

STATISTICAL ANALYSIS PLAN

Version 1.0

March 9, 2018

**A Randomized Within-subject, Double-blind, Placebo-controlled Study  
of Dexamethasone Irrigation of the Parotid Glands in Primary  
Sjögren's Syndrome Subjects**

PROTOCOL NUMBER 11-D-0094

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**DOCUMENT VERSION CONTROL**

<b>Version Number</b>	<b>Date</b>	<b>Comments/Changes</b>
0.1	23SEP2013	Initial Draft
1.0	09MAR2018	<p>Added Section 10 Changes to the Statistical Analysis after Database Lock. This summarizes changes to the SAP.</p> <p>Although the study was completed at the time of SAP finalization, the grammatical tense was left as future tense to be in keeping with the common text of a planning document. Only the tense in Section 10 and Section 11 were changed, because these sections focus specifically on changes subsequent to database lock and unblinding.</p>

**APPROVALS**

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## **LIST OF ABBREVIATIONS**

ADC	apparent diffusion coefficient
AE	adverse event
CBC	complete blood count
CFTR	cystic fibrosis transmembrane conductance regulator
CROMS	Clinical Research Operations and Management Support
CRP	C-reactive protein
DSMC	Data and Safety Monitoring Committee
eCRF	electronic case report form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
GEE	generalized estimating equations
Ig	immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
mCi	millicurie
MRI	magnetic resonance imaging
MSG	minor salivary gland
MPTB	Molecular Physiology and Therapeutics Branch
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drug
PEP	Primary Efficacy Population
SAE	serious adverse event
SD	standard deviation
SEP	Secondary Efficacy Population
SOP	standard operating procedure
SS	Sjögren's syndrome

## **1. THE STATISTICAL ANALYSIS PLAN**

The Statistical Analysis Plan is not a stand-alone document but expands in further detail the statistical analysis and considerations already outlined the protocol. The protocol background information, objectives, design, and procedures are fully described in the study protocol.

## 2. PROTOCOL SUMMARY

A brief summary of protocol objectives and study design are described below. For further details refer to the protocol.

### 2.1 Study Objectives

This study is designed to evaluate the efficacy of low-dose topical corticosteroid (dexamethasone) irrigation of the parotid gland in reducing salivary dysfunction in subjects with Sjögren's syndrome (SS), and also to evaluate the effects of treatment on inflammation and other possible mechanistic processes.

The primary objective of this study is to determine whether irrigation of the parotid gland with low-dose topical dexamethasone improves parotid salivary gland flow in SS subjects.

The secondary objectives are:

- To perform mechanistic studies to determine the mechanisms of action of low-dose topical corticosteroid irrigation of the parotid gland.
- To assess biomarkers of inflammation and salivary gland dysfunction in SS subjects treated with low-dose topical corticosteroid irrigation of the parotid glands.
- To assess localized safety of dexamethasone irrigation of the parotid gland, as compared with placebo.

### 2.2 Study Design

This will be a single-site, randomized-within-subject, double-blind, placebo-controlled, phase 2 pilot study in which all subjects receive both active drug (dexamethasone) and placebo (normal saline), thereby acting as their own controls. A total of 20 adult females will be enrolled to have 16 subjects randomized and treated. The study will recruit subjects with a focus score of  $\geq 1$  on minor salivary gland biopsy in the previous 7 years and measurable stimulated bilateral parotid salivary flow ( $\geq 0.01$  mL/min per gland), who were diagnosed with Sjögren's syndrome (SS) in protocol 84-D-0056 or 99-D-0070.

The study design is doubly-repeated measures; within a subject, measures are repeated in both time and treatment (i.e., one side of mouth receives dexamethasone while the other receives placebo.) After baseline assessment of salivary flow and other measurements of salivary function, subjects will be randomly assigned, in a double-blind fashion, to dexamethasone irrigation of one parotid gland and normal saline irrigation of the other parotid gland (i.e. active drug randomized to either left side or right side, with placebo administered in the opposite gland). They will undergo a total of 2 treatment sessions, 4 weeks apart (Days 0 and 28). Post-treatment assessments of salivary flow, dry mouth symptoms, and adverse events (AEs) will be performed at specified intervals.

