91-100%), covered with a full layer of new epithelial growth

- Crusting/Scabbing

  0 = none

  1 = slight (up to 30%)

  2 = moderate (31%-60%)

  3 = extensive (61%- 90%)

  4 = almost complete or complete (91%-100%)

- Smoothness

  0 = rough, uneven wound

  1 = mild smoothness

  2 = moderate smoothness

  3 = extensive smoothness

  4 = complete smooth, even wound

- General Wound Appearance

  0 = Poor

  1 = Fair

  2 = Good

  3 = Very good

  4 = Excellent

Half-point grading will be allowed.

4.1.2 **Scarring Assessment**

- Color

  1 = Perfect

  2 = Slight mismatch with surrounding skin

  3 = Obvious mismatch with surrounding skin

  4 = Gross mismatch with surrounding skin

- Finish (matte versus shiny)

  1 = Matte

  2 = Shiny

- Contour

  1 = Flush with surrounding skin

  2 = Slightly proud/indented

  3 = Hypertrophic

  4 = Keloid

- Distortion

  1 = None

  2 = Mild

  3 = Moderate

  4 = Severe

- Texture

  1 = Normal

  2 = Just palpable

  3 = Firm

  4 = Hard

[redacted]

[redacted]

[redacted]

[redacted]

4.1.5 **TEWL Measurements**

TEWL measurements will be performed for each wound site on Day 0 through Day 14*. The duplicate values of TEWL at each assessment time point will be averaged as the final response value.

[redacted]

[redacted]

4.1.7 **Self-Assessment Questionnaire**

Self-Assessment Questionnaire will be conducted for each wound site on Day 0 through Day 4.

[redacted]

4.2 Efficacy Endpoints

4.2.1 Primary Efficacy Endpoint

The primary endpoint of the study will be "Time to Complete Healing". "Time to Complete Healing" is defined as the time (in days) elapsed from the time of wound creation to 12 PM of the day on which the composite healing score (calculated from the clinical grading of wound healing parameters, as defined below) first meets the complete healing criterion of being at least a score of 8. If a composite healing score does not meet the complete healing criterion by Day 16, the time to complete healing will be censored at the last day on which the composite healing score is available.

The composite healing score will be calculated from the clinical grading of wound healing parameters as follows:

Composite Healing Score = [general wound appearance score + smoothness score + epithelial confluence score] – [erythema score + edema score + crusting/scabbing score]

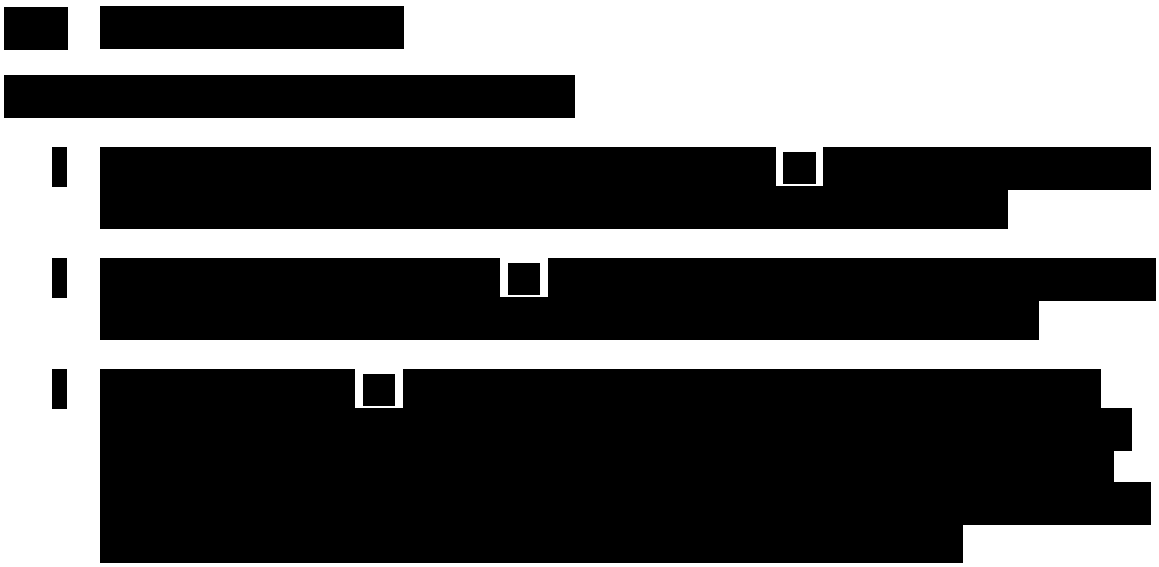
The composite healing score on a 25-point scale (-12 thru +12) is indicative of the extent of wound healing and will be calculated for each wound site at each evaluation day.

