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

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The Surgeon General, Department of the Army

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Investigator's Agreement

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

"I have read this protocol and agree to conduct the study as outlined herein in accordance with International Conference on Harmonization Good Clinical Practice Guideline and FDA, DoD, and United States Army Regulations."

_____ _____

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2. 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, IN 46825

Principal Investigator:
Jeffery L. Milleman, DDS, MPA
Sub-Investigator:
Kimberly R. Milleman, RDH, BSEd, MS (Examiner)

Study Period (years):	**Phase of development:** 2
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:
35

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 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 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 as 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: Four 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 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 from baseline in the Quigley-Hein Turesky Plaque 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. 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.

Two proof of concept (efficacy) endpoints will be assessed. The first, 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 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 proof of concept 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 assess the chances for a successful demonstration of KSL-W efficacy in future phase 3 studies utilizing QHT evaluations, 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.

The second proof of efficacy endpoint will assess the reduction in plaque based on sub-scores from specific regions of the upper jaw, lower jaw, buccal and lingual surface.

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.

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4. List of Abbreviations and Definitions of Terms

The following abbreviations are used in this study protocol.

Table 2: 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
POC	Proof of Concept
PP	Per Protocol Population
PT	Preferred Term
PSSB	Product Safety Surveillance Branch, CSSD, USAMMDA
QHT	Quigley-Hein Turesky Plaque Index

Abbreviation	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
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

5. Introduction

5.1 Military Relevance

Dental caries and periodontal disease pose threats to operational readiness. The effects of poor oral hygiene and diet of deployed soldiers can lead to the uncontrolled accumulation of oral bacteria in dental plaque. Dental plaque is associated with caries, gingivitis, and other oral infections. Dental emergencies requiring soldiers to seek treatment and resulting in lost duty time occur at a rate of approximately 150 per 1,000 deployed service members with an overwhelming number of these (approximately 40%) due to caries and approximately 5% due to periodontal diseases such as acute gingivitis (Allen and Smith-1992; Chaffin et al-2001; Deutsch and Simecek-1996; Dunn et al-2004; Mahoney and Coombs-2000; Moss-2002). There is a need for a product that is capable of arresting and preventing dental plaque build-up and augmenting and replenishing host defense, and is suitable for inclusion in a health package.

5.2 Rationale for Study

The emergence of resistance to conventional antibiotics observed in oral pathogens strongly suggests the need to develop new and safe antimicrobial agents for the treatment and/or prevention of oral infections (Davies-1994; Koeleman et al-2001; Leng et al-1997; Lynch and Zhanel-2005; Okamoto et al-2001; Schutze et al-1994; Stein-2005). The use of a novel antimicrobial peptide (KSL-W) in a chewing gum formulation to help control plaque growth is the primary goal of this capability development. KSL-W exhibits selective bactericidal activity against cariogenic bacteria (*Streptococcus mutans*, *S. sobrinus*, and *Lactobacillus acidophilus*) and early colonizers (*Actinomyces naeslundii*) (Na et al-2007) but shows little effect on some of the members of the normal oral flora (*S. mitis* and *S. oralis*) (unpublished data). Furthermore, per in vitro data, the peptide is degraded in gastrointestinal environments; therefore, suggesting it has no deleterious effect on the resident intestinal flora (unpublished data). The use of chewing gum formulations has additional beneficial effects on oral health by stimulating saliva flow and thereby promoting remineralization of tooth enamel. The peptide exhibits significant adsorption to hydroxyapatite (HA) (tooth-like material), an important characteristic for an antiplaque agent (Faraj et al-2007; Na et al-2007).

The most common methods for removing supragingival plaque are daily tooth brushing, flossing and/or use of antimicrobial mouthwash (Haps et al-2008). Inability for daily practice of good oral hygiene due to poverty, military deployment or general lack of compliance, are further reasons for the development of a chewing gum that would assist with daily oral care and reduction of oral plaque.