### **2.3 Sample Size Determination**

The primary endpoint is the change in salivary flow (Day 56 – Day 0) following either saline (placebo) or dexamethasone irrigation. Because each subject will simultaneously receive both irrigation treatments over several time points, the experimental design is a doubly-repeated-measures design with one repeated effect for treatment and another repeated effect for study day, and random effects for subject. The expected treatment effect of the dexamethasone irrigation over the saline (placebo) irrigation is an improvement in salivary flow of at least 40%.

The power and sample size computations assume the final primary analysis will be doubly-repeated-measures analysis, including an unstructured variance and random effects for subject to account for the non-independence between glands within a subject. The “unstructured variance” allows the variances (standard deviations [SDs]) of the change in salivary flow for each treatment to differ from each other. The power analysis was performed in SAS using the methodology described by Kononoff and Hanford.<sup>1</sup>

The SDs of the change in salivary flow for the placebo and dexamethasone irrigations were estimated from data published by Izumi et al.<sup>2</sup> The standard deviation of the change in salivary flow was assumed to be 0.0168 for the saline-irrigated parotid gland, and 0.0906 for the dexamethasone-irrigated parotid gland. The within-subject correlation between two glands was assumed to be 0.15. The mean measures and SDs of change in total salivary flow during 2 minutes were converted to flow from a single parotid gland

during 1 minute by multiplying by 0.1625 (0.65 for the proportion of total flow from the parotid glands x 0.5 for a single parotid gland x 0.5 for 1 minute). This conversion assumes a very high correlation between total salivary flow and parotid salivary flow.

A total of 16 patients would be required to have 80% power to detect a one-sided 40% increase in dexamethasone-irrigated parotid glands compared with the saline-irrigated parotid glands with respect to change in salivary flow from Day 0 to Day 56.

Approximately 20 subjects will be screened to ensure that 16 subjects will be randomized and treated with dexamethasone irrigation. Subjects who discontinue from the study before the Stage I screening parotid irrigation will be replaced. Subjects who do not receive the first irrigation treatment and at least 1 post-treatment salivary flow assessment will also be replaced.

### 3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study. These are general guidelines and reporting conventions may deviate from these for publication and presentation purposes:

- Categorical variables will be summarized using counts (n) and percents (%) and will be presented in the form n (%).
- Mean, bias, standard deviation, and precision will be reported at 1 more significant digit than the precision of the data.
- Order statistics including median, min and max will be reported to the same level of precision as the original observations. If any values are calculated to have more significant digits then the value should be rounded so that it is the same level of precision as the original data.
- The median will be reported as the average of the two middle numbers if the dataset contains even numbers.
- P-values will be reported to 3 decimal places if greater than 0.001. If less than 0.001 then report '<0.001'. P-values and significant levels will be displayed as 0.05 rather than .05.
- No preliminary rounding should be performed; rounding should only occur after analysis. For rounding, digit to right of last significant digit will be considered: if < 5 rounded down, if >=5 rounded up.

## **4. ANALYSIS POPULATIONS**

### **4.1 Safety Population**

The safety population will include all subjects who receive any parotid saline irrigation used to determine parotid filling volume during Stage I screening.

### **4.2 Primary Efficacy Population**

The primary efficacy population (PEP) will include subjects who receive all parotid irrigations on study Days 0 and 28, have the same treatment applied to the same parotid (regardless of random assignment) at both visits, and have values for the primary endpoint (i.e., change in salivary flow from Day 0 to Day 56). The PEP will be used in the primary analysis.

### **4.3 Secondary Efficacy Population**

The Secondary Efficacy Population (SEP) will include all enrolled subjects who receive at least one on-treatment set of parotid irrigations and have at least one salivary flow assessment after study Day 0. The SEP will be used in some secondary analyses.