4.2.2 Secondary Efficacy Endpoint

The secondary endpoints for this study are the change from baseline* to each applicable time point (see Table 2) for the following parameters:

- Change from baseline* to each applicable time point (see Table 2) for the following parameters:
    - TEWL measurements
    - Clinical Grading of Wound Healing – Erythema
    - Clinical Grading of Wound Healing – Edema
    - Subject self-assessment questions 1, 3, and 5.
    - Composite Scar Score – calculated as the sum of the individual parameters on the Manchester Scar Scale (Color, Finish, Contour, Distortion and Texture). Composite Scare Scores range from 5 to 18, with 5 representing clinically best scars and 18 representing clinically worst scars.
- Subject self-assessment questions 2 and 4 at each applicable time point.

*Baseline is considered the Day 0 Pre-Wound time point for all endpoints except the subject self-assessment questions. For the subject self-assessment questions, baseline is considered the Day 0 Post-Wound time point.



4.3 Safety Assessments and Endpoints

Safety assessments consist of Adverse Events.

- Number and percentage of subjects with treatment-emergent adverse event
- Number and percentage of subjects with treatment-related adverse event
- Number and percentage of subjects with serious adverse event

4.4 Other Endpoints

Not applicable.

4.5 Covariates

For the analyses of Change from Baseline in TEWL measurements, erythema, edema, the composite scar score, corresponding baseline value will be included in the models as covariate.

5 HANDLING OF MISSING VALUES

No imputation of missing data will be performed.

6 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

The Biostatistics Group at the Sponsor will be responsible for the statistical analysis of the primary and secondary endpoints. Summary statistics will be provided at each time point for the primary and secondary efficacy and safety assessments. For continuous variables, descriptive summaries will include number of subjects, mean, standard deviation, median, minimum and maximum values. Distributions of categorical variables

will be summarized by presenting the number and percent of subjects in each response category.

6.1 Statistical Hypotheses

The between-product comparison will be based on the median complete healing times. The following null hypothesis will be tested using the bootstrap re-sampling method

$$H_0\colon\ M_1 = M_2$$

against the two-sided alternative

$$H_A\colon M_1 \neq M_2$$

where M_1 and M_2 are the median complete healing times of the two product groups to be compared, respectively.

6.2 Statistical Decision Rules

This is a proof-of-principle study, all hypothesis tests will be conducted at 0.05 level without adjustment of multiple comparisons, it serves as exploratory purpose.

6.3 Statistical Methods

Summary statistics will be provided at each time point for the primary and secondary efficacy.

Time to complete healing will be analyzed using a survival analysis method. The survival function (cumulative percentage of wounds healed at each time point) will be estimated by the Kaplan-Meier method for each treatment separately. The median time to complete healing will be derived from the estimated survival functions and be compared using the bootstrap re-sampling method.

The pairwise comparison of median complete healing times is performed by the following steps:

1) Independently take B=200 bootstrap samples with subject as the sampling unit. Each bootstrap sample has the same size as the original sample size and is obtained by sampling subjects with replacement with the original time to complete healing data, say $\{(t_1^b, \cdots, t_8^b),\ b = 1, \cdots, B\}$.

