A Double-Blind, Randomized, Placebo Controlled, Clinical Trial of an Antiplaque Chewing Gum (30 mg) – Phase 2 Proof of Concept in a Generally Healthy Patient Population

Statistical Analysis Plan

Final

28 February 2017

Sponsor The Surgeon General, Department of the Army

Senior Statistician Michael Miller, PhD
ClinSmart CRO
2080 Cabot Blvd West, Suite 201
Langhorne, PA 19047
215-710-3220
Fax: 215-702-2899
Email: mmiller@clinsmart.com

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Signature Page

Prepared by: _____ Date: 2/28/2017

Michael Miller, PhD
ClinSmart CRO
2080 Cabot Blvd West, Suite 201
Langhorne, PA 19047

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Approved by: _____ Date: _____

Sharon Gilbert, MBA, MS, PhD (Contractor – TGS)
Biostatistics Support
Clinical Services Support Division
U.S. Army Medical Material Development

1. Synopsis

Name of Sponsor:
The Surgeon General, Department of the Army

Name of Investigational Product:
Anti-Plaque Chewing Gum (APCG)

Name of Active Ingredient:
KSL-W (30 mg)

Title of Study: A Double-Blind, Randomized, Placebo-Controlled, Clinical Trial of an Antiplaque Chewing Gum (30 mg) - Phase 2 Proof of Concept in a Generally Healthy Patient Population

Study Center:
Salus Research
1220 Medical Park Dr, Bldg #4
Fort Wayne, IN46825

Principal Investigator:
Jeffery L. Milleman, DDS, MPA

Sub-Investigator:
Kimberly R. Milleman, RDH, BSEd, MS

Study Period (years):
Estimated date first subject enrolled: August 2016
Estimated date last subject completed: August 2016

Objectives:

Primary:

- To assess the safety and tolerability of KSL-W (30 mg dose) delivered in a chewing gum formulation compared to a placebo gum formulation

Secondary:

- To assess the proof of concept change in plaque regrowth from baseline in the Quigley Hein-Turesky Plaque Index (QHT) of KSL-W (30 mg dose) compared to a placebo gum formulation
- To evaluate the proof of concept of KSL-W (30 mg) in change in plaque regrowth based on sub-scores from specific regions of the upper jaw, lower jaw, buccal and lingual surface based on the QHT

Methodology: This study is a Phase 2 two-armed placebo-controlled, double-blind, randomized (1:1), multiple dose, single center study to evaluate the safety and proof of concept of 30 mg KSL-W administered in a chewing gum formulation 3 times per day over 4 treatment days. Oral hygiene (teeth brushing, flossing and/or mouth wash rinse) is prohibited throughout the trial beginning 12 to 16 hours before both the screening and Baseline (Day 0) visits, during the 4 days of treatment (Days 0, 1, 2, and 3) and ending after the periodontal examination and plaque assessment on Day 4. The ability of KSL-W to reduce existing supragingival plaque will be assessed. The oral soft (OST) and oral hard tissues (OHT) will be examined. Changes from baseline, such as soft tissue erythema, ulceration and sloughing, will be noted.

Estimated Number of Subjects Screened: 36

Estimated Number of Subjects Enrolled: 26

Number of Subjects (planned): 24

A sample size of at least 12 subjects per study arm (KSL-W, Placebo) yields at least a posterior 94% chance of observing any KSL-W improvement in the sample mean QHT scores, and at least an 81% posterior chance (given that an improvement was observed) that the projected sample size for a similar, later-phase, confirmatory study, using a 2-tailed p = 0.05, power = 90% criterion, is no more than 100 per study arm. This is based on the results of the phase 2a trial at Day 14, where for the 30-mg dose the observed QHT mean change from baseline was -0.31 with n= 7 subjects, and for the placebo subjects the QHT mean change from baseline was -0.03 with

n = 16. The observed QHT error standard deviation was 0.22. It was assumed that these Day 14 results from phase 2a apply to this study having 4 days of treatment.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Male and female subjects between the ages of 18 and 64 (inclusive at the time of screening) who are in good health with a minimum of 20 natural teeth will participate in this study.

Investigational Product Dosage, Schedule, and Mode of Administration:

Subjects will receive 30-mg oral doses of KSL-W or placebo chewing gum in tablet form. After a dental examination including teeth polishing, subjects will receive the first dose under supervision in the clinic. The remaining 11 doses will be self-administered and unsupervised. The maximum dose of KSL-W in a 24 hour period is three 30-mg chewing gum tablets (90 mg total). Each dose consists of 1 piece of gum (tablet). The gum will be chewed for 20 minutes balanced equally as possible between both sides of the mouth. The gum will be chewed preferably after a meal or in 4-6 hour intervals three times a day for a total of 4 days.

Duration of Treatment: 4 days

Reference Therapy, Dosage, Schedule, and Mode of Administration:

This is a double-blind, two-armed, randomized placebo-controlled study. The KSL-W and placebo tablets will be identical in appearance.

Criteria for Evaluation:

Safety:

Occurrence of local oral mucosal reactions; systemic reactions such as fever, nausea, headache, diarrhea, and changes in blood pressure; and serious total body reactions will be assessed. In addition, physical examinations and vital signs will be taken before treatment and at the end of the study.

Proof of Concept (Efficacy/Effectiveness):

Changes in the Quigley-Hein TureskyPlaque Index (QHT) will be calculated as whole-mouth scores. Average scores of selected subsets of measurements sites (interproximal, facial, lingual, maxillary, mandibular, and posterior) will be calculated as exploratory endpoints.

Statistical Methods:

Two evaluators will be used for this study, and each subject's randomly assigned evaluator will stay with that subject throughout the study. The randomization to the study arm (KSL-W, placebo) will be 1:1 within evaluator. All adverse events (AE) will be presented in by-subject data listings. Treatment-emergent AEs will be tabulated where treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment, or any medical or dental condition that is present at baseline but worsens in intensity subsequent to the administration of the first dose of study treatment. In addition to the subject listings, summaries by study arm, noting severity and relationship to study treatment, will include AE incidence proportions and rates by system organ class (SOC) and by preferred term (PT) within SOC. Incidence rates (in events per subject week) will be estimated as the number of treatment emergent AEs divided by the total number of patient-weeks.AE incidence proportion will be estimated based on the number of subjects having at least one AE of a particular type divided by the number of subjects exposed.

Data from physical examinations and vital signs will be summarized for each evaluation time point. Any abnormal physical examination findings noted at the end-of-study exam on Day 4 will be tabulated as a listing. For vital signs, change from baseline to the end-of-study evaluation time points will be summarized.

The primary proof of concept (efficacy) endpoint will use the QHT whole-mouth scores from the full analysis set (FAS) and will be based on the mean change from baseline to Day 4. The QHT whole-mouth average will be the average of scores only from surfaces evaluable for QHT. The QHT score is based on each subject having at least 20 teeth with 6 evaluable surfaces per tooth.

An analysis of covariance (ANCOVA) model will be used to compare 30 mg KSL-W with placebo. The primary model will include the baseline score and study arm (KSL-W, placebo). Sensitivity assessments will be employed to determine whether the effects of treatment on the slope of the baseline covariate, and the effect of evaluator on the treatment placebo comparison can be ignored.

While a formal *p* value comparison based on the final primary ANCOVA model will be generated and summarized, this will not be the primary evaluation, since this study has not been powered for detection of a minimally clinically important improvement in QHT. The primary summaries for this study will include the

estimated difference, KSL-W minus placebo, in the mean (QHT) change from baseline, and the estimated error standard deviation from the primary ANCOVA model. This information will be critical to assessing the chances for a successful demonstration of KSL-W efficacy in future phase 3 studies, as a function of the sample size of these studies.

Similar ANCOVA models will be used for the per protocol (PP) population, and secondary mean scores (FAS and PP), and the results from each model will be summarized.

Descriptive and inferential summaries for FAS and PP will be presented for all scores by study arm overall, and by study arm and evaluator. The summaries will include the mean, standard error, minimum, 25th percentile, median, 75th percentile, and maximum, for baseline, Day 4, and change from baseline to Day 4. *P* values will be given for study arm comparisons but will not be adjusted for multiple comparisons.

Missing data will not be imputed. A missing QHT score will occur if there are insufficient numbers of surfaces evaluable for QHT. A subject will be considered lost to follow-up if their Day 4 morning evaluation occurs more than 24 hours after the scheduled time.

2. Table of Contents

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3. List of Abbreviations and Definitions of Terms

The following abbreviations are used in this SAP.

Table 1: Abbreviations

Abbreviation	Explanation
AE	Adverse event
APCG	Antiplaque chewing gum
ANCOVA	Analysis of Covariance
AR	Army Regulation
C	Celsius
CPC	Cetylpyridinium chloride
CFR	Code of Federal Regulation
Cm	Centimeter
CSSD	Clinical Services Support Division, USAMMDA
DA	Department of the Army
DoD	Department of Defense
eCRF	Electronic Case Report Form
F	Fahrenheit
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Processes
HA	Hydroxyapatite
HIPAA	Health Insurance Portability Accountability Act
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
Mg	Milligram
mL	Milliliter
Mm	Millimeter
OHT	Oral hard tissue
OST	Oral soft tissue
OHRP	Office for Human Research Protections, Department of Health and Human Services
ORP, HRPO	Office of Research Protections, Human Research Protection Office
PI	Plaque Index
PP	Per Protocol Population
PT	Preferred Term

Table 1: Abbreviations (Continued)

Abbreviation	Explanation
POC	Proof of Concept
PSSB	Product Safety Surveillance Branch, CSSD, USAMMDA
QHT	Quigley-Hein Turesky Plaque Index
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Statistical Analysis Report
SOC	System organ class
SOP	Standard operating procedure
TMD	Temporomandibular disorder
TSG-DA	The Surgeon General, Department of the Army
USAMMDA	United States Army Medical Material Development Activity
USAMRMC	United States Army Medical Research and Material Command

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is:

- To assess the safety and tolerability of KSL-W (30 mg dose) delivered in a chewing gum formulation compared with a placebo formulation during the 4 study days.