## **5. STUDY SUBJECTS**

### **5.1 Disposition of Subjects**

Subject disposition will be summarized for all enrolled subjects. The number of subjects enrolled, randomized, and the number subjects in each of the analysis populations (safety, PEP, and SEP) will be presented by frequency and percentage. The number of subjects who completed the study through Day 56, the number who discontinued before Day 56 and the reason for discontinuation, and the number of subjects who completed the safety follow-up assessment will be summarized.

### **5.2 Protocol Deviations**

The number of subjects with at least one protocol deviation, the number of protocol deviations, type of protocol deviations, and impact of protocol deviation will be summarized for the safety population. Each protocol deviations will be listed.

## 6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following characteristics will be summarized for all subjects included in the safety population, as well as presented in data listings:

- Sex
- Age (years)
- Race (Hispanic, Non-Hispanic, Unknown)
- Weight (kg)
- Height (cm)
- Waist (cm)

The following baseline variables pertaining to the parotid gland will be summarized by their assigned treatment for the safety population and presented in data listings:

- MRI results (Normal, Abnormal-Not Clinically Significant, Abnormal- Clinically Significant)
- Technetium results (Normal, Abnormal) including isotope uptake (Yes, No) and release with stimulation (Yes, No).
- Salivary flow rate (mL/min)
- Fill volume (mL)
- Focus score

Baseline is defined as the last evaluation prior to the first irrigation treatment.

Age will be calculated as the number of years from the date of birth to the date of first dose.

Continuous variables (age, weight, height, waist, salivary flow rate, fill volume, and focus score) will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). Categorical variables (sex, race, MRI results, and technetium results) will be summarized using counts and percentages for each category. The differences between parotid glands by the assigned treatment will be estimated along with their 90% confidence intervals.

To assess overall health of the study subjects prior to study treatment, any significant medical history will be included in the subject listings.

## 7. STATISTICAL ANALYSES

### 7.1 Overview of Primary Statistical Analyses

#### 7.1.1 Handling of Dropouts or Missing Data

Subjects who discontinue from the study before the Stage I screening parotid irrigation will be replaced. Subjects who do not receive the first irrigation treatment and at least 1 post-treatment salivary flow assessment will also be replaced.

### 7.2 Efficacy Variables

The primary efficacy endpoint is the change in salivary flow from Day 0 to Day 56.

Secondary efficacy endpoints include:

- Changes in salivary flow from Day 0 to study Days 14, 28, 42, and 56.
- Change in focus score on parotid biopsy from Stage II screening to Day 56
- Changes in assessments on the Patient Dry Mouth Questionnaire from Day 0 to study Days 14, 28, 42, and 56
- Changes in assessments on the Sjögren's Disease Activity Index from Day 0 to study Days 14, 28, 42, and 56
- Changes in MRI and technetium scan of the salivary glands from baseline to study Day 56

Exploratory endpoints will be the changes in mechanistic endpoints from baseline to study Days 14, 28, 42, and 56.

### 7.3 Analysis Methods

#### 7.3.1 Primary Efficacy Analyses

The primary analysis will compare the change from Day 0 in salivary flow in the dexamethasone-irrigated parotid glands (active treatment) with the saline-irrigated parotid glands (placebo treatment) at study Day 56. The analysis will be performed on the PEP population.

The study has a doubly repeated measures design with each subject measured repeatedly in two dimensions: treatment versus placebo (of the paired parotid glands); and, study day. A linear mixed effect model will be fit to a dataset including all the saliva flow measurements of both parotids from study days 0, 14, 28, 42, and 56. The model included all time points for improved power. However, the primary analysis will only focus on the treatment effects of the change in saliva flow from baseline in parotid salivary flow at Day56. The statistical model will include parotid saliva flow as the dependent variable, a covariate for baseline saliva flow, parotid treatment and study day and their interaction as fixed effects, and subject as a random effect.

*Null hypothesis:* No improvement in the saliva flow rate of the dexamethasone irrigated parotid glands compared to the saline irrigated parotid glands with respect to change from Day 0 in salivary flow at Day 56.