5.3 Background

The discovery of a large number of naturally occurring invertebrate and vertebrate antimicrobial peptides has resulted in the emergence of alternative classes of peptide antimicrobials that exhibit selectivity for prokaryotes and minimize problems of inducing microbial resistance (Boman-1998; Gilmore et al-2009; Hancock and Chapple-1999; Hancock and Lehrer-1998; Hancock and Sahl-2006; Nizet et al-2001; Zasloff-2002; Zhang and Falla-2009). In general, antimicrobial peptides are cationic amphiphilic molecules that can be categorized into different

structural groupings (Hancock-1997; Hancock et al-1995; Hancock and Lehrer-1998; Henderson et al-1998):

- Cysteine-rich, amphiphilic β-sheet peptides (α- and β-defensins, protegrins, and tachyplesins)
- Cysteine-disulfide ring peptides with or without amphiphilic tails (bactenecin, ranalexin, and brevinins)
- Amphiphilic α-helical peptides without cysteine (magainins and cecropins)
- Linear peptides (Bac 5, Bac 7, PR39, and indolicidin) with 1 or 2 predominant amino acids (proline or tryptophan)

While more potent antibiotics exist, antimicrobial peptides exhibit pronounced cidal activity against some significant antibiotic-resistant bacterial pathogens found in medical treatment facilities (eg *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococci*). Bacterial killing by antimicrobial peptides is thought to begin when the positively charged peptides interact with the negatively charged components of microbial membranes including lipopolysaccharides in gram-negative bacteria and teichoic acid in gram-positive bacteria as a result of electrostatic interactions. The bound peptides then cause membrane destabilization through pore/channel formation or by exerting a detergent-like action. This destabilization is followed by subsequent changes of membrane permeability and the loss of membrane integrity leading to cell death (Hancock-1997; Hancock and Chapple-1999; Hancock and Lehrer-1998; Koczulla and Bals-2003; Patrzykat and Douglas-2005; Yount and Yeaman-2005; Zasloff-2002).

In other cases, peptides can enter the cell without damaging the membranes (ie the non-membrane effects of cationic peptides). Once within the cell, they may disturb intracellular bacterial functions such as DNA and/or protein synthesis or interfere with vital housekeeping cell functions such as chaperone-assisted protein folding (Otvos et al-2000; Patrzykat and Douglas-2005; Patrzykat et al-2002). Further, some of these peptides also possess other biologic activities that can impact cell proliferation, immune induction, cytokine release, chemotaxis, and tissue repair (Bateman et al-1991; Elsbach-2003; Koczulla and Bals-2003; Koczulla et al-2003).

Acquired resistance toward antimicrobial peptides is uncommon (Boman-1998; Hancock and Chapple-1999; Hancock and Lehrer-1998; Koczulla and Bals-2003; Nizet et al-2001; Yeaman and Yount-2003; Zasloff-2002), though some bacterial strains are naturally resistant to certain antimicrobial peptides (Peschel et al-1999). Resistance mechanisms, if developed, may include: reductions in transmembrane potential with a concomitant decrease in the attraction of cationic peptide antimicrobials (Yeaman et al-1998), sequestration of peptide antimicrobials by cell surface-associated anionic exopolysaccharides (Friedrich et al-1999), microbial degradation of peptides (Guina et al-2000), modification of the cytoplasmic membrane by a decrease in anionic phospholipid levels (Dorrer and Teuber-1977), and efflux of peptide antimicrobials (Bengoechea and Skurnik-2000). However, the fact that naturally occurring antimicrobial peptides have been conserved and remained functional throughout evolution is a strong testament to their efficacy and importance as effectors of innate defense (Peschel et al-1999; Yount et al-2006; Yount and Yeaman-2005).

Many synthetic analogs have been created in attempts to improve the antimicrobial activity of some of the naturally occurring antibacterial peptides. Some such as Dhvar 5, an analog of histatin 5, one of the antimicrobial histatin peptides derived from saliva (Helmerhorst et al-1999; Mickels et al-2001) and IB-367, an analog of protegrins, the antimicrobial peptides that were isolated from porcine leukocytes, are more effective in inhibiting bacterial growth and are easier to synthesize than their native counterparts.

5.4 Name and Description of the Investigational Product

The drug product, Antiplaque Chewing Gum (APCG), contains the active ingredient, KSL-W which is a cationic antimicrobial decapeptide. (KSL-W is $C_{68}H_{106}N_{16}O_{10}$). The KSL-W dose formulation of the APCG being used in this clinical trial is 30 mg (active).

Other components of the APCG are cetylpyridinium chloride (CPC) as an additive, isomalt as a bulk sweetener, peppermint powder for flavoring, sucralose as an intense sweetener, colloidal silicon dioxide as a flow enhancer, magnesium stearate as a process aid, and the proprietary gum base formulation produced by Fertin Pharma A/S.

KSL-W is synthesized by standard solid-phase procedures using 9-fluorenylmethoxycarbony1 (Fmoc) chemistry on a semi-automatic peptide synthesizer. The synthetic peptides are purified by reverse-phase high-performance liquid chromatography using a reverse phase C18 media. The bulk drug substance is stored in lyophilized form at -20°C until formulation of APCG (KSL-W IB 2016).