4.2. Secondary Objectives

The secondary objectives are:

- To assess the proof of concept (efficacy) using plaque re-growth [baseline minus Day 4 QHT score] of KSL-W (30mg dose) delivered in a chewing gum formulation compared to a placebo formulation.
- To evaluate the proof of concept (efficacy)of KSL-W (30 mg) in reducing plaque based on sub-scores from specific regions of the upper jaw, lower jaw, buccal and lingual surface based on the QHT.

5. Study Design

This is a Phase 2, double-blind, two-armed, placebo-controlled, randomized, single-center, multiple-dose study to evaluate the safety and proof of concept of KSL-W administered as a chewing gum formulation (APCG) 3 times per day over 4 treatment days, as outlined in Table 2.

Table 2: Study Design

Treatment Day	**Dosage * KSL-W / Placebo**	**# of Chews per Day ****
Day 0	30 mg / 0 mg	3
Day 1	30 mg / 0 mg	3
Day 2	30 mg / 0 mg	3
Day 3	30 mg / 0 mg	3
* Subjects randomized to either KSL-W or placebo **Each dose taken preferably after each meal (breakfast, lunch and dinner) or every 4-6 hours for a maximum of 3 chews per day		

Table 3 provides an outline of the study events and their timing.

Table 3: Study Event Schedule

			Study Visit/Day				
	Visit 1	**Visit 2**	**Visit 3**				**Visit 4**
	Screening (Day -18 to -14)	**Screening (Day -10 to – 8)**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**
General Procedures							
Written Informed Consent/HIPAA	X						
Evaluation Inclusion/ Exclusion Criteria	X		X				
Demographic Data	X						
Medical History	X						
Vital Signs (BP, HR, RR Temperature)	X		X				X
Physical Exam		X					X[a]
Urine Drug Screen	X						
Urine Pregnancy Test	X[b]						X[b]
Periodontal Examination	X[c]						
Intraoral Exam (OHT, OST)	X		X				X
Oral Hygiene Check	X[d]		X[d]				X[d]
Randomization (1:1)			X				
Plaque Index Score	X		X[e]				X
Teeth Polishing			X				
Dispense Study Drug for Supervised and Unsupervised Use			X[f]				
Study Drug Administration			X[g]	X[g]	X[g]	X[g]	
Collect Used Study Drug			X[h]				X[h]
Electronic Diary Information System			X[i]	X[i]	X[i]	X[i]	
Adverse Event Reporting			X				X
Concomitant Medications	X		X				X
Study Discharge							X

BP-blood pressure, HIPAA-Health Insurance Portability and Accountability Act, HR-heart rate, RR-respiration rate, OHT-oral hard tissue, OST – oral soft tissue, QHT-Quigley-Hein Turesky Plaque Index

[a]Brief symptom oriented physical exam (based upon reported adverse events)

[b] Pregnancy test for females of childbearing potential

[c] Includes determination of number of teeth, score-able surfaces and pocket depths around teeth

[d] Confirm subject has refrained from all oral hygiene procedures (flossing, brushing of teeth, mouth wash rinse) for 12 to 16 hours prior to Screening and Day 0 (Baseline). On Day 4, confirm subject has refrained from all oral hygiene procedures since chewing their last dose on Day 3.

[e]Measured after randomization, but before teeth polishing

[f]Subject will be allocated 14 tablets of gum for the 4 day study period.

[g]Subject will chew one tablet of gum for 20 minutes preferably after a meal (breakfast, lunch, dinner) or every 4 to 6 hours for a maximum of 3 chews per day. Chewing will be balanced as equally as possible between both sides of the mouth. The first tablet will be given under supervision in the clinic. Oral hygiene is not allowed at any time during the 4 day treatment. Oral hygiene cannot resume until after the determination of the Plaque Index Score on Day 4.

[h] After each chewing period, the gum is disposed of in individual labeled bags. Subject records time/date of gum disposal on each bag. Subject will return all used/unused bags to the site on Day 4.

[i]Subject records all start /stop times of gum chewing via the internet using the electronic diary information system (ePRO).

5.1. Randomization

A permuted block randomization list will be generated using SAS Version 9.3 (PROC PLAN) for the 15 active and 15 placebo blinded product vials. To maintain the blind, further details of the generation of the randomization list (block size) will be outlined in a separate Randomization Plan.

The unblinded statistician will send the randomization list to the following authorized product preparation staff at Salus Research in order for them to appropriately label the package materials with RANDOMIZATION NUMBERS according to Section 7.3.2 of the protocol.

Joan Staller Salus Research Joan.Staller@SalusResearch.us

Aaron Staller Salus Research Aaron.Staller@SalusResearch.us

1220 Medical Park Drive, Bldg #4

Fort Wayne, IN 46825

In addition, the unblinded statistician will send the product preparation staff individual sealed security envelopes for each RANDOMIZATION NUMBER with the treatment assignment enclosed to be used only in the event of an emergency unblinding. These individual sealed envelopes containing the treatment assignment associated with each RANDOMIZATION NUMBER will be stored in a secured location only accessible to the unblinded product preparation staff.

Thirty-six subjects are projected to be screened at Visit 1 (Day -18 to -14) and Visit 2 (Day -10 to -8) and assigned a sequential SUBJECT NUMBER with the anticipation of enrolling 26 eligible subjects to obtain 24 subjects projected to complete the study. This SUBJECT NUMBER will be associated with the subject throughout the trial and linked to a separate RANDOMIZATION NUMBER to be assigned at randomization.

At Visit 3 (Day 0), each subject will be reevaluated by the next available evaluator for the study inclusion and exclusion criteria. If eligible and still consenting, the subject's vital signs will be

measured, an intraoral dental exam will be conducted (OST and OHT), the subject will be asked to confirm that he/she did not perform any oral hygiene procedures for 12-16 hours prior to Day 0. At this point the subject will be randomized and the evaluator will obtain the next available investigation product according to the randomization list from a central location that is easily accessible to both evaluators. The subject will then be considered randomized to the trial. This procedure will ensure that the next subject to be randomized into the trial will always receive the treatment corresponding to the next free number in the randomization list. After entering the RANDOMIZATION NUMBER as recorded on the investigational product into the eCRF, study procedures will continue with the supragingival assessment and each subject's teeth will be polished by a licensed dental hygienist. The first chew will then be supervised by the site study staff.

Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Principal Investigator. Procedures outlined in Section 7.3.3 of the protocol should be followed. Only the Principal Investigator or Sponsor can authorize emergency unblinding and the reason for unblinding should be clearly identified in the eCRF.

5.2. Blinding

For this double-blind study, the investigator, study biostatistician, staff not involved in product preparation, study subjects, and sponsor will be blinded to the treatment assignments throughout the duration of the study.

Salus Research will receive the investigational gum product directly from Fertin Pharma. Authorized product preparation staff at Salus Research will repackage the product into blinded individual opaque plastic vials in accordance with the randomization schedule. The product preparation staff will have no other responsibilities or involvement in the study. No other personnel are permitted in the preparation room during preparation of the blinded product.

The product preparation staff will receive a randomization schedule from the unblinded independent biostatistician. Each unique subject identification number will be assigned a treatment and this list will be used by the product preparation staff to prepare the blinded product. The blinded product will be labeled as shown in Figure 1. Salus Research will be provided with individually sealed envelopes identifying each subject’s specific treatment assignment. Salus Research will store these envelopes in a secure location accessible to the principal investigator in the event that the blind needs to be broken. The randomization, repackaging and labeling of the study product will be performed as per approved procedures in place at Salus Research.

Figure 1: Example Label for Blinded Product Vials

Subject ID Number:

Directions for Subject: Chew 1 tablet for 20 minutes balanced equally on both sides of the mouth. Each dose should be taken preferably after each meal (breakfast, lunch and dinner) or every 4-6 hours for a maximum of 3 chews per day.

Storage Instructions: Material to be stored at ambient room temperature, out of direct sunlight. Do not expose to extreme heat or cold.

Caution: New Drug – Limited by Federal (or U.S) law for investigational use.

Distributed by: Salus Research

Phenylketonurics: Contains Phenylalanine

KEEP OUT OF REACH OF CHILDREN

Dr. Jeffrey Milleman, Principal Investigator Study S-16-10

Emergency Phone #: 260-413-7777

Non-emergency Phone #: 260-755-1099

5.3. Procedures for Unblinding

Emergency unblinding of a subject should only be done in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study product is essential for the clinical management or welfare of the subject. In such an emergency situation, the Principal Investigator may unblind a subject's treatment without first discussing with the Sponsor's Safety Physician. While it is recommended to discuss with the Sponsor's safety physician prior to unblinding, the safety of the subject is the highest priority. The Sponsor will be notified by the Principal Investigator when emergency unblinding has occurred. Only the Principal Investigator or Sponsor can authorize emergency unblinding. The reason for unblinding should be clearly specified in the source documentation.

The individual treatment codes for each subject will be given to Salus Research in sealed envelopes. Each individual envelope will contain the subject identification number and their specific treatment assignment. These envelopes will be stored in a secure location accessible to the Principal Investigator in the event that the blind needs to be broken for emergency unblinding or individual emergency safety unblinding.