*Alternative Hypothesis:* Improvement in the saliva flow rate of the dexamethasone irrigated parotid glands compared to the saline irrigated parotid glands with respect to change from Day 0 in salivary flow at Day 56.

The least squares mean and its one-sided 95% confidence interval of the difference between dexamethasone and saline treatments with respect to the change from Day 0 in salivary flow at Day 56 will be reported. The one-sided 95% confidence interval will be directly derived from the two-sided 90% confidence interval estimated in the model. The alternative hypothesis will be accepted if the least squares mean estimate for treatment differences in change from baseline at Day 56 is positive and the lower bound of the one-sided 95% confidence interval does not include 0. The SAS code to be used is listed below:

```
PROC MIXED data=a;  
  CLASS treatment day subjid;  
  MODEL change= baseline_rate treatment|day;  
  REPEATED treatment day/ subject=subjid type=un@cs;  
  RANDOM subjid(treatment);  
  LSMEANS treatment*day / diff cl alpha=0.90;
```

RUN;

If above mixed model fails to converge or their residual analysis indicates model assumptions are highly questionable, then a paired t-test of the change in saliva flow from baseline at Day 56 using Satterthwaite's approximation will be used to test the primary efficacy endpoint.

The above models will also be fit using log-transformed values for salivary flow. If residual analysis shows the log-transformed saliva flow to better fit model assumptions then the primary analysis will be based on the log-transformed model and the antilog of least squares mean estimate (and confidence interval) of the primary endpoint will be reported as a ratio saliva flow at study Day 56 over its baseline value.

### **7.3.2 Secondary Efficacy Analyses**

The secondary analyses will be performed on the SEP population. If the second on-treatment irrigation was discordant with the first treatment irrigation, endpoints following the second on-treatment irrigation will be set to missing.

#### *Changes in salivary flow:*

The changes in salivary flow from baseline (Day 0) to Days 14, 28 and 42 will be analyzed using the same doubly-repeated-measures analysis described in Section 7.3.1. If significant treatment effects are found between baseline and any of the other study days (including Day 56), then additional analysis will be performed to test pair-wise differences in salivary flow change between Day 0 and other study days using two-sided tests. For instance, if a significant treatment effect is indicated by one-sided test between Day 0 and Day 42, then 2-sided tests will be performed to test whether salivary flow change from Day 0 to Day 42 is greater than or less than the change from Day 0 to Day 56, the change from Day 0 to Day 28, and the change from Day 0 to Day 14. Note that if the second treatment on Day 28 is different from the treatment on Day 0 for any reasons, any endpoints collected following second treatment on Day 28 will be set to missing.

*Change in focus score on parotid biopsy*

Focus score and changes from screening to Day 56 will be summarized with descriptive statistics by visit and listed.

*Changes in assessments on the Patient Dry Mouth Questionnaire:*

Patient Dry Mouth Questionnaire responses and changes from baseline (Day 0) to Days 14, 28, 42, and 56 will be summarized using frequencies and percentages by visit.

Further analyses pertaining to symptoms of SS will be performed for the following binary outcome questions:

- Do you have difficulty chewing your food?
- Have you experienced any changes in your sense of smell?
- Have you experienced any changes in your sense of taste?
- Do you have any pain or burning in your mouth or head and neck region?
- Do you use anything to keep your mouth moist?
- Does your mouth feel dry when you eat a meal?
- Does your mouth feel dry other times of the day?
- Do you have difficulty swallowing dry foods without additional liquids?

Change from baseline assessments of the symptoms of SS will be displayed graphically over time. The frequency of subjects who answered ‘Yes’ to the applicable question will be displayed on the y- axis and days will be displayed on the x-axis for each assessment performed over multiple time points. In addition, shift tables will be presented for changes from baseline (Day 0) to Day 14, baseline to Day 42, and baseline to Day 56 for questions related to symptoms of SS. The shift from baseline in frequencies will be further evaluated using the McNemar’s test, in cases where the shift appears to be substantial.

