EVALUATION OF J-PLASMA DERMAL RESURFACING

STATISTICAL ANALYSIS PLAN

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1 PURPOSE

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under the Bovie Medical Corporation study, "A Prospective, Multicenter, Single Arm Clinical Study Evaluating the Use of J-Plasma® for Dermal Resurfacing."

2 SCOPE

This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the plan has been developed with respect to Study protocol version 1, dated 31 July 2017. Any further changes to the protocol or eCRF may necessitate updates to the SAP.

3 APPLICABLE DOCUMENTS

Document Number	Document Title
VP-1558	A Prospective, Multicenter, Single Arm Clinical Study Evaluating the Use of J-Plasma® for Dermal Resurfacing Study Protocol
STATSOP-002	Statistics Standard Operating Procedure – Statistical Analysis Plan
SRS vX	Study Requirements Specification (includes Case Report Form requirements)

4 SOFTWARE

All tables, listings and figures will be primarily produced using SAS Version 9.3 (SAS Institute, Cary, NC) or a later version of SAS.

5 ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
CRF	Case Report Form
DRM	Data Review Meeting
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FSS	Fitzpatrick Skin Scale
FWS	Fitzpatrick Wrinkle and Elastosis Scale
Modified GAIS	Modified Global Aesthetic Improvement Scale
ITT	Intent to Treat
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale

6 STUDY OBJECTIVES

The primary objectives of this study are to demonstrate the safety and efficacy of the J-Plasma system for use in dermal skin resurfacing.

7 STUDY ENDPOINTS

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this clinical investigation is a comparison of the proportion of subjects (i.e. percentage of treatment responders) with a ≥1-score improvement on the Fitzpatrick Wrinkle and Elastosis Scale (FWS) at the 3 month visit, as compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers. The study design assumes a 75% success rate of subjects with treated wrinkles with a ≥ 1-score change on the FWS.

7.2 Primary Safety Variable

The primary safety variable is the evaluation of adverse events through 3 months post-treatment.

7.3 Secondary Efficacy Endpoint

Subjects with a ≥ 1-score improvement on the FWS and at least a self-reported "improved" rating on the modified GAIS at the 3-month visit will be considered to have an aesthetic pleasing outcome. The modified GAIS is a measure of aesthetic improvement relative to the baseline, pre-treatment condition.

7.4 Secondary Safety Variable

The secondary safety variable is the evaluation of the pain and discomfort after treatment as reported by the subject on a visual analog scale (VAS).

7.5 Additional Endpoints

Other endpoints to be evaluated include:

1. FWS ≥ 1-score improvement and ≥ 75% agreement with at least an "improved" rating by the subject on the modified GAIS. The modified GAIS is a measure of aesthetic improvement relative to the baseline, pre-treatment condition.
2. Magnitude of improvement measured by the mean change in FWS from baseline to 3 months visit.
3. Subject satisfaction with procedure recorded at the 3-month visit.
4. Achievement of re-epithelialization by facial zone and across all facial zones at the 10 day, 1-month and 3-month follow-up visits as reported by the investigator.
5. Mean duration until study subject feels comfortable going in public after treatment as reported by the study subject.
6. Daily 10-point Visual Analog Scale (VAS) pain assessment following treatment through the 10 day follow-up visit by diary day with a change from the VAS pain score at baseline.

8 STUDY DESIGN

8.1 Overview

This is a multi-center, single arm, evaluator-blind prospective study of 55 study subjects who are seeking a procedure to reduce the appearance of wrinkles and rhytides at up to 5 investigational centers in the United States.

Study subjects that meet study eligibility criteria and have provided informed consent will be enrolled in the study. During the procedure, the investigators will use J-Plasma® on applicable facial zones to reduce wrinkles and rhytides.

Study subjects will be followed immediately following the procedure, at 10 days, 1, 3, and 6 months post-procedure for study assessments.