Contact Information for Emergency Unblinding:

Responsible person:

- Salus Research: Dr. Jeffrey Milleman,
  Phone: 260-755-1099

- Army: Acting-Director, Clinical Services Support Division

  Phone: 301-619-0317

5.4. Sample Size Justification

A sample size of at least 12 subjects per study arm (KSL-W, Placebo) is planned. This projection was based on certain results from the phase 2a trial (sponsor study number S-11-14). At Day 14, for the 30 mg dose (n = 7 subjects) the observed QHT mean change from baseline was 0.31 and for placebo (n = 16 subjects) the observed QHT mean change from baseline was 0.03. The observed QHT error standard deviation was 0.22. Using these results to form the basis of a prior joint distribution of means and error variance, a sample size of at least 12 subjects per study arm (KSL-W, Placebo) yields at least a posterior 94% chance of observing any KSL-W improvement in the sample mean QHT scores, and at least an 81% posterior chance (given that an improvement was observed) that the projected sample size for a similar, later phase, confirmatory study, using a 2-tailed p = 0.05, power = 90% criterion, is no more than 100 per study arm. It was assumed that these Day 14 results from phase 2a apply to this study having 4 days of treatment.

6. Statistical Procedures

6.1. Data Handling Conventions

6.1.1. Study Analysis Populations

The Safety Population consists of all subjects receiving at least one dose of study medication. These will most likely be randomized subjects receiving study therapy at Visit 3 (Day 0). The safety population will be analyzed according to the treatment actually received (KSL-W or placebo).

The Full Analysis Set (FAS) is defined as all randomized subjects having Baseline and Day 4 QHT evaluations, with the Day 4 evaluation occurring on the morning following the last chewing gum treatment from the previous day. The FAS population will be analyzed according to their randomized treatment assignment. A randomized subject with a missing Day 4 QHT whole mouth score will not have this score imputed, and will not be in the FAS cohort.

The Per Protocol Population (PP) is a subset of FAS and consists of all subjects with no major protocol violations itemized as follows: failure to obtain valid informed consent, accidental distribution of incorrect study medication, not following the inclusion/exclusion criteria, evidence that study medication was not taken, and the performance of oral hygiene other than chewing the study gum was during the study period, Day 4 evaluation performed later than on the morning following the last chewing gum treatment from the previous day. Analysis of the PP will be according to the treatment actually received by the subject.

6.1.2. Study Exposure

The baseline visit will be at Visit 3, Day 0, and the first dose of the study medication will be administered after randomization, determination of the baseline QHT score, and tooth polishing. The study exposure, in days, will be measured from Day 0 (date of randomization) to the last day

the subject was in the study. For subjects completing Visit 4, Day 4, the exposure will be 4 days (counting Day 0), regardless of whether the subject took any of the self-administered treatment. For early withdrawal subjects the study exposure will be from Day 0 to (and including) the subject's last day when the subject informs the study site of their early withdrawal. If the subject is lost to follow-up, the study site personnel will attempt to contact the subject to determine the day when they stopped study participation, and any adverse events that occurred during their self-administration time. Randomized subjects who are lost to follow-up and who are unable to be contacted will be assigned one day of study exposure, namely Day 0.

6.2. Specification of Safety Measurements (Endpoints)

6.2.1. Vital Signs

Vital signs measurements include blood pressure (systolic and diastolic), heart rate, respiration rate, and body temperature. These measurements will be collected after the subject has been seated for at least 5 minutes during screening and on Day 0 and Day 4.

6.2.2. Physical Examination

During the screening visit a physical examination will be performed. A brief symptom-oriented physical exam will be performed on Day 4 and will involve observation of the physical appearance of the subject. Any unexpected abnormalities or changes from baseline will be assessed and documented. Findings that are considered to be of clinical significance will be recorded as AEs.

6.2.3. Intraoral Examination

6.2.3.1. Oral Soft Tissue Examination

The OST examination will be performed by visually inspecting the oral cavity and perioral area using a dental light, dental mirror, periodontal probe and gauze. Any abnormalities at baseline will be recorded in order to detect changes such as the development of erythema, ulceration, or tissue sloughing should they occur during the four day study period.

The structures examined will include the labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area, salivary glands, temporomandibular joint, and any other area as deemed necessary by the investigator. The same examiner will conduct the subject's OST during the study.

OST observations will be listed as "Normal" or "Abnormal." Abnormal observations will be documented and described in the subject's study records. Any changes will be recorded, severity assessed according to standard dental examination procedures, and a decision made with respect to whether or not these changes are related to treatment with the study drug. New or worsened OST findings occurring after the first use of the study product will be recorded as AEs.

6.2.3.2. Oral Hard Tissue Examination

The OHT examination will assess irregularities in tooth enamel, tooth fracture, decay, faulty restorations and implants. OHT observations will be listed as "Absent" or "Present" and any "Present" observations will be described.

6.2.4. Adverse Event Determination and Assessment

6.2.4.1. Adverse Event or Suspected Adverse Reaction

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Treatment-emergent AEs is defined as any AE that occurs on or after administration of the first dose of study treatment (Day 0) or any medical or dental condition that is present at baseline (Day 0) but worsens in intensity subsequent to the administration of the first dose of study treatment.

Solicited Adverse Event

This section is not applicable.

Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias

or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Unanticipated Problems Involving Risks to Subjects or Others

Federal regulations require that unanticipated problems that are serious adverse events involving risks to subjects or others be promptly reported to the IRB within5 business days of the investigator becoming aware of the event. Any other unanticipated problem should be reported to the IRB within 10 days of the investigator becoming aware of the problem. These events encompass a broader category of events than SAEs and may include issues such as problems with loss of control of subject data or the investigational product; adverse psychological reactions; or breach of confidentiality. Risks to others (e.g., program personnel) must also be reported.

Unanticipated problems involving risks to subjects or others are any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the procedures that are described in the protocol, investigators brochure or informed consent document; and (b) the characteristics of the subject population;
- Related or possibly related to a subject's participation in the study; and
- Suggests that the study places subjects or others at a greater risk of harm than was previously known or recognized.

The IRB and/or the ORP will evaluate the Principal Investigator's and Research Monitor's reports to determine whether a given incident, experience or outcome constitutes an unanticipated problem involving risk to subjects or others and, in coordination with USAMRMC CSSD, ensure reporting of the unanticipated problems involving risk to subjects or others to the appropriate regulatory offices, as applicable.

6.2.4.2. Relationship to Investigational Product

The investigator must assign a relationship of each AE to the receipt of the investigational product. The investigator will use clinical judgment in conjunction with the assessment of a

plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. The following guidelines should be used by the investigator to assess the relationship of an AE to study product administration. **ONLY A PHYSICIAN CAN MAKE THIS DETERMINATION.**

Not related: Relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.

Unlikely: Likely unrelated to the investigational product. Likely to be related to factors other than investigational product, but cannot be ruled out with certainty.

Possible: An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the subject's clinical status or underlying factors including other therapy.

Probable: There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the subject's clinical state or factors including other therapy.

Definite: An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

6.2.4.3. Severity Assessment

All AEs will be assessed for severity by the investigator. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. Each event will be assigned one of the following categories: mild, moderate, severe, or life-threatening.

Table 4: Severity Assessment Scale

Category	Grade	Description
Mild	1	Mild symptoms; clinical or diagnostic observation only. (Does not interfere with routine activities, minimal discomfort)
Moderate	2	Interferes with routine activities Moderate level of discomfort
Severe	3	Severe or medically significant but not immediately life-threatening; hospitalization indicated; Unable to perform routine activities; Significant level of discomfort
Life-threatening	4	Urgent intervention indicated (Hospitalization or ER visit for potentially life-threatening event)
Death	5	Death related to AE

The severity assessment criteria may be used for any symptom not included in the grading scale. Any grade 4 (life-threatening) AE must be reported as an SAE. The eCRF for AEs will reflect

only the highest severity for continuous days an event occurred. The criteria in Table 4 will be followed; however, if a subject is evaluated in an emergency room setting for nonlife threatening illness or symptoms (i.e., visits emergency department on weekend for mild problems because the physician's office is closed), the information from that visit will be reviewed and severity of the AE will be assessed according to the subject's clinical signs and symptoms.

As defined by the ICH guideline for GCP, the term "severe" is often used to describe intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however, may be of relatively minor medical significance (such as severe headache).This is **not** the same as "serious", which is based on subject/event **outcome** or **action** criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

6.2.4.4. Recording Adverse Events

Methods/Timing for Assessing, Recording and Analyzing Safety Measurements (Endpoints)

AEs and SAEs will be assessed at each study visit and documented in the source records. All AEs will be recorded on the eCRFs using accepted medical terms and/or the diagnoses that accurately characterizes the event. SAEs will be documented using the SAE paper form. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected on both forms, the forms must be completed in a consistent manner. For example, the same event term should be used on both forms.

When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess and record for all AEs/SAEs: a description of the event (if the event consists of a cluster of signs and symptoms, a diagnosis should be recorded rather than each sign and symptom): onset date and time, and resolution date and time: intensity (recorded as mild, moderate or severe): relationship to study drug (recorded as unrelated, unlikely related, possibly related, probably related and definitely related): outcome (recorded as recovered, recovering, resolved with sequelae, not resolved, fatal, ongoing (end of study) or unknown if applicable): action taken with the study product (recorded as no action taken, dose reduced, interrupted, discontinued). When an event has not resolved by study closure, it will be documented on the AE eCRF as "ongoing."

The timeframe for the collection of AEs and SAEs for each subject begins at the first administration of investigational product (Visit 3, Day 0) through Visit 4, Day 4.

Duration of Follow-Up of Subjects after Adverse Events

Investigators are required to follow SAEs to resolution, even if this extends beyond the prescribed reporting period. Resolution is the return to baseline status or stabilization of the condition with the probability that it will become chronic. The SAE outcomes will be reported to the sponsor's representative using the Serious Adverse Event Report Form.

Investigators are not obligated to actively seek SAEs in former subjects; however, if an SAE, considered to be related to the investigational product is brought to the attention of the investigator *at any time* following completion of the study, the event will be reported to the

sponsor's safety office (see below).Other extensive reporting requirements are given in the study protocol.