*Changes in assessments on the Sjögren’s Disease Activity Index:*

Sjögren’s Disease Activity Index results and changes from baseline (Day 0) to Days 14, 28, 42, and 56 will be assessed. Categorical outcomes will be summarized using

frequencies and percentages by visit. Ordinal outcomes will be summarized with descriptive statistics by visit.

Further analyses pertaining to symptoms of SS will be performed for the following assessments:

- Evaluation of Disease Activity (Ordinal scale: 0-10, Nominal scale: Inactive/Low/Moderate/High)
- Evaluation of minimal disease activity state (Binomial outcome: Yes/No)
- Evaluation of patient's symptoms (Ordinal scale: 0-10)
- Evaluation of change in disease activity (Nominal scale: Much better/Better/The same/Worse/Much worse)
- Determination of disease flare (Binomial outcome: Yes/No)

For binomial categorical outcomes, the frequency of subjects who answered 'Yes' to the applicable question will be displayed on the y- axis and days will be displayed on the x- axis for each assessment performed over multiple time points. For ordinal-scaled outcomes, the median score among subjects will be displayed on the y-axis and days will be displayed on the x-axis for assessments performed over multiple time points. In addition, shift tables will be presented for changes from baseline (Day 0) to Day 14, to Day 42, and to Day 56 for questions related to symptoms of SS. The shift from baseline in frequencies for binary outcomes will be further evaluated using the McNemar's test, if the shift is substantial. The results from Sjögren's Disease Activity Index will be listed.

*Changes in MRI and technetium scan of the salivary glands:*

Scan results and changes from baseline for MRI and technetium scan will be summarized and visit. Shift tables will also be displayed for the changes in the scan results between Day 0 and Day 56 (normal-abnormal, abnormal-normal, no change).

### 7.3.3 Exploratory Efficacy Analyses

#### Exploratory analyses of mechanistic and inflammatory endpoints:

Mechanistic and inflammatory endpoints will be studied to gain insight into the molecular mechanism of action of the dexamethasone treatments and to generate hypotheses for future research. The mechanistic outcome measures may include, but will not be limited to, single-protein single-channel recordings, organellar and single-cell current ( $\text{Ca}^{+2}$ , and pH), fluid secretion by acinar cells, and ductal secretory and signaling functions. These mechanistic endpoints as well as their change from baseline results will be summarized by study day. Summary statistics may include means, geometric means, minimum and maximum, standard deviations, 90% confidence limits, medians, and frequencies as appropriate for the measure. Log or other transformations may be used if they improve the distributional properties of the outcome measure.

Saliva-derived biomarkers of inflammation and salivary gland dysfunction may be identified from the exosomal microRNAs and non-coding small RNAs. The frequency of the presence/absence of these biomarkers in the saliva both before and after treatment will be reported. Concentrations of biomarkers above the threshold of detection will be summarized using the summary statistics listed above. Biomarkers for inflammation other than non-coding RNAs might be measured in saliva, but those biomarkers will be determined by findings in the biopsies.

Finally, mechanistic endpoints and biomarkers (including changes from baseline) that appear promising will be tested for association with inflammation, salivary flow, or other measures of salivary gland dysfunction. Cross-sectional analyses may include measures of correlation such as Kendall's tau, Spearman rank correlation, and polyserial correlation, as appropriate for the measure. Biomarkers or outcomes that show evidence of correlation with salivary flow, dexamethasone versus saline treatment, or salivary gland dysfunction may be further analyzed longitudinally using mixed-models analysis. These analyses are considered exploratory and hypothesis generating and, as such, will not be corrected for multiple comparisons.

## **8. SAFETY EVALUATION**

### **8.1 Adverse Events**

AEs with a start date on or after the treatment initiation on Day 0 will be considered treatment-emergent AEs.

AEs reported prior to treatment initiation will be summarized separately from treatment-emergent AEs.

Treatment-emergent AEs will be summarized over all subjects, and by relationship to study drug (unrelated, possibly, probably or definitely related) and severity (mild, moderate and severe) on the basis of incidence rates by system organ class and preferred term. Displays will be sorted by descending order of overall incidence by treatment.