Refer to section 7.4 for additional information.

5.5 Summary of Nonclinical and Clinical Trials

5.5.1 Nonclinical Studies

The following studies, with study numbers in parentheses, were conducted by or sub-contracted through WIL Research Laboratories, LLC to evaluate the toxicity potential of KSL-W, when co-administered with CPC in non-clinical laboratory studies. The ratio of 8:1 (KSL-W:CPC) was selected for the animal studies because it demonstrated the most effective bactericidal activity in pre-formulation and bactericidal experiments. Where appropriate, the studies included separate KSL-W and CPC groups.

- A 5-Day Repeated-Dose Oral (Gavage) Toxicity Range Finding Study of in Rats (WIL-485012)
- A 28-Day Oral (Gavage) Toxicity Study in Albino Rats (WIL-485005)
- A 5-Day Oral (Gavage) Repeated Dose Study in Beagle Dogs (WIL-485003)
- A 28-Day Oral (Gavage) Toxicity Study in Beagle Dogs (WIL-485006)
- A 7-Day Repeated-Dose Gingival Mucosal Tolerance Study in Beagle Dogs (WIL-485016)
- Genetic toxicology testing (WIL-485007)

  - Ames Test (WIL-485007-l)
  - Mouse Lymphoma Assay (WIL-485007-2)
  - Chromosome Aberration (CA) Assay (WIL-485007-3)
  - Micronucleus Test (WIL-485007-4)
- Immunogenicity Testing (WIL-485008)
- KSL-W Bioanalytical method validation (WIL-485009)
- CPC Bioanalytical method validation (WIL-485010)
- Method validation for determination of KSL-W and CPC in aqueous formulations (WIL-485011)

The highlights from these studies are as follows:

- KSL-W, when tested in the presence of CPC at a ratio of 8:1, was not genotoxic in four different tests (Ames test, mouse lymphoma assay, CA, and micronucleus test).
- KSL-W was found not to be immunogenic. Efforts at developing an assay for anti-KSL-W antibodies were eventually ceased.
- KSL-W was found to degrade very rapidly even in chilled plasma; as a result, efforts at developing a bioassay for the presence of KSL-W in plasma were eventually dropped. As a decapeptide, it can be anticipated that KSL-W would be rapidly degraded by natural enteric digestion. When administered in a slow release buccal preparation, such as a chewing gum, it can be anticipated that the systemic exposure to KSL-W would be very low, if not non-existent.
- No gross evidence of irritation was observed when KSL-W and CPC were applied to the gingival tissue of beagle dogs
- In a 28-day rat study, the No Observed Adverse Effect Level (NOAEL) was 32/6.4 mg/kg/day (KSL-W/CPC), while at 320/64 mg/kg/day (KSL-W/CPC) potential adverse effects were characterized by rales, slightly decreased body weight gain and small changes in clinical pathology. In a 28-day dog study, the NOAEL was found to be 60/7.5 mg/kg/day (KSL-W/CPC), while effects at 200/25 mg/kg/day (KSL-W/CPC) were characterized by excessive salivation, abnormal excreta, slightly lower body weight gain, and minor non-adverse clinical pathology findings. Given that there was no systemic exposure to KSL-W in these studies, while there was proven systemic exposure to CPC, it can be assumed that all the relatively minor findings in the mammalian toxicity studies were due to CPC and not to the KSL-W.

In general, the studies conducted thus far indicate that KSL-W, when administered in the presence of CPC, is not genotoxic, is not antigenic, does not cause localized buccal irritation and is not systemically observed to any appreciable extent.

5.5.2 Clinical Studies

Oral Health Research Institute Indiana University School of Dentistry in Indianapolis, Indiana conducted the first APCG trial in humans entitled: "A Double-Blind, Randomized, Controlled,

Dose Escalation Clinical Trial of an Antiplaque Chewing Gum - Phase 1 Safety and Tolerability and Phase 2a Safety, Tolerability and Proof of Concept in a Gingivitis Population." The study was a 2-part trial with 9 dosing cohorts in Phase 1 (2-100 mg) and 7 dosing cohorts in Phase 2a (4 -75 mg). Dosing began with 2 mg and increased sequentially. The safety of each dose was evaluated prior to administering the next higher dose. Subjects in the Phase 1 portion of the study received a single dose of the study medication. Subjects in the Phase 2a portion of the study received multiple oral doses over 28 days.