6.2.4.5. AE-related Withdrawal of Consent

Any AE-related withdrawal of consent during the study must be reported *immediately* **(within 72 hours of identification)** by email or fax to the sponsor's representative. Report the withdrawal to US Investigational Review Board (IRB of Record) and/or the USAMRMC ORP in accordance with IRB policy.

6.2.4.6. Pregnancy

Each pregnancy must be reported **within 72 hours of identification** by completing and submitting the Sponsor approved Pregnancy Report Form (paper) via email or fax to the sponsor's safety office (CSSD, Product Safety Surveillance Branch). Report the incident to US Investigational Review Board and/or the USAMRMC ORP in accordance with IRB policy.

Subjects who become pregnant after Day 0 will be followed to term, and the following information will be gathered, documented, and reported on the follow-up Pregnancy Report Form for outcome, date and type of delivery, Apgar scores, health status of the mother and child including the child's gender, height and weight. Complications and or abnormalities should be reported including any premature terminations. A pregnancy is reported as an AE or SAE only when there is suspicion that the investigational product may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy including a spontaneous abortion or an elective termination for medical rationale.

The decision on whether to remove the participant from the study will be made by the investigator and the participant following consultation with the Sponsor.

6.3. Proof of Concept Evaluations (Secondary Analysis)

6.3.1. Quigley Hein-Turesky Plaque Index (QHT) Whole Mouth Score

The mouth generally contains 28 teeth arranged in four quadrants, 7 teeth per quadrant (maxillary-buccal, maxillary-lingual, mandibular-buccal, mandibular-lingual). Each tooth has 6 surfaces for plaque evaluation so that a mouth with all teeth and surfaces present has4 x 7 x 6 = 168 surfaces. For each evaluable surface the evaluator assigns a numerical score from 0 to 5 relative to the plaque present, with 0 meaning no plaque, and 5 the worst or highest plaque determination. Criteria for each score is given in [Tureskey-1970].

Some of the 168 possible surfaces may not be evaluable due to either the particular tooth is missing or due to other dental issues as determined by the evaluator.

The whole mouth QHT score at a given dental appointment is the sum all scores divided by the number of evaluable surfaces. In other words, the QHT is the arithmetic average of all scores from the evaluable surfaces, so that scores for surfaces not evaluable are not imputed.

The QHT evaluations for each subject are planned to occur at Screening (Visit 1), Day 0 (Visit 3), and Day 4 (Visit 4).

6.3.1.1. Valid QHT Whole Mouth Score

A subject must have at least 20 teeth with all 6 surfaces evaluable in order for the QHT whole mouth score to be used in this study. Subjects who do not satisfy this criterion at the baseline evaluation will be excused from the study. Generally this determination will be made at the screening visit, and most likely a subject qualifying at screening will also qualify at baseline.

6.3.1.2. QHT Quadrant Scores

The arithmetic average of the scores obtained from each of the 4 quadrants (maxillary-buccal, maxillary-lingual, mandibular-buccal, mandibular-lingual) will be assessed again using only the evaluable surfaces from each quadrant. No additional restriction on the number of evaluable surfaces from each quadrant will be made.

6.3.1.3. QHT Tooth Surface Scores

A set of up to 168 individual surface scores will be obtained at each of the QHT evaluations for each subject and will be part of the data set for the study.

7. Statistical Methods for Data Analysis

7.1. Primary (Safety) Analyses

7.1.1. Adverse Events

A subject listing of deaths, other serious AEs, and discontinuations due to adverse events will be presented in tabular form by treatment received. Information will include a description of the event, the study day when the event was first observed, severity if applicable, relationship to study drug, resolution status of the event, subject status within the study (if applicable).

Summaries of adverse events by SOC only, and by event severity will be given by study arm. Separate tabular summaries by study arm, system organ class (SOC) and by preferred term (PT) within SOC will be given for:

- All AEs
- AEs possibly, probably, definitely related to study medication.

For each SOC and SOC, PT combination the estimated incidence proportions and estimated incidence rates will be given by treatment received.

The incidence proportion will be calculated as the number of subjects with a given treatment (KSL-W, placebo) having at least one AE with that SOC or SOC-PT classification, divided by the number of subjects with that treatment (expressed as a percent).

The incidence rate will be calculated as the number of adverse events with that SOC or SOC-PT classification divided by the total study exposure from all subjects with a given treatment. The study exposure is determined in days (see 3.1.2), but the total study exposure will be converted to subject-weeks. The total number of events and the rate in events per subject-week will be given. Since incidence rate takes into account exposure, this may be the measure more applicable to combine with other studies.

Subject listings of adverse events will include the verbatim AE terms as well as the SOC, PT. Severity, relationship with study drug, resolution of the event, and ongoing status of the subject within the study will also be shown in the subject listings, which will be presented by treatment and subject within treatment.

Adverse event data collected on paper forms will be described in the final Clinical Study Report and not displayed in a table or listing. This will include any additional maternal or paternal adverse events which will be collected on the Pregnancy Surveillance Form as well as any data collected on the Serious Adverse Event Form.

7.1.2. Vital Signs

Descriptive summaries will be provided by treatment for systolic, diastolic BP, heart rate, temperature, and respiration, at screen, Day 0, and Day 4. Change from baseline will be computed as the Day 4 assessment minus the Day 0 assessment. For each variable at each visit, and change from baseline the sample mean, standard deviation, minimum, maximum, 25thpercentile, median, and 75th percentile will be provided.

7.1.3. Physical Exam and Urine Pregnancy Test

The percent of subjects by treatment with "relevant physical exam findings" will be presented for the screening and Day 4 visits. The description of the relevant findings will be found in the physical exam subject listing, classified by treatment, subject, and visit. If very few relevant findings are discovered they will be listed on the summary table.

The number and percent of women of child-bearing age will be summarized at the screening and Day 4 visits by treatment received. The number of such women taking the urine pregnancy test, and the findings of the test (positive or negative) will be summarized again by visit and treatment.

7.2. Plaque Re-growth: Secondary Proof of Concept Analyses

7.2.1. Whole Mouth QHT Score

An analysis of covariance (ANCOVA) model will be fit to the subjects' change in plaque re-growth from baseline in the QHT score (baseline minus Day 4) for subjects in the FAS population.

Primary POC model: The primary model will include randomized study arm (KSL-W, placebo) and the baseline QHT score.

Least squares means and standard errors will be summarized for KSL-W, placebo, and the KSL-W minus placebo mean difference. A 95% confidence bound will be presented for the mean difference along with a 2-tailed p value testing the null hypothesis that the mean difference in the mean change in plaque re-growth is zero. The estimated common error variance together with a 95% (equal tailed) confidence bound will be presented.

The model assumptions include the following:

- Baseline minus Day 4 subject QHT differences have a normal distribution, conditioned on the baseline observation.

- The relationship between the mean difference and baseline is linear, with slope not dependent on study arm.
- The model error variance does not depend on study arm or the mean difference.
- The QHT evaluator has no effect on the mean difference, error variance, or baseline slope.

Each of these model assumptions will be checked, and the findings of these determinations will be summarized along with the above information. Violations of the model assumptions affecting later decisions based on this information will be investigated, particularly their impact on the conclusions of the study.

Secondary Investigations: A secondary investigation involving a full model including study arm, baseline QHT score, QHT evaluator and all possible 2-factor interactions will be conducted.

Results of the primary model applied to the per-protocol (PP) population whole-mouth QHT scores will be summarized as with the FAS population, as well as the primary and secondary model parameter estimates for the PP population.

This study was not powered for a specific expected effect size, hence all p values are descriptive and no adjustment will be made for multiple p values.

The results of the primary and secondary investigations will be summarized in a Statistical Analysis Report (SAR), including the model assumptions investigations and estimates, standard errors of the primary and secondary model parameters.

7.2.2. QHT Score by Mouth Quadrant

Least squares means and standard errors will be summarized for KSL-W, placebo, and the KSL-W minus placebo mean difference for each of the 4 mouth quadrants using the primary model. Also, 95% confidence bounds will be presented for the mean difference by quadrant, along with a 2-tailed p value for the null hypothesis that the mean difference in the mean change in plaque re-growth for that quadrant is zero. This summary will be generated for both the FAS and PP populations.

The FAS population, the study arms are being compared regardless of the treatment actually received, while for the PP population the results are compared based on the actual treatment received. It is expected that treatment actually received will very likely correspond to the study arm assignment.

7.2.3. Descriptive Summary of QHT Scores

The mean, standard deviation, minimum, median, and maximum will be summarized by study arm (treatment) and by visit (baseline, Day 4) for the whole-mouth QHT scores and for each of the 4 mouth quadrant QHT scores. These summaries will be generated for the FAS and PP populations.

Individual surface summary distributions will be presented by visit and study arm to allow spot comparisons of the change in score from baseline to day 4 by treatment.

7.3. Intra-oral Exam: Hard and Soft Tissue

Summaries of the number and percent present for each of 5 hard tissue issues will be summarized by study arm and visit (Screen, Day 0, and Day 4) for the Safety, FAS, and PP populations. A similar summary will be generated for the 14 soft tissue issues. Listings will also be prepared by subject.

7.4. Demographic and Background Assessments

7.4.1. Demographic Assessments

Age, gender, ethnicity, and race will be summarized by study arm and overall for the Safety, FAS, and PP populations.

The mean, standard deviation, minimum, median, and maximum will be presented for subject age (in years) at screening. Gender, ethnicity, and race will be summarized by the distribution of subjects over the categories, presenting n as the number of subjects in a given category, with the percent being 100 (n/N) rounded to the first decimal place.

7.4.2. Medical History, Urine Drug Screen

The number and percent of subjects with any “relevant medical history” will be summarized by study arm and overall, for the Safety, FAS, and PP populations. The specific relevant medical history will be described in the medical histories subject listings. The onset date and end date (or still ongoing) will be provided.