All summary tables will include counts of subjects. Therefore, if a subject has more than 1 adverse event within a system organ class, the subject will be counted only once in that system organ class. If a subject has more than 1 adverse event that codes to the same preferred term, the subject will be counted only once for that preferred term. If a subject experiences more than 1 episode of a particular adverse event, that subject will be counted only once for that event under the maximum severity or most related category for the study drug. Similarly, in the unlikely event that severity data are missing, the study analysis will follow the assumption of maximum severity in the summary tables.

All AEs will be listed by subject. AEs prior to treatment initiation and treatment-emergent AEs will be only be presented in data listings.

### **8.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events**

The most common AEs (experienced by >2% patients), serious AEs, AEs leading to study discontinuation, and deaths will be reported in frequency tables by system organ class and preferred term. AEs leading to discontinuation, AEs leading to death, and serious AEs will be listed.

### **8.3 Routine Clinical Laboratory Evaluation**

Clinical laboratory tests will be performed at Screening, Day 0, Day 28 and Day 56. All laboratory results (hematology, chemistry, and urinalysis) will be listed. Summary statistics (mean, standard deviation, median, minimum, maximum and number of patients) will be provided for continuous results, including change from baseline results, by visit. Changes from baseline for inflammatory markers: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) will be summarized separately.

### **8.4 Additional Clinical Laboratory Evaluation**

Other laboratory tests of immunologic function will be collected on Days 0, 28, and 56. Immunologic assessments will include:

- antinuclear antibodies, extractable nuclear antigens
- rheumatoid factor
- C3 complement, C4 complement
- immunoglobulin (Ig)A, IgG, and IgM.A

Summary statistics (mean, standard deviation, median, minimum, maximum and number of patients) will be provided by visit.

In addition, on Days 0 and 28, blood samples will be drawn for measurement of plasma concentrations of dexamethasone prior to randomized irrigation to obtain a pre-irrigation baseline measure and post-irrigation measure. The dexamethasone concentration and change from baseline results will be summarized using descriptive statistics by visit.

### **8.5 Vital Signs, Physical Findings, and Other Observations Related to Safety**

#### **8.5.1 Vital Signs**

Vital signs (blood pressure, respiration rate, oral body temperature, and pulse rate) will be collected at Screening, Day 0, Day 14, Day 28, Day 42, Day 56, and Follow-up.

Summary statistics for results and changes from baseline will be provided for each vital sign parameter by time point. Additionally, vital signs will be listed by subject.

### **8.5.2 Physical Examinations**

Complete physical examinations will be performed on Days 0, 29 and 56. A shift table will be provided to summarize change from baseline to each post-treatment period by body system. The shift categories will include:

- Normal at baseline to Abnormal at post-treatment(unfavorable change)
- Abnormal at baseline to Normal at post-treatment (favorable change)
- No change from baseline to post-Treatment

All physical examination data will be presented in a listing.

### **8.5.3 Concomitant Medications**

Concomitant medications include all medications that continued after or started after treatment initiation. The concomitant medications will be presented in a listing.

### **8.5.4 Other Safety Evaluations**

The ultra-sound-guided core needle biopsy of right parotid gland and minor salivary gland biopsy will be displayed in the listings.

## **9. INTERIM ANALYSES AND DATA MONITORING**

No interim analyses are planned.

## 10. SUBSTANTIVE CHANGES TO THE STATISTICAL ANALYSIS PLAN AFTER DATABASE LOCK

The study was terminated early due to difficulties in recruiting study subjects. Only 9 of the planned 16 subjects had been treated prior to termination. The database was locked on March 25, 2016. At the time of database lock, the SAP was in draft form. This locked draft (version 0.1) of the SAP is available upon request.

Listed below are the substantive changes made to the SAP subsequent to database lock and unblinding but prior to any statistical analysis of the study.

1) Section 5. Demographic and Other Baseline Characteristics.

Added: “To assess overall health of the study subjects prior to study treatment, any significant medical history will be included in the subject listings”

2) Section 7.3.1. Primary Efficacy Analysis.