2) Within each bootstrap sample, estimate the median survival time using KM method for each treatment separately, say $\{\hat{m}_i^b : i = 1,2, \ldots,8,\ b = 1, \cdots, B\}$.

3) Calculate the pairwise difference in median times to complete healing $\hat{\tau}^b = \hat{m}_{i1}^b - \hat{m}_{i2}^b,\ b = 1, \cdots, B$.

4) Estimate the variance of the median time difference by

$$v(\hat{\tau}) = \frac{1}{B-1}\sum_{b=1}^{B}(\hat{\tau}^b - \bar{\hat{\tau}})^2$$

where $\bar{\hat{\tau}} = \sum_{b=1}^{B}\hat{\tau}^b/B$

The null hypothesis of $H_0: M_{i1} = M_{i2}$ can be tested by the following test statistics

$$z = \frac{\widehat{M}_{i1} - \widehat{M}_{i2}}{\sqrt{v(\hat{\tau})}}$$

Under the null hypothesis, this test statistics asymptotically follows the standard normal distribution. Hence the 2-sided p-value and the 95% confidence interval can be calculated by

$$p = 2 \times \{1 - \Phi(|z|)\}$$

and

$$(\widehat{M}_{i1} - \widehat{M}_{i2} - z_{0.975} * \sqrt{v(\hat{\tau})}\ ,\ \widehat{M}_{i1} - \widehat{M}_{i2} + z_{0.975} * \sqrt{v(\hat{\tau})})$$

where $\Phi(s)$ is the cumulative probability function of the standard normal.

TEWL measurements, erythema, edema, the composite scar score, and self-assessment questions 1, 3, and 5 will be analyzed within-treatment and between-treatment. The within-treatment comparison will be performed at each post-baseline time point by comparing the post-baseline scores with the baseline score within each treatment using the paired t-test. The between-treatment comparison will be performed by comparing the change from baseline between treatments using a mixed effect analysis of covariance (ANCOVA) model. The ANCOVA model will include the treatment as the factor and the baseline value as the covariate. The model will include subject as a random effect to incorporate the within-subject correlation. The adjusted mean of each product from the ANCOVA model will be compared between the IPs and the negative control, between the IPs and the IP – [redacted] between the IPs (except the IP – [redacted] and the IP – Benchmark Control 1, and between the IPs (except the IP – [redacted] and the IP – Benchmark Control 1) and the IP – Benchmark Control 2.

The mixed effect analysis of covariance model can be performed by the following SAS codes

PROC MIXED DATA = <dataset>;

CLASS subjid treatment;

MODEL chg = treatment baseline/solution ddfm = contain;

RANDOM subjid ;

LSMEANS treatment/diff cl;

ESTIMATE "IP – [redacted] vs. Negative Control" treatment 1 0 0 0 0 0 0 -1 /cl;

ESTIMATE "Product #1 vs. Negative Control" treatment 0 0 0 1 0 0 0 -1/cl;

…

RUN;

Note:

[redacted]

Self-assessment questions 2 and 4 will be summarized by frequency distribution for each treatment at each collection time point.

6.4 DEMOGRAPHIC AND BASELINE CHARACRISTICS

Summary statistics (number of subjects, mean, standard deviation, median, minimum and maximum) will be provided for numerical variable age.

Frequency summary (number and percentage of subjects) will be provided for categorical variables including sex, race, ethnicity and Fitzpatrick skin type classification.

6.5 SAFETY ANALYSIS

All subjects who have IP applied at least once will be included in the safety analysis. All AEs reported during the AE reporting period will be listed by subject number.

The number and percentage of subjects experiencing treatment-emergent adverse events will be presented by body system and preferred term. Treatment-emergent adverse events are those with a start date and time on or after the date and time of first use of investigational product, or the AEs started before the first use of investigational product and worsened after it. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used as the adverse event classification system.