The urine drug screen should have been performed on all subjects in the three analysis populations, and should be negative in order for the subjects to be enrolled in the study. Urine drug screen results will be tabulated, and results by subject will be listed.

7.4.3. Screen Periodontal Exam

The number and percent of “relevant periodontal exam findings” will be summarized by study arm and overall, for the Safety, FAS, and PP populations. The specific relevant periodontal exam findings will be described in the periodontal exam subject listings.

7.4.4. Major Protocol Violations

Major protocol violations will be listed by subject as well as summarized by study arm for the FAS population.

8. Data Receipt and Analysis Plan Modification

Refinements to this analysis plan were made during the course of the study. The changes from the original analysis plan are incorporated in this final analysis plan, which was completed and approved by the study sponsor and ClinSmart before database lock and unblinding. Any deviations to the SAP will be explained in the SAR and final CSR.

9. Interim Analysis, DSMB

No interim analysis will be performed, and no data safety monitoring board will be used for this study.

10. Display and Formatting of Tables and Listings

All tables and listings will be produced in Rich Text Format, landscape mode. A separate copy of the tables and listings will be produced in an Adobe format.

A reference to appropriate subject listings will be provided below each table.

Rounding Conventions

- All computations will be generated using data with full decimal expansion, and rounding will occur only for the outputted summaries.
- All summarized QHT scores will be rounded to the nearest hundredth, and a 5 in the hundredth's place will always be rounded to 6. For example, the score 3.285 will be rounded to 3.29.
- Adverse event rates (number of events/total exposure) will be rounded to the nearest hundredth.
- All other summary percentages will be rounded to the nearest tenth: 100*(3/9) = 33.3333 will be recorded as 33.3%.

11. Table Shells

11.1. List of Table Shells

Table	Title
TREF01	Subject Disposition
TREF02	Analysis Populations
TREF03.1	Demographic Assessments: Safety Population
TREF04.1	Medical History, Urine Drug Screen: Safety Population
TREF05.1	Screen Periodontal Exam: Safety Population
TREF06.1	Vital Signs by Visit: Safety Population
TREF07.1	Physical Exam by Visit: Safety Population
TREF08.1	Urine Pregnancy Test by Visit: Safety Population
TREF09	Concomitant Medication Summary: Safety Population
TREF10	Summary of Chew Compliance During Study Days 0, 1, 2, 3: Number and Percent of Subjects Performing Protocol Specified Chews: Safety Population
TREF11	Summary of Extent of Exposure and Adverse Event Incidence Proportion, Rate: Safety Population
TREF12	Serious Adverse Events, Discontinuations Due to Adverse Events, Deaths: Safety Population
TREF13	Summary of Adverse Event Proportion, Rate by Body System Organ Class (All Treatment Emergent Adverse Events): Safety Population
TREF14	Summary of Adverse Event Proportion, Rate by Body System Organ Class and Preferred Term: All Treatment Emergent Adverse Events): Safety Population
TREF15	Summary of Adverse Event Proportion, Rate by Event Severity: Safety Population
TREF16.1	Summary of Adverse Event Proportion, Rate by Body System Organ Class and Preferred Term: Possibly, Probably, Definitely Related to Study Medication: Safety Population
TREF16.2	Summary of Adverse Event Proportion, Rate by System Organ Class and Preferred Term Unrelated, Unlikely Related to Study Medication: Safety Population
TREF17.1	Intra-oral Exam by Visit – Oral Hard Tissue: Safety Population
TREF17.2	Intra-oral Exam by Visit – Oral Soft Tissue: Safety Population

TREF18	Major Protocol Deviations: Full Analysis Set
TREF19.1	Descriptive Summary of QHT Scores, Whole Mouth and by Quadrant, by Visit: Full Analysis Set
TREF20.1	Whole Mouth QHT Score (Baseline – Day 4) Study Arm Comparison: Full Analysis Set
TREF21.1	QHT Score by Quadrant – Study Arm Comparison at Day 4: Full Analysis Set
TREF22.1	Summary of QHT Plaque Score Distribution by Individual Surface: Full Analysis Set

11.2. Table Shells

TREF01 **Subject Disposition**			
	Total	**KSL-W**	**Placebo**
Number Screened	xx		
Number Randomized	xx	xx	xx
Number Receiving Study Drug	xx	xx	xx
End of Study Status			
Number (%)* Completing Study	xx (%)	xx (%)	xx (%)
Number (%) with Early Discontinuation	xx (%)	xx (%)	xx (%)
Reason for Early Discontinuation Screening failure Adverse Event Lost to Follow-up Terminated by Principal Investigator Major Protocol Deviation/Deviation Subject requested to be withdrawn Sponsor decision to withdrawal	xx	xx	xx

*(%) = percentage of those randomized, within total and each study arm

Subject Listing: LREF01, LREF12, LREF21b, LREF13

TREF02 **Analysis Populations**			
	Total	**KSL-W**	**Placebo**
Number in Safety Population*	xx	xx (%)	xx (%)
Number in Full Analysis Set**	xx	xx (%)	xx (%)
Number in Per-Protocol Population***	xx	xx (%)	xx (%)

(%) = Percent of total

*Subjects randomized receiving at least one dose of study therapy, analyzed according to the therapy received

**Subjects having a valid QHT evaluation at Study Days 1 and 4, analyzed as randomized

***Subjects in the Full Analysis Set with no major protocol deviations (see table TREf15 for a summary of major protocol deviations)

Subject Listing LREF12, LREF21b, LREF18

number screened: ENROLLMENT.ICFDT pg 2 eCRF

number randomized: RAND.RANDYN pg 36 eCRF

number in Safety pop: DRUGADMIN.DISPSCYN pg 46 eCRF

Number in Per-Protocol Population: from protocol dev. pg 101 eCRF, and a list of subjects with no major protocol Deviations

TREF03.1 **Demographic Assessments** **Safety Population: KSL-W (N=xx), Placebo (N=xx)**			
	KSL-W	**Placebo**	**Total**
Age (years)			
mean (std. dev)	xx.x (x.x)	..	..
Minimum, Median, Maximum	..	..	..
	..	..	..
Gender, n (%)			
male	xx (xx)	..	..
female	..	..	..
unknown (not given)	..	..	..
Ethnicity, n (%)			
Hispanic or Latino	Xx (XX) (%)	..	..
Not Hispanic or Latino	..	..	..
Not reported, Unknown	..	..	..

Race, n (%)			
White		..	..
Native Hawaiian, Other Pacific Islander	..	..	..
Black or African American	..	..	..
Asian	..	..	..
Other	..	..	..

Percentages may not add up due to rounding

Subject listing: LREF01

(TREF03.2 FAS, TREF03.3 Per-Protocol Population)

From Enrollment, pg 2 eCRF

TREF04.1 **Medical History, Urine Drug Screen** **Safety Population: KSL-W (N=xx), Placebo (N=xx)**				
		KSL-W	**Placebo**	**Total**
Does the subject have any relevant medical history? (past/concomitant diseases or surgeries)				
Yes*		n (%)	n (%)	
No		n (%)	n (%)	
Not collected		n (%)	n (%)	

Was Urine Drug Screen Performed?				
Yes		n (%)	n (%)	
	Result			
	positive	n (% of yes)	n (% of yes)	
	negative	n (% of yes)		
No		n (%)		

*Subject listings of all indicated relevant medical histories are found in LREF03

Subject listings of the urine drug screen including reasons not performed are found in LREF06

(TREF04.2 FAS, TREF04.3 Per-Protocol population)

Medical History pg 6 eCRF

DRUGSCRN pg 8 eCRF

TREF05.1

Screen Periodontal Exam

Safety Population: KSL-W (N=xx), Placebo (N=xx)

		KSL-W	Placebo	Total
Was Periodontal Exam Performed?				
Yes		n (%)	n (%)	
	Were there any relevant periodontal exam findings?			
	Yes*	n (%)	n (%)	
	No	n (%)	n (%)	
No*		n (%)	n (%)	

*Subject listings of all responses to the periodontal exam, including relevant findings and reasons for not performing the exam are found in LREF08

TREF05.2 FAS, TREF05.3 Per-protocol population

Periodontal Exam pg 10 eCRF

TREF06.1

Vital Signs by Visit

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W					**Placebo**			
	Screen (N=xx)	Day 0 (N=xx)	Day 4 (N=xx)	Day 4 - Day 0		Screen (N=xx)	Day 0 (N=xx)	Day 4 (N=xx)	Day 4 - Day 0
Systolic BP (mmHg)									
mean (Std. Dev), min, max									
(1st quartile, median, 3rd quartile)									
Diastolic BP (mmHg)									
mean (Std. Dev), min, max									
(1st quartile, median, 3rd quartile)									
Heart Rate (bpm)									
mean (Std. Dev), min, max									
(1st quartile, median, 3rd quartile)									
Temperature (F)									
mean (Std. Dev), min, max									
(1st quartile, median, 3rd quartile)									
Respiration Rate (bpm)									
mean (Std. Dev), min, max									
(1st quartile, median, 3rd quartile)									

Subject listing: LREF04

TREF06.2 FAS, TREF06.3 Per-protocol population

Vital Signs pg 7 (screen), pg 31 (day 0), pg 75 (day 4) eCRF

TREF07.1

Physical Exam by Visit

Safety Population: KSL-W (N=xx), Placebo (N=xx)

Brief Physical Examination		**KSL-W**	**Placebo**	**Total**
Screen		N=xx	N=xx	N=xx
Were there any relevant physical examination findings?				
Yes*		n (%)	n (%)	
No		n (%)	n (%)	
Not performed		n (%)	n (%)	
Day 4		N=xx	N=xx	N=xx
Were there any relevant physical examination findings?				
Yes*		n (%)	n (%)	
No		n (%)	n (%)	
Not performed Unscheduled		n (%)	n (%)	

(TREF07.2 FAS, TREF07.3 Per-protocol population)

Subject Listing: LREF05.