The mixed model for the primary efficacy analysis was simplified from a direct product first-order auto-regressive covariance structure (un@ar(1)) to a direct product compound symmetry covariance structure (un@cs). The statistical model was simplified because of the reduced sample size. A baseline saliva flow covariate was also added to the model to adjust for possible baseline effects on changes in saliva flow (this covariate was specified in the protocol). In addition, a paired t-test was included as an alternative, simplified model to be used if the mixed model fails to converge. The revised SAP also added that log-transformation of the model’s endpoint may be considered if it improves the model’s fit to the data, based upon residual analysis. These changes to the primary analysis will also affect the secondary efficacy models whose models were based upon the primary efficacy models.

3) Section 7.3.2. Secondary Efficacy Analyses, *Changes in salivary flow*.

When discussing the secondary endpoint, changes in salivary flow at Study Days 14, 28, and 42, the original draft SAP stated : “If significant treatment effects are

found between baseline and any of the other study days, then additional analysis will be performed to test pair-wise differences in salivary flow change between Day 0 and other study days using two-sided tests. “ However comparing differences among the Study Days with respect to change from baseline should have also included Study Day 56. Indeed, Day 56 was listed in the secondary endpoint description in the protocol (Protocol Section 9.2 Secondary Outcome Measures) and the previous SAP (Section 7.2 Efficacy Variables), but was not previously included in the secondary analysis description of this parameter. The revised SAP was modified to include Study Day 56 in these statistical comparisons among the study days.

4) Section 7.3.2. Secondary Efficacy Analyses, *Changes in assessments on the Patient Dry Mouth Questionnaire.*

The generalized estimating equations (GEE) analyses were removed from the analysis of responses to the Sjögren’s Disease Activity Index since with the reduced sample size such a complex model would be of limited value.

5) Section 7.3.2. Secondary Efficacy Analyses, *Changes in assessment on Sjögren’s Disease Activity Index*

The original draft of SAP stated that shift tables will be presented for changes from baseline at Day 14, Day 42, and Day 56 for questions related to symptoms of SS. The finalized SAP adds a shift table for change from baseline at Day 28 for purposes of completeness and consistency with the protocol.

Finally, the generalized estimating equations (GEE) analyses were removed from the analysis of responses to the Sjögren’s Disease Activity Index because the reduced sample size is not conducive to being analyzed with such a complex model. GEE models were mentioned in the protocol, but only recommended if the data were rich enough to warrant such analyses; therefore this is not a change from the original protocol.

6) Section 8.5.3. Concomitant Medications.

This final version of the SAP eliminated the table summarizing the concomitant medications by therapeutic drug class and generic name. Review of these data can be facilitated by a data listing alone.

- 7) Appendix A: The table shell for Demographics and Baseline Characteristics was separated into 2, so that the baseline assessment of sidedness parameters could be properly summarized as described in Section 6.

## **11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL**

There were no substantive changes from the analyses planned in the protocol.

Modifications from version 0.1 to version 1.0 of the SAP are noted in Section 10.

## **12. REFERENCES**

- <sup>1</sup> Kononoff PJ, Hanford KJ. Technical note: estimating statistical power of mixed models used in dairy nutrition experiments. *J Dairy Sci.* 2006;89:3968-71.
- <sup>2</sup> Izumi M, Eguchi K, Nakamura H, Takagi Y, Kawabe Y, Nakamura T. Corticosteroid irrigation of parotid gland for treatment of xerostomia in patients with Sjögren's syndrome. *Ann Rheum Dis.* 1998;57:464-69.

### **13. APPENDICES**

#### Appendix A – Sample Subset of Tables Shells.

Changes to the structure and content of final data displays do not require an amendment to the SAP, unless they reflect analyses that are different from those described in earlier sections of this document.