Study enrollment is expected to occur over 3-6 months. Imaging and study assessments will continue through 6 months post-procedure. Total study duration is expected to be approximately 9-12 months. It is expected that the 510(k) application for the device will be submitted based on 3 month post-procedure results. However, this clinical trial will continue until every enrolled subject has reached 6 months following their procedure. At that time, the trial will be considered complete, the final results will be determined, and a final report will be prepared.

Table 1. Study Required Procedures

	Baseline/ Pre-Procedure Screening[1]	**Procedure**	**10 Days** 10+4/-1 days	**1 mo** 30±7 days	**3 mo** 90±10 days	**6 mo** 180±14 days
Informed Consent	√					
Assess Inclusion/Exclusion Criteria	√					
Urine Pregnancy Test[2]	√	√				
Medical History	√					
General Physical Exam	√					
Review Medications	√		√	√	√	√
Photographic Images[3]	√		√	√	√	√
Fitzpatrick Skin Scale (FSS)	√					
Fitzpatrick Wrinkle and Elastosis Scale (FWS)[4]	√		√	√	√	√
Visual Analog Scale (10-point VAS)[5]		√	√	√	√	√
Study Procedure		√				
Subject Diary (10-point VAS)[6]		√	√			
Adverse Event Assessment		√	√	√	√	√
Re-epithelization and Down Time[7]			√	√	√	
Modified Global Aesthetic Improvement Scale (GAIS)[8]			√	√	√	√

[1] Pre-procedure Screening assessments to take place within 21 days prior to undergoing the procedure.
[2] Up to two urine pregnancy tests must be obtained prior to study procedure for females with child-bearing potential (one at pre-procedure screening and one on the day of the procedure prior to the procedure if screening and procedure are not performed on the same day).
[3] Digital photographs of the subject's face will be taken and labeled according to Photography Instructions.
[4] To be completed by Investigator and Independent Photographic Reviewers (IPRs).
[5] To be completed by the study subject on a day of the procedure (prior to the procedure and immediately following the procedure) and at all follow-up visits.
[6] To be completed by the study subject daily starting from the day of procedure (after procedure, at home) until the 10 day follow-up visit.
[7] To be completed by Investigator and/or Independent Photographic Reviewer (as applicable) to capture achievement of epidermal recovery status at follow-up visits; and date when study subject felt comfortable, willing and able to go in public following study procedure (assessed at the 10 day follow-up visit).
[8] To be completed by Investigator and study subject at all study follow-up visits.

8.2 Randomization

This is a single arm study, thus randomization is not used.

8.3 Blinding

The primary efficacy endpoint is the comparison of the proportion of subjects (i.e. percentage of treatment responders) with a ≥ 1-score improvement on the FWS at the 3-month visit, as compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers.

8.4 Sample Size Considerations

The objective of this study is to demonstrate that study participants positively respond to the J-Plasma® therapy, thus the primary endpoint will be assessed via the percentage of study participants that demonstrated an improvement in the FWS from baseline to the 3-month visit. An improvement is clinically important when there is ≥ 1-score change. The planned sample size to provide sufficient power for a statistical comparison of the proportion of treatment responders (P) versus a reasonable cutoff (P_0) was based on a power calculation utilizing the (one proportion) binomial exact test based on the following assumptions.

- H_0: $P \leq P_0$ versus H_a: $P > P_0$
- Type I error rate: $\alpha = 0.05$ (one-sided)
- Population proportion under the null hypothesis: $P_0 = 0.75$
- Population proportion under the alternative hypothesis: $P = 0.90$
- Total N: 50 study participants

Based on the above assumptions, the study power is estimated to be approximately 88%. To account for possible missing data (up to 10% attrition), a total of 55 subjects will be enrolled. Other tests (i.e., a test of the mean improvement of FWS) would be expected to provide more power.

One study investigating the effects of radiofrequency energy on the improvement of appearance of wrinkles and rhytides (De Novo, Newa™) utilized a FWS cutoff as 75%, supporting this value in the present sample size computation.[1]

9 DATA STRUCTURE AND HANDLING

9.1 Data Handling and Transfer

Data management will be undertaken by NAMSA Data Management. NAMSA Biostatistics will either be provided access to download SAS datasets or NAMSA Data Management will provide them upon request.