Physical Exam pg 26 (screen), pg76 (day 4)

PREGTEST pg 9 (screen), pg 77 (day 4) Unscheduled visit

TREF08.1

Urine Pregnancy Test by Visit

Safety Population: KSL-W (N=xx), Placebo (N=xx)

		KSL-W	Placebo	Total
Screen		**N=xx**	**N=xx**	**N=xx**
Is the subject a woman of childbearing potential? (Yes nw/N %)		nw/N (%)	nw/N (%)	
If Yes was Urine Pregnancy Test performed? (Yes np/nw)		np/nw (%)	np/nw (%)	
If performed, Pregnancy Test result:	positive	n+/np (%)	n+/np (%)	
	negative	n-/np(%)	n-/np(%)	
Day 4				
Is the subject a woman of childbearing potential? (Yes nw/N %)		nw/N (%)	nw/N (%)	
If Yes was Urine Pregnancy Test performed? (Yes np/nw)		np/nw (%)	np/nw (%)	
If performed, Pregnancy Test result:	positive	n+/np (%)	n+/np (%)	
	negative	n-/np(%)	n-/np(%)	

Subject Listing: LREF07

(TREF07.2 FAS, TREF07.3 Per-protocol population)

Physical Exam pg 26 (screen), pg76 (day 4)

PREGTEST pg 9 (screen), pg 77 (day 4)

TREF09 **Concomitant Medication Summary** **Safety Population: KSL-W (N=xx), Placebo (N=xx)**				
		KSL-W	**Placebo**	**Total**
		n/N (%)	**n/N (%)**	**n/N (%)**
Subjects with one or more Concomitant Medications		**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**
General Medication Category	**Specific Medication**	**n**	**n**	**n**
xxxxxx	(Total)	xx	xx	xx
	xxxxxx	xx	xx	xx
	xx xxx	xx	xx	xx
xxxxxxx	(Total)			
	xxxxx			
	xxxxx			

* n = Number of subjects with at least one use of the indicated medication or medication category. A subject may be counted more than once due to multiple medications used.

Subject Listing : LREF17

CMEDS pg 99 eCRF

TREF10

Summary of Chew Compliance During Study Days 0, 1, 2, 3

Number and Percent of Subjects Performing Protocol Specified Chews

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W			Placebo		
Study Day	**Chew 1 (Morning)**	**Chew 2 (Afternoon)**	**Chew 3 (Dinner)**	**Chew 1 (Morning)**	**Chew 2 (Afternoon)**	**Chew 3 (Dinner)**
0	n (%)*	n (%)	n (%)	n (%)	n (%)	n (%)
1						
2						
3						

n = number of subjects with a date and time of starting the chew, % = 100*n/N

Subject listing of all chew occasions: LREF18: Chewing Documentation

TREF11

Summary of Extent of Exposure and Adverse Event Incidence Proportion, Rate

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W	Placebo	Total
Total Exposure (subject-weeks)*	xx.x		
Number of Treatment Emergent Adverse Events	xx		
Estimated Incidence Rate (events/sbj-wk)**	xx.xx		
Number of Subjects with at least one adverse event	xx		
Estimated Incidence Proportion (%)	xx.x		

* Time, in weeks, measured from the date of randomization to the date of last follow-up

**Number of events divided by the total exposure

Subject Listing: Exposure LREF12, LREF13 and Adverse events LREF15

Randomization date: RAND.RANDDT pg 36 eCRF

Last follow-up : See SAP section 3.1.2 pgs 11-12. If subject completed the study then the last date is the date of Day 4 visit (VISITDT, pg 73 eCRF). If early withdrawal then last date is STATUS.WDRAWDT, pg 97 eCRF)

Adverse events from AES, page 100 eCRF tables and listings would come from ADaM adae after MeDRA coding.

TREF12

Summary of Serious Adverse Events , Discontinuations Due to Adverse Events, Deaths,

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W	Placebo	Total
Number (%) of Subjects With Serious Adverse Events	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number (%) of Discontinuations Due to Adverse Events			
Number (%) of Deaths			

Subject listing of deaths, SAE's, and adverse event discontinuations: LREF16a, LREF16b

events from AES, page 100 eCRF tables and listings would come from ADaM adae after MeDRA coding.

Table TREF13

Summary of Adverse Event Proportion, Rate by System Organ Class
All Treatment Emergent Adverse Events

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W			Placebo		
System Organ Class	**Number (%)***	**Number of Events****	**Event Rate (evt/sbj-wk)*****	**Number (%)**	**Number of Events**	**Event Rate (evt/sbj-wk)**
xxxxx	xx (xx.x%)	xx	x.xx	xx (xx.x%)	xx	x.xx
xxxxx						

*Number of subjects, n, with at least one event, and % is 100 n/N.
**Total number of events from the given category
*** Total number of events divided by the total study exposure.

Subject listing: LREF16a

TREF14

Summary of Adverse Event Proportion, Rate by System Organ Class and Preferred Term
All Treatment Emergent Adverse Events

Safety Population: KSL-W (N=xx), Placebo (N=xx)

		KSL-W			Placebo		
System Organ Class	**Preferred Term**	**Number of Subjects (%)***	**Number** of Events**	**Event Rate (evt/sbj-wk)*****	**Number of Subjects (%)**	**Number of Events**	**Event Rate (evt/sbj-wk)**
xxx	(Total)	xx (xx.x%)	xx	x.xx	xx (xx.x%)	xx	x.xx
	xxxx						
	xxxx						
	xxxx						
xxxxx	(Total)						
	xxxx						
	xxxx						

*Number of subjects, n, with at least one event, and % is 100 n/N.

**Total number of events from the given category

*** Total number of events divided by the total study exposure.

Subject listing LREF16a
Events from AES, page 100 eCRF tables and listings would come from ADaM adae after MeDRA coding0 eCRF and total exposure for event rate

TREF15

Summary of Adverse Event Proportion, Rate by Event Severity

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W			Placebo		
Severity	**Number of Subjects (%)***	**Number** of Events**	**Event Rate (evt/sbj-wk)*****	**Number of Subjects (%)**	**Number of Events**	**Event Rate (evt/sbj-wk)**
Mild	xx (xx.x%)	xx	x.xx	xx (xx.x%)	xx	x.xx
Moderate						
Severe						
Potentially Life-Threatening						
Death						

*Number of subjects, n, with at least one event, and % is 100 n/N.

**Total number of events from the given category

*** Total number of events divided by the total study exposure.

Subject listing LREF16a

events from AES, page 100 eCRF tables and listings would come from ADaM adae after MeDRA coding. and total exposure for event rate

TREF16.1

**Summary of Adverse Event Proportion, Rate by System Organ Class and Preferred Term
Possibly, Probably, Definitely Related to Study Medication**

Safety Population: KSL-W (N=xx), Placebo (N=xx)

Possibly Related

		KSL-W			Placebo		
System Organ Class	**Preferred Term**	**Number of Subjects (%)***	**Number** of Events**	**Event Rate (evt/sbj-wk)*****	**Number of Subjects (%)**	**Number of Events**	**Event Rate (evt/sbj-wk)**
xxx	(Total)	xx (xx.x%)	xx	x.xx	xx (xx.x%)	xx	x.xx
	xxxx						
	xxxx						
	xxxx						
xxxxx	(Total)						
	xxxx						
	xxxx						

Probably Related

		KSL-W			Placebo		
System Organ Class	**Preferred Term**	**Number of Subjects (%)***	**Number** of Events**	**Event Rate (evt/sbj-wk)*****	**Number of Subjects (%)**	**Number of Events**	**Event Rate (evt/sbj-wk)**
xxx	(Total)	xx (xx.x%)	xx	x.xx	xx (xx.x%)	xx	x.xx
	xxxx						
	xxxx						
	xxxx						
xxxxx	(Total)						
	xxxx						

	xxxx						

Definitely Related

		KSL-W			Placebo		
System Organ Class	**Preferred Term**	**Number of Subjects (%)***	**Number** of Events**	**Event Rate (evt/sbj-wk)*****	**Number of Subjects (%)**	**Number of Events**	**Event Rate (evt/sbj-wk)**
xxx	(Total)	xx (xx.x%)	xx	x.xx	xx (xx.x%)	xx	x.xx
	xxxx						
	xxxx						
	xxxx						
xxxxx	(Total)						
	xxxx						
	xxxx						

*Number of subjects, n, with at least one event, and % is 100 n/N.