Table X. Summary of Patient Disposition  
 All Consented (Enrolled) Subjects

	Dexamethasone (left) & placebo (right)	Dexamethasone (right) & placebo (left)	Total
	N=xx n (%)	N=xx n (%)	N=xx n (%)
Enrolled	xx	xx	xx
Randomized	xx (xx.x)	xx (xx.x)	xx (xx.x)
Analysis populations			
Safety	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary Efficacy Population (FEP)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Secondary Efficacy Population (SEP)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study completion			
Completed study through Day 56	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued before Day 56	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed safety follow-up assessment	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for discontinuation before Day 56			
Withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)
No longer meets eligibility criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator discretion	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table X. Summary of Protocol Deviations

Safety Population			
	Dexamethasone (left) & placebo (right) N=xx n (%)	Dexamethasone (right) & placebo (left) N=xx n (%)	Total N=xx n (%)
All deviations	xx	xx	xx
Type of Deviation			
Informed consent	xx (xx.x)	xx (xx.x)	xx (xx.x)
Eligibility	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study drug	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missed visit			
Out-of-window visit			
Study procedure	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)
Impact of Deviation			
Patient safety			
Outcome measurements	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
No impact	xx (xx.x)	xx (xx.x)	xx (xx.x)
Type of Deviation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Informed consent	xx (xx.x)	xx (xx.x)	xx (xx.x)
Eligibility	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study drug	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table X. Summary of Demographic and Baseline Characteristics  
 Safety Population

Characteristics	Dexamethasone (left) & placebo (right)	Dexamethasone (right) & placebo (left)	Total
	N=xx n (%)	N=xx n (%)	N=xx n (%)
Sex - n (%)			
Female	xx (100)	xx (100)	xx (100)
Age (years)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Range (Min, Max)	(xx, xx)	(xx, xx)	(xx, xx)
Race - n (%)			
Hispanic	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non Hispanic American	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity - n (%)			
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline height (cm)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Range (Min, Max)	(xx, xx)	(xx, xx)	(xx, xx)
Baseline weight (lb)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Range (Min, Max)	(xx, xx)	(xx, xx)	(xx, xx)
Baseline waist (cm)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Range (Min, Max)	(xx, xx)	(xx, xx)	(xx, xx)

Table X. Summary of Baseline Characteristics Associated with  
 Later-Treated Body Side  
 Safety Population

	Dexamethasone <sup>1</sup> N=xx	Placebo <sup>1</sup> N=xx	Overall N=xx
MRI results			
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal-not clinically significant	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal-clinically significant	xx (xx.x)	xx (xx.x)	xx (xx.x)
Technetium results			
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)
Salivary flow rate (mL/min)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Range (Min, Max)	(xx, xx)	(xx, xx)	(xx, xx)
Focus Score			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Range (Min, Max)	(xx, xx)	(xx, xx)	(xx, xx)

<sup>1</sup> Baseline assessment of body side -- later treated with product indicated.

Table X. Summary of Change in Salivary flow from Day 0 to Day 56  
Primary Efficacy Population

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Statistics	Dexamethasone N=xx	Placebo N=xx
Estimated LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
95% CI for LS Mean	(xx.x, xx.x)	(xx.x, xx.x)
Estimated LS Mean Difference vs Placebo	xx.x (xx.xx)	
One-sided 95% CI for LS Mean Difference	(xx.x, xx.x)	

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Note: The linear mixed effect model with doubly-repeated measures was used including treatment and day as fixed effects, subject as a random effect and baseline salivary flow as a covariate.

LS = Least Squares; CI = Confidence Interval; SE= Standard Error.

Table X. Summary of Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term for Events with a Sidedness Aspect

Safety Population

System organ class Preferred term	Dexamethasone	Placebo	Total
	N=xx n (%)	N=xx n (%)	N=xx n (%)
Any AEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
System organ class 1			
Preferred term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
System organ class 2			
Preferred term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.			

Note: n= Number of subjects reporting at least one adverse event with System Organ Class/Preferred Term;

Note: If a subject experienced more than one episode of an adverse event, the subject is counted once for that Preferred Term. If a subject had more than one adverse event in a System Organ Class, the subject is counted only once in that System Organ Class.