Programming of analysis datasets, tables, figures and listings will be conducted during the data management phase of the study. Tables, figures, and listings may be reviewed prior to final data lock for data review. Any data values requiring investigation or correction will be identified, and protocol deviations will be reviewed. The final run of outputs will take place after the data is deemed final.

9.2 Missing Data

If applicable, a list of subjects who were withdrawn/lost to follow-up from the study and associated reasons will be provided.

Subjects with missing 3-month FWS data will be imputed as having no change from baseline. No other imputations for missing data will be employed. Furthermore, no estimation of missing data for self-reported pain within the 10 day Subject Diary will be imputed.

9.3 Visit Windows

All data attributed to a time point per the CRF will be included in the analysis of that time point, regardless of if it is out of window. Unscheduled visit data will be included in summaries that are not specific to a time point.

9.4 Pooling Data Across Sites

Pooling of outcome data from different clinical study sites will be performed by evaluating the homogeneity of the efficacy endpoint across sites, using the Chi-square test statistic. If homogeneity is demonstrated across sites, then the endpoint results will be combined across all clinical study sites.

If significant heterogeneity is observed amongst sites (significant difference in Chi-square test), then the primary endpoint will be additionally presented with a random site adjusted estimate and confidence interval.

Sites with less than five (5) patients enrolled will be combined into a pseudo-site for purposes of analysis. To protect against having an overly large pseudo-site, when one pseudo-site exceeds ten subjects, a second pseudo-site will be formed. This process will continue as needed each time a pseudo-site exceeds ten subjects.

10 STATISTICAL ANALYSES

10.1 General Considerations

Data will be presented using summary statistics. For example, categorical data may be presented as proportions and counts; continuous data may be presented with the mean, median, minimum, maximum, and/or standard deviation.

10.2 Analysis Populations

10.2.1 Intent-to-Treat

All subjects who enrolled in the study and underwent study procedure will be included in the intent-to-treat (ITT) population. All safety analyses will be evaluated in the ITT population.

10.2.2 Full Analysis Set (FAS)

All subjects enrolled in the study who have a FWS value at baseline will be included in the FAS. Subjects with missing FWS data at the 3-month visit will be imputed as no change and included in the FAS population. Efficacy outcomes will be evaluated in the FAS.

10.2.3 Per Protocol Set (PPS)

The PPS is the subset of subjects in the FAS without major protocol deviations. Major protocol deviations will be decided and finalized at a data review meeting (DRM) that will be conducted prior to database lock. The efficacy analyses will be repeated on the PP population if there is at least a 10% difference in the number of subjects in the PPS and intent-to-treat (ITT) populations.

10.3 Subject Disposition

Subject disposition will be presented by:

- Status of subjects follow-up
- Summary of early withdrawal and reason for early withdrawal

10.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics of enrolled subjects will be summarized. The factors will include (but not limited to):

- Age
- Gender
- Ethnicity
- Weight
- Height

10.5 Primary Efficacy Endpoint Analyses

The primary efficacy endpoint is the comparison of the proportion of subjects (i.e. percentage of treatment responders) with a ≥ 1-score improvement on the FWS at the 3-month visit, as compared to baseline as determined by at least 2 out of 3 blinded Independent Photographic Reviewers. The study design assumes a 75% success rate of subjects with treated wrinkles with a ≥ 1-score change on the FWS. The percentage

of subjects with a ≥ 1-score improvement will be summarized as counts and percentages. This percentage will be compared to the cutoff of 75% using a binomial exact test (one-sided). Descriptive upper 95% confidence limit will be provided for the difference between treatment and cutoff rate and the associated p-value will also be provided.

10.6 Secondary Efficacy Endpoint Analyses

Subjects with a ≥ 1-score improvement on the FWS and at least a self-reported "improved" rating on the modified GAIS at the 3-month visit will be considered to have an aesthetic pleasing outcome. An "improvement" on the modified GAIS by the treating investigator at the 3-month visit will be classified as "improved," "much improved," or "very much improved." All other ratings on the modified GAIS will be classified as "no improvement." Cross-tabulation of improvement status of modified GAIS versus 1-score FWS response will then be summarized as counts and percentages.