**Total number of events from the given category

*** Total number of events divided by the total study exposure.

Subject listing LREF16a

events from AES, page 100 eCRF tables and listings would come from ADaM adae after MeDRA coding and total exposure for event rate

TREF16.2

**Summary of Adverse Event Proportion, Rate by System Organ Class and Preferred Term
Unrelated, Unlikely Related to Study Medication**

Safety Population: KSL-W (N=xx), Placebo (N=xx)

NOTE: this Table will follow the same layout as TREF15.1

TREF17.1

Intra-oral Exam by Visit

Oral Hard Tissue

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W		**Placebo**	
Screen	**N=xx**		**N=xx**	
	Present	**Absent**	**Present**	**Absent**
Enamel Irregularities	n (%)	n	n (%)	n
Tooth Fracture	n (%)	n	n (%)	n
Gross Decay	n (%)	n	n (%)	n
Implants	n (%)	n	n (%)	n
Faulty Restorations	n (%)	n	n (%)	n

n = number with condition Present, (%) = 100 n/N, with N = total for study arm

Subject listing of Oral Hard Tissue: LREF10

(TREF16.2 FAS, TREF16.3 Per-protocol population)

OHTE pgs 11 (screen), 32 (Day 0), 80 (Day 4) eCRF

TREF17.2

Intra-oral Exam by Visit

Oral Hard Tissue

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W		Placebo	
Day 0	**N=xx**		**N=xx**	
	Present	**Absent**	**Present**	**Absent**
Enamel Irregularities	n (%)	n	n (%)	n
Tooth Fracture	n (%)	n	n (%)	n
Gross Decay	n (%)	n	n (%)	n
Implants	n (%)	n	n (%)	n
Faulty Restorations	n (%)	n	n (%)	n

n = number with condition Present, (%) = 100 n/N, with N = total for study arm

Subject listing of Oral Hard,: LREF10

(TREF16.2 FAS, TREF16.3 Per-protocol population)

OHTE pgs 11 (screen), 32 (Day 0), 80 (Day 4) eCRF

TREF16.1

Intra-oral Exam by Visit

Oral Hard Tissue

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W		**Placebo**	
Day 4	**N=xx**		**N=xx**	
	Present	**Absent**	**Present**	**Absent**
Enamel Irregularities	n (%)	n	n (%)	n
Tooth Fracture	n (%)	n	n (%)	n
Gross Decay	n (%)	n	n (%)	n
Implants	n (%)	n	n (%)	n
Faulty Restorations	n (%)	n	n (%)	n

n = number with condition Present, (%) = 100 n/N, with N = total for study arm

Subject listing of Intra-oral Exam: LREF09

(TREF16.2 FAS, TREF16.3 Per-protocol population)

OHTE pgs 11 (screen), 32 (Day 0), 80 (Day 4) eCRF

TREF17.1

Intra-oral Exam by Visit

Oral Soft Tissue

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W		**Placebo**	
Screen	**N=xx**		**N=xx**	
	Present	Absent	Present	Absent
Gingival Mucosa	n (%)	n	n (%)	n
Labial Mucosa (Including Lips)	n (%)	n	n (%)	n
Buccal Mucosa	n (%)	n	n (%)	n
Mucogingival Folds	n (%)	n	n (%)	n
Hard Palate	n (%)	n	n (%)	n
Soft Palate	n (%)	n	n (%)	n
Tonsillar Area	n (%)	n	n (%)	n
Pharyngeal Area	n (%)	n	n (%)	n
Sublingual Area	n (%)	n	n (%)	n
Submandibular Area	n (%)	n	n (%)	n
Salivary Glands	n (%)	n	n (%)	n
Tongue	n (%)	n	n (%)	n
TMJ	n (%)	n	n (%)	n
Other	n (%)	n	n (%)	n

n = number with condition Present, (%) = 100 n/N, with N = total for study arm

Subject listing of Intra-oral Exam: LREF09

(TREF17.2 FAS, TREF17.3 Per-protocol population)

OSTE pgs 12 (screen), 33 (Day 0), 78 (Day 4) eCRF

TREF17.1

Intra-oral Exam by Visit

Oral Soft Tissue

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W		**Placebo**	
Day 0	**N=xx**		**N=xx**	
	Present	**Absent**	**Present**	**Absent**
Gingival Mucosa	n (%)	n	n (%)	n
Labial Mucosa (Including Lips)	n (%)	n	n (%)	n
Buccal Mucosa	n (%)	n	n (%)	n
Mucogingival Folds	n (%)	n	n (%)	n
Hard Palate	n (%)	n	n (%)	n
Soft Palate	n (%)	n	n (%)	n
Tonsillar Area	n (%)	n	n (%)	n
Pharyngeal Area	n (%)	n	n (%)	n
Sublingual Area	n (%)	n	n (%)	n
Submandibular Area	n (%)	n	n (%)	n
Salivary Glands	n (%)	n	n (%)	n
Tongue	n (%)	n	n (%)	n
TMJ	n (%)	n	n (%)	n
Other	n (%)	n	n (%)	n

n = number with condition Present, (%) = 100 n/N, with N = total for study arm

Subject listing of Intra-oral Exam: LREF09

(TREF17.2 FAS, TREF17.3 Per-protocol population)

OSTE pgs 12 (screen), 33 (Day 0), 78 (Day 4) eCRF

TREF17.1

Intra-oral Exam by Visit

Oral Soft Tissue

Safety Population: KSL-W (N=xx), Placebo (N=xx)

	KSL-W		**Placebo**	
Day 4	**N=xx**		**N=xx**	
	Present	**Absent**	**Present**	**Absent**
Gingival Mucosa	n (%)	n	n (%)	n
Labial Mucosa (Including Lips)	n (%)	n	n (%)	n
Buccal Mucosa	n (%)	n	n (%)	n
Mucogingival Folds	n (%)	n	n (%)	n
Hard Palate	n (%)	n	n (%)	n
Soft Palate	n (%)	n	n (%)	n
Tonsillar Area	n (%)	n	n (%)	n
Pharyngeal Area	n (%)	n	n (%)	n
Sublingual Area	n (%)	n	n (%)	n
Submandibular Area	n (%)	n	n (%)	n
Salivary Glands	n (%)	n	n (%)	n
Tongue	n (%)	n	n (%)	n
TMJ	n (%)	n	n (%)	n
Other	n (%)	n	n (%)	n

n = number with condition Present, (%) = 100 n/N, with N = total for study arm

Subject listing of Intra-oral Exam: LREF09

(TREF17.2 FAS, TREF17.3 Per-protocol population)

OSTE pgs 12 (screen), 33 (Day 0), 78 (Day 4) eCRF

TREF18

Major Protocol Deviations

Full Analysis Set: KSL-W (N=xx), Placebo (N=xx)

	KSL-W	Placebo	Total
Randomized subject did not give valid informed consent	n (%)	n (%)	
Accidental distribution of incorrect study medication	n (%)	n (%)	
Randomized subject violates inclusion/exclusion criteria	n (%)	n (%)	
Evidence that study medication was not taken	n (%)	n (%)	
Performance of oral hygiene other than chewing the study gum during the study period	n (%)	n (%)	
Day 4 evaluation performed later than the morning following the last chewing gum treatment from the previous day			
Other	n (%)	n (%)	

n = number with particular deviation, (%) = 100 n/N, with N = total for study arm

Subject Listing: LREF18

TREF19.1

Descriptive Summary of QHT Scores, Whole Mouth and by Quadrant, by Visit

Full Analysis Set: KSL-W (N=xx), Placebo (N=xx)

		Day 0 (Baseline)		Day 4	
Study Arm	**QHT Score, Subscore**	**N, Mean (Std. Dev.)**	**Min, Median, Max**	**N, Mean (Std. Dev.)**	**Min, Median, Max**
KSL-W	Whole Mouth	N, x.xx (x.xx)	x.xx, x.xx, x,xx	N, x.xx (x.xx)	x.xx, x.xx, x,xx
	Maxillary Facial				
	Maxillary Palatal				
	Mandibular Facial				
	Mandibular Lingual				
Placebo	Whole Mouth				
	Maxillary Facial				
	Maxillary Palatal				
	Mandibular Facial				
	Mandibular Lingual				

Subject listing: LREF23

(TREF19.2 Per-protocol population)

ADaM dataset based on PQEXAM pgs 37 (Day 0), 82 (Day 4) eCRF

TREF20.1

Whole Mouth QHT Score (Baseline - Day 4) Study Arm Comparison

Full Analysis Set: KSL-W (N=xx), Placebo (N=xx)

Least Square Means (Baseline - Day 4)				
KSL-W (std error)	**Placebo (std error)**	**Difference = (KSL-W) - Pbs (std error)**	**95% Confidence Bounds on Difference**	**P value (2-tailed)**
x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	(x.xx, x.xx)	0.xxx

Model Error Variance			
	Estimate	**95% Confidence Bounds**	
	xx.xx	(xx.xx, xx.xx)	

*Analysis of covariance model includes study arm, baseline QHT whole mouth score

Subject listing: LREF23

TREF20.2 Per-Protocol

ADaM dataset based on PQEXAM pgs 37 (Day 0), 82 (Day 4) eCRF

TREF20.2

Whole Mouth QHT Score (Baseline - Day 4) Study Arm Comparison: Secondary Analysis for Evaluator Effect

Full Analysis Set: KSL-W (N=xx), Placebo (N=xx)

Least Square Means (Baseline - Day 4)				
	Difference in Whole Mouth QHT Score Baseline - Day 4) (std error)	**Difference = KSL-W – Placebo (std error)**	**95% Confidence Bounds on Difference**	**P value (2-tailed)**
Evaluator A				
KSL-W	x.xx (x.xx)	x.xx (x.xx)	(x.xx, x.xx)	0.xxx
Placebo	x.xx (x.xx)			
Evaluator B				
KSL-W	x.xx (x.xx)	x.xx (x.xx)	(x.xx, x.xx)	0.xxx
Placebo	x.xx (x.xx)			

Model Error Variance			
	Estimate	**95% Confidence Bounds**	
	xx.xx	(xx.xx, xx.xx)	

*Analysis of covariance model includes evaluator, study arm, baseline QHT whole mouth score

Subject listing: LREF23

TREF20.2 Per-Protocol

ADaM dataset based on PQEXAM pgs 37 (Day 0), 82 (Day 4) eCRF

TREF21.1

QHT Score by Quadrant - Study Arm Comparison at Day 4

Full Analysis Set: KSL-W (N=xx), Placebo (N=xx)

	Least Square Means*				
Quadrant	**KSL-W estimate (std error)**	**Placebo estimate (std error)**	**Difference = (KSL-W) - Pbs (std error)**	**95% Confidence Bounds on Difference**	**P value (2-tailed)**
Maxillary Facial	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	(x.xx, x.xx)	0.xxx
Maxillary Palatal	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	(x.xx, x.xx)	0.xxx
Mandibular Facial	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	(x.xx, x.xx)	0.xxx
Mandibular Lingual	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	(x.xx, x.xx)	0.xxx

*Analysis of covariance model includes study arm, baseline QHT quadrant score

Subject listing of QHT whole mouth and quadrant scores: LREF23

(TREF21.2 Per-protocol population)

ADaM dataset based on PQEXAM pgs 37 (Day 0), 82 (Day 4) eCRF

Table TREF22.1

Summary of QHT Plaque Score Distribution by Individual Surface

Full Analysis Set: KSL-W (N=xx), Placebo (N=xx)

Tooth Surface				QHT evaluation (%)						
Quadrant	**Surface ID**	**Study Arm**	**Visit**	**0**	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
Maxillary Buccal	**2D**	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
	2G	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
	2M	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
	….			**0**	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
Maxillary Lingual	**15D**	**KSL-W**	Day 0 (N = xx)	xxx.x						

			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
	15G	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
	15M	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
	….			**0**	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
Mandibular Buccal	**31D**	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
	31G	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**

	31M	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							

….