The proof of concept analyses in the Phase 2a portion of the study indicate APCG efficacy against plaque formation after 2-4 weeks of active treatment. Results regarding gingivitis were not as consistent across the active treatment doses.

No deaths or other serious adverse events (SAEs) occurred in either the placebo- controlled, single dose escalating (2, 4, 6, 10, 20, 30, 50, 75, or 100 mg) phase or the placebo- controlled, 28 day, multiple-dose (4, 6, 10, 20, 30, 50, or 75 mg) phase of the study.

All 71 subjects enrolled in the escalating, single-dose phase completed the study. A total of 10 adverse events (AEs) were reported: [6 in the APCG group (abdominal discomfort, dyspepsia, mouth swelling, increase in blood pressure, headache and throat irritation) and 4 in the placebo group (mouth ulceration, muscle strain, oral mucosal erythema, musculoskeletal stiffness). All AEs in both groups were considered mild.

Sixty-four subjects were enrolled in the 28-day, multiple-dose Phase 2a study and 58 subjects completed the study per protocol. For the active treatment group, 5 of 45 subjects who received at least one of the active treatment doses withdrew or were withdrawn from the study. The reasons for withdrawal of these 5 subjects were: lost to follow-up (1), protocol violation (1 - antibiotic use), and subjects' request [change of job (1), need to be out of town (1) and religious purposes (1)]. For the placebo group, 1 of the 19 subjects receiving placebo treatment withdrew, due to a family emergency.

There were a total of 54 AEs in the multiple-dose study phase of which 45 were considered mild, 9 were considered moderate, and none were considered severe. AEs reported once for the lower-dose active treatment groups (4 mg, 6 mg, 10 mg, 20 mg, 30 mg) included: abdominal discomfort, dyspepsia, flatulence, food poisoning, gingival ulceration, mouth hemorrhage, mouth ulceration, oral pain, ear infection, sinusitis, mouth injury, muscle strain, thermal burn, increase in blood glucose, glucose in urine, headache and oropharyngeal pain. In addition, oral mucosal erythema and nasopharyngitis were reported twice for the lower-dose active treatment groups. The higher dose treatment groups (50 mg, 75 mg) had 3 reports of tongue coated with 50 mg, and 2 reports of tooth discoloration with both the 50 and the 75 mg doses. The 50 mg dose also had 2 reports of dysgeuia,

1 report of food poisoning and 1 report of arthropod bite. The 75 mg dose had 3 reports of nasopharyngitis and dysgeuia as well as 1 report of abdominal discomfort, coating in mouth, tongue pigmentation, ageusia and throat tightness.

From a review of all the AEs reported in Phase 2a, the following types of AEs were found to be possibly, probably or definitely related to study drug: abdominal discomfort, tongue coated, tooth discoloration, flatulence, dysgeusia, tongue pigmentation, throat tightness and ageusia. All

of these AEs were mild in intensity with the exception of 1 incidence of tongue coated which was deemed moderate in intensity.

The clinical findings of altered taste perception, signs of teeth staining and brown coating on the dorsum of the tongue reported at the higher doses of 50 mg and 75 mg are mainly of esthetic concern and are commonly observed with the extended use of currently marketed antimicrobial mouth rinses and are not considered to be a health risk.

There were no study-related laboratory findings, notable vital signs, or physical examination findings, or other observations that were considered to be of clinically signification in either the single-dose or multiple-dose phases of the study (Clinical Study Report #S-11-14, Listing 19).

5.5.3 Rationale for Four Day Proof of Concept Study

The primary objectives for the Phase 1/2a study were to evaluate the safety and tolerance to the active gum. In the Phase 2a study, the proof of concept efficacy assessment for plaque accumulation and changes of gingivitis conditions were included and the assessments occurred on Days 0 (baseline), 14, 28 and 34 (follow-up). The rationale for conducting a 4-day treatment study is to determine if the active gum (vs. placebo gum) can reduce plaque regrowth during early time points (4 days).

5.6 Known and Potential Risks and Benefits to Human Subjects

5.6.1 Risks/Discomfort to Subjects and Precautions to Minimize Risk

Outlined below are anticipated and unexpected adverse reactions, and a brief description of procedures to ameliorate risks and symptoms. All known risks and precautions described here are explained in detail in the informed consent.

5.6.1.1 Local Reactions

Subjects participating in this study are at risk for local reactions such as: coated tongue, tooth discoloration, dysgeusia, tongue pigmentation, throat tightness and ageusia. Subjects with known TMD will not be enrolled in the study, and subjects will receive oral examinations throughout the study. In the first Phase 1/2a trial, altered taste perception, brown coating on dorsum of the tongue and teeth staining were noted at the higher doses of 50 mg and 75 mg.