10.7 Primary Safety Analysis

The primary safety variable is the evaluation of adverse events up to the 3-month visit after treatment. Adverse events reported at each scheduled study visit.. Adverse event rates (total and categorized by duration) will be summarized as counts and percentages. Stratification on type, onset after treatment, duration (0-7 days, 8-14 days, 15-28 days, and more than 28 days), severity, and relationship to study device and/or procedure will also be provided. Adverse events self-reported in the Subject Diary will be summarized in patient listings.

10.8 Secondary Safety Analysis

The secondary safety variable is the evaluation of the pain and discomfort after treatment as reported by the subject on a 10-point visual analog scale (VAS). Results of the VAS on a scale of 0 to 10 will be summarized descriptively utilizing mean, standard deviation, minimum, maximum, median, and the 95% confidence interval of the mean and mean change from baseline.

10.9 Additional Analyses

Other endpoints to be evaluated include:

10.9.1 FWS ≥ 1-score improvement and ≥ 75% agreement with at least an "improved" rating by the subject on the modified GAIS. An "improvement" on the modified GAIS by the subject at the 3-month visit will be classified as "improved," "much improved," or "very much improved." All other ratings on the modified GAIS will be classified as "no improvement." Cross-tabulation of improvement status of modified GAIS versus 1-score FWS response will then be summarized as counts and percentages.

10.9.1.1 Magnitude of improvement measured by the mean change in FWS from baseline to 3-month visit. Descriptive summary statistics (number of observations, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean) will be used for summarizing the change in FWS from baseline to the 3-month visit. The FWS from baseline to the 3-month visit will also be stratified on both the treating-investigator and subject modified GAIS.

10.9.1.2 Subject satisfaction with procedure recorded at the 3-month visit. Results of VAS on a scale of 0 to 10 will be summarized descriptively utilizing mean, standard deviation, minimum, maximum, median, and the 95% confidence interval of the mean. Cross tabulation of subject satisfaction/improvement versus 1-score FWS response will be summarized as counts and percentages.

10.9.1.3 Achievement of re-epithelialization by facial zone (and across facial zones) at the 10-day, 1-month and 3-month follow-up visits as reported by the study investigator and/or Independent

Photographic Reviewers (as applicable). Descriptive summary statistics (number of observations, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean) will be used for summarizing the achievement of re-epithelialization by facial zone and across facial zones at all follow-up visits through the 3-month visit.

10.9.1.4 Mean duration (days) until subject feels comfortable going in public after treatment as reported the study subject. Descriptive summary statistics (number of observations, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean) will be used for summarizing the mean duration for study subject to feel comfortable after treatment.

10.9.1.5 Daily 10-point Visual Analog Scale (VAS) pain assessments following treatment through the 10 day follow-up visit by diary day with a change from the VAS pain score at baseline.
Descriptive summary statistics by diary day (number of observations, mean, standard deviation, minimum, maximum, median, 95% confidence interval of the mean) and the change from the VAS pain score at baseline will be provided.

10.10 Exploratory Analyses

Additional, ad hoc exploratory analyses may also be conducted. These may include informational inference tests and will be clearly described as exploratory analyses.

10.11 Subgroup Analyses

Subgroup analyses will include stratifying the primary endpoint (percent treatment responders on FWS), on age, gender, race/ethnicity, and Fitzpatrick Skin Scale (FSS). Additionally, the degree of improvement on FWS (e.g. 2, 3 or 4-score improvement) will be reported.

10.12 Other Data

10.12.1 Protocol deviations

All protocol deviations will be summarized.

11 REFERENCES

1. EndyMed Medical Ltd., De Novo Classification Request for Newa™: Submission Number: DEN150005. January 16, 2015.

12 VERSION HISTORY

Version	Date	Changes
1.0	28Mar2018	Initial Release