				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
Mandibular Lingual	**18D**	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
	18G	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							
				0	**1**	**2**	**3**	**4**	**5**	**Surface Missing**
	18M	**KSL-W**	Day 0 (N = xx)	xxx.x						
			Day 4 (N = xx)							
		Placebo	Day 0 (N = xx)							
			Day 4 (N = xx)							

42 surfaces over 4 quadrants = 168 surfaces

Subject listing: LREF22(a,b,c,d)

(TREF22.2 Per-protocol population)

ADaM dataset based on PQEXAM pgs 37 (Day 0), 82 (Day 4) eCRF

12. Listing Shells

12.1. List of Listing Shells

Listing	Title
LREF01	Demography
LREF02	Eligibility
LREF02.a	Inclusion and Exclusion Criteria
LREF03	Medical History
LREF04	Vital Signs
LREF05	Physical Exam
LREF06	Drug Screen
LREF07	Urine Pregnancy Test
LREF08	Screening Periodontal Exam
LREF09	Oral Soft Tissue Exam
LREF10	Oral Hard Tissue Exam
LREF11	Oral Hygiene Check
LREF12	Randomization
LREF13	Subject Status (All Randomized Subject)
LREF13.a	Screen Failures
LREF14	Teeth Polish
LREF15	Adverse Events and Concomitant Medication Question
LREF16	Adverse Events
LREF17	Concomitant Medication
LREF18	Protocol Deviation
LREF19	Collection of Used Study Drug
LREF20	Chewing Documentation
LREF21.a	Drug Administration Part A
LREF21.b	Drug Administration Part B
LREF22.a	Plaque Exam – Maxillary Buccal Tooth
LREF22.b	Plaque Exam – Maxillary Lingual Tooth
LREF22.c	Plaque Exam – Mandibular Buccal Tooth
LREF22.d	Plaque Exam – Mandibular Lingual Tooth
LREF23	Plaque Exam Summary

12.2. Listing Shells

LREF01: Demography

Subject ID	Informed Consent Date	Birth Date	Age	Gender	Ethnicity	Race/Other
XXX						
XXX*						

* Randomized subject

LREF02: Eligibility

Subject ID	Eligibility Check (Screen) Re-check (Day 0)	Eligible for Study (Y, N)	Reason not Eligible
XXXXX	Screen		
	Day 0		

Use eligibility response and STATUS.DISCSF

LREF02.a: Inclusion and Exclusion Criteria

Subject ID	Inclusion/Exclusion Criterion	Does the Subject Meet the Criterion? (Y/N)
XXXXX	Screen	
	Day 0	

Use eligibility response and STATUS.DISCSF

LREF03: Medical History

Subject ID	Any Relevant Medical History	Not Collected Reason	Medical History Date	MH Condition/Surgery	Onset Date	End Date	Ongoing

LREF04: Vital Signs

Subject ID	Visit	Were Vital Signs taken? (Y,N)	Reason not taken	Vital Signs Date	Time	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)	Temperature (Fahrenheit)	Respiration Rate (bpm)

LREF05: Physical Exam

Subject ID	Visit	Physical Exam Performed	Brief Symptom-oriented PE Performed	Not Done Reason	Physical Exam Date	Physical Exam Finding (Yes/No)	Specify Relevant Finding

LREF06: Urine Drug Screen

Subject ID	Visit	Drug Screen Performed	Not Performed Reason	Collected Date	Result

LREF07: Urine Pregnancy Test

Subject ID	Visit	Woman of Childbearing Potential	Urine Pregnancy Performed	Not Performed Reason	Lab Test Name	Date of Test	Pregnancy Test Result

LREF08: Screening Periodontal Exam

Subject ID	Periodontal Exam Performed	Not Done Reason	Date Periodontal Exam	Number of Teeth Six Scorable Surfaces	Periodontal Pockets Greater than 4 millimeters	Periodontal Exam Finding (Yes/No)	Specify Relevant Finding

LREF09: Oral Soft Tissue Exam

Subject ID	Visit	Oral Soft tissue Exam Performed	Not Done Reason	Oral Soft Tissue Date	Examiner Initials	Exam Type	Normal/Abnormal	Abnormal Specify
XX XX						Gingival Mucosa …….. TMJ Other Gingival Mucosa …. TMJ Other		

LREF10 Oral Hard Tissue Exam

Subject ID	Visit	Oral Hard Tissue Exam Performed	Not Done Reason	Oral Hard Tissue Date	Examiner Initials	Hard tissue Check	Absent/Present	Present Specify

LREF11: Oral Hygiene Check

Subject ID	Visit	Refrained from All Oral Hygiene Procedures for 12 to 16 hours Prior to Day 0	Refrain from All Oral Hygiene Procedures since Last Visit (All 4 days of Study Treatment)

LREF12: Randomization

Subject ID	Randomized (Yes/No)	Not Randomized Reason	Randomized Date	Randomization Number

LREF13: Subject Status (All Randomized Subjects)

Subject ID	Visit	Complete Study (Yes/No)	Completion Date	Withdrew Date	Withdrawal Reason

LREF13.a: Screen Failures

Subject ID	Visit	Screen Failure Date	Reason for Screen Failure

LREF14: Teeth Polish

Subject ID	Visit	Teeth Polishing (Yes/No)	Not Performed Reason

LREF15: Adverse Events and Concomitant Medication Question

Subject ID	Visit	Subject Experience any Adverse Events (Yes/No)	Subject take any Concomitant Medications (Yes/No)

LREF16.: Adverse Events

Subject ID	Visit	Line #	Adverse Event	System Organ Class	Preferred Term	Start Date/Time	End Date/Time	Ongoing	Serious	Severity	Relationship to Study Treatment	Action Taken with Study Treatment	Outcome

LREF17: Concomitant Medication

Subject ID	Visit	Line #	Medication/Therapy Name	Indication	Dose/Dose Unit	Frequency	Route	Start Date	Prior to Study	End Date	Ongoing

LREF18: Protocol Deviations

Subject ID	Visit	Any Protocol Deviations	Describe Protocol Deviation	Start Date	End Date	Action Taken

LREF19: Collection of Used Study Drug

Subject ID	Visit	Used Study Drug Collected for Unsupervised Chews	Not Collected Reason	Number of Used Doses	Number of Unused Doses

LREF20: Chewing Documentation

Subject ID	Visit	Chewed Date	Chewed Time

LREF21.a: Drug Administration Part A

Subject ID	Chewing and on-line diary instructions to subject?	Collection bags to subject?	Place used gum into production bag?	Instructed to use one bag per chewed?	Instructed to label each bag with time and date of chew?	Return all used product bags containing chewed gum and used study drug at next visit?

LREF21.b: Drug Administration Part B

Subject ID	Instructed how to use internet to access ePRO to record chewing gun?	Reminded no oral hygiene of any kind allowed?	Study drug dispensed for supervised chew?	Was study drug collected for supervised chew?	Dispensed for unsupervised chews?

LREF22.a: Plaque Exam – Maxillary Buccal Tooth

							Maxillary Buccal Tooth		
Subject ID	**Visit**	**Plaque Exam Performed**	**Not Performed Reason**	**Plaque Exam Date**	**Examiner Initials**	**Tooth**	**Location**	**Missing Tooth**	**Plaque Score**

LREF22.b: Plaque Exam – Maxillary Lingual Tooth

							Maxillary Lingual Tooth		
Subject ID	**Visit**	**Plaque Exam Performed**	**Not Performed Reason**	**Plaque Exam Date**	**Examiner Initials**	**Tooth**	**Location**	**Missing Tooth**	**Plaque Score**

LREF22.c: Plaque Exam – Mandibular Buccal Tooth

							Mandibular Buccal Tooth		
Subject ID	**Visit**	**Plaque Exam Performed**	**Not Performed Reason**	**Plaque Exam Date**	**Examiner Initials**	**Tooth**	**Location**	**Missing Tooth**	**Plaque Score**

LREF22.d: Plaque Exam – Mandibular Lingual Tooth

							Mandibular Lingual Tooth		
Subject ID	**Visit**	**Plaque Exam Performed**	**Not Performed Reason**	**Plaque Exam Date**	**Examiner Initials**	**Tooth**	**Location**	**Missing Tooth**	**Plaque Score**

LREF23: Plaque Exam Summary

				Maxillary Buccal Tooth		Maxillary Lingual Tooth		Mandibular Buccal Tooth		Mandibular Lingual Tooth				
Subject ID	**Visit**	**Examiner Initials**	**CRF Plaque Mean Score**	**Sum**	**Number of Surfaces**	**Sum**	**Number of Surfaces**	**Sum**	**Number of Surfaces**	**Sum**	**Number of Surfaces**	**Total Score**	**Total Number of Surfaces**	**Calculated Average Score**

13. References

Turesky S, et al, 1970. “Quigely Hein Index.” Ed. Kaban Moslehzadeh. Malmo University: Oral Health Database. www.mah.se.