Number and percentage of subjects with serious adverse events will be summarized by MedDRA system organ class and preferred term.

Number and percentage of subjects with treatment-related adverse events will be summarized by MedDRA system organ class and preferred term. Treatment-related AEs are events evaluated by the investigator as possible, probable or very likely related to

investigational product. AEs with unknown relationship to treatment will be considered as treatment-related.

APPENDICES

APPENDIX 1: SUMMARY TABLES AND FIGURES

The following tables and figures are planned for subsections in Sections 14 of the Clinical Study Report. The numbering and titles of tables and figures in this document serves as guidance; the exact numbers and titles may be modified as appropriate.

Section / Table No	Title	Population / Analysis Sets
14.1 Subject Disposition and Baseline Information		
Table 14.1.1	Disposition of Subjects	All randomized subjects
Table 14.1.2	Demography and Baseline Characteristics	All randomized subjects
14.2 Efficacy		
Table 14.2.1	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Complete Healing	Intent-to-Treat Subjects
Table 14.2.2	Analysis of Change from Baseline in Trans Epidermal Water Loss (TEWL) Measurement	Intent-to-Treat Subjects
Table 14.2.3	Analysis of Change from Baseline in Erythema Measurement	Intent-to-Treat Subjects
Table 14.2.4	Analysis of Chance from Baseline in Edema Measurement	Intent-to-Treat Subjects
Table 14.2.5	Analysis of Change from Baseline in the Composite Scar Score Measurement	Intent-to-Treat Subjects
Table 14.2.6	Analysis of Change from Baseline in Painful Score with Arm Resting by Side (Self-Assessment Questions 1)	Intent-to-Treat Subjects
Table 14.2.7	Analysis of Change from Baseline in Painful Score with Arm in Normal Motion (Self-Assessment Questions 3)	Intent-to-Treat Subjects
Table 14.2.8	Analysis of Change from Baseline in Itchy Score (Self-Assessment Questions 5)	Intent-to-Treat Subjects
Table 14.2.9	Summary of Pain with Arm Resting by Side (Self-Assessment Questions 2)	Intent-to-Treat Subjects
Table 14.2.10	Summary of Pain with Arm in Normal Motion (Self-Assessment Questions 4)	Intent-to-Treat Subjects
14.3 Safety		
Section / Table No	**Title**	**Population / Analysis Sets**
Table 14.3.1	Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.2	Subjects with Treatment-related Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set

Table 14.3.3	Subjects with Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set

FIGURES:

14.1 Survival Function

Figure 14.1.1	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Complete Healing	Intent-to-Treat Subjects

APPENDIX 2: DATA LISTINGS

The following listings are planned for subsections in Appendix of Clinical Study Report. The numbering and titles of data listings in this document serve as guidance; the exact numbers and titles may be modified as appropriate.

Listing No.	Title	Population
16.1.7	Randomization Scheme and Codes	All randomized Subjects
16.2.1.1	Subject Disposition Listing	All randomized Subjects
16.2.1.2	Discontinued Subjects	All randomized Subjects
16.2.2	Subjects with Protocol Deviations	All randomized Subjects
16.2.3	Subjects Excluded from the Primary Analysis	All randomized Subjects
16.2.4.1	Demographic and Baseline Characteristics	All randomized Subjects
16.2.6.1	Clinical Grading of Wound Healing Parameters Measurements	All randomized Subjects
16.2.6.2	Trans Epidermal Water Loss (TEWL) Measurements	All randomized Subjects
16.2.6.3	Manchester Scarring Assessment Measurements	All randomized Subjects
16.2.6.4	Self-Assessment Questions	All randomized Subjects
16.2.7.1	Subjects with Adverse Events	All randomized Subjects
16.2.7.2	Subjects with Serious Adverse Events	All randomized Subjects
16.2.7.3	Subjects Withdrawn from Investigational Product due to Adverse Events	All randomized Subjects