5.6.1.2 Systemic Reactions

Based on review of the nonclinical data, no direct systemic AEs from administration of the study drug are expected. Review of the clinical data indicates that subjects participating in this study may experience: abdominal discomfort and flatulence. Subjects will be asked at each visit to report any new symptoms or concomitant medications used.

5.6.1.3 Pregnancy

Risks to unborn babies are unknown at this time. Pregnant females will be excluded from this study. Female subjects should not become pregnant for at least 3 months after receiving the last dose of investigational product. Male subjects should not have unprotected sex for at least 3 months after receiving the last dose of investigational product.

5.6.1.4 Lactation

Risks to nursing infants are unknown at this time; breastfeeding females will be excluded from this study. Lactating females must agree not to breast feed while on the study and for 3 months after the last dose of investigational product.

5.6.1.5 Allergic Reaction

As with any Investigational New Drug (IND), product administration, no matter what precautions are taken, there is always the risk of a serious, or even life-threatening, allergic reaction. Medical emergency equipment is available on site at Salus Research to handle emergencies, such as anaphylaxis, angioedema, bronchospasm, and laryngospasm.

5.6.1.6 Unknown Risks

Furthermore, as with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

5.6.2 Alternatives to this IND Product or Study

The alternative to using this IND Product is to not participate in the study and for the subject to practice normal oral hygiene procedures.

5.6.3 Intended Benefit for Subjects

There is no intended benefit to the subjects in this research study; however, subjects will receive oral soft tissue (OST) and oral hard tissue (OHT) examinations as part of the periodontal examination and all subjects will have their teeth polished following randomization.

5.6.4 Risks to the Study Personnel and the Environment

The principal risk in the clinical setting is similar to those in any medical or dental clinic. Adherence to standard operating procedures (SOPs) for working with dental patients and universal precautions will reduce the risk of exposure to blood.

There are no known risks to the environment other than those associated with the generation of biohazardous waste attendant to dental procedures in humans. All biohazardous waste will be disposed of as stipulated by local, state, and Federal regulations and in accordance with study site SOPs.

5.7 Route of Administration, Dosage Regimen, Treatment Period, and Justification

A total of 26 subjects will participate in the study in order to obtain 24 completers. Thirteen (13) subjects will receive KSL-W and 13 subjects will receive placebo in accordance to the randomization schedule. Subjects will receive 30 mg multiple oral doses of KSL-W chewing gum or placebo chewing gum in tablet form over the course of 4 days. The 30 mg dose was selected based on the "Day 14 change in plaque index" data from the "Phase1/2a Dose Escalation Study of an Antiplaque Chewing Gum Study." Each dose consists of 1 piece of gum in tablet form. Subjects who drop out of the study will not be replaced.

Subjects will receive the first dose of chewing gum under supervision in the clinic. The remaining 11 doses will be self-administered and unsupervised. These unsupervised gum chews

should occur preferably after a meal or at 4-6 hour intervals 3 times a day for a total of 4 days. The gum will be chewed for 20 minutes and chewing will be balanced as equally as possible between both sides of the mouth. The maximum dose of KSL-W in a 24 hour period is three 30 mg chewing gum tablets (90 mg total). Subjects will be instructed to use the same chewing procedure for each self-administered, unsupervised chew.

5.8 Compliance Statement

The study will be conducted according to the protocol and in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP), Belmont Principles, and other applicable regulatory and Department of Defense (DoD) requirements. All identified study personnel will be trained to perform their roles and will carry out their responsibilities in accordance with ICH GCP guideline and clinical site SOPs. Roles and responsibilities of study staff are presented in Appendix A.

5.9 Study Population

It is anticipated that approximately 35 subjects will be screened for study participation. The study population will be comprised of 26 males and females (on contraceptives or postmenopausal) between the ages of 18 and 64 (inclusive). Subjects will be generally healthy, without organ system diseases. Refer to Section 12.2 for a justification of the sample size.

5.10 Study Site

The study will be conducted at Salus Research located at 1220 Medical Park Drive, Bld#4, Fort Wayne, IN 46825. The Fort Wayne, Indiana Metropolitan Statistical Area (MSA) is a federally designated metropolitan area consisting of three counties in northeastern Indiana (i.e. Allen, Wells and Whitley counties), anchored by the city of Fort Wayne. As of the 2010 census, the MSA had a population of 416,257. The Fort Wayne metropolitan area is part of the Northern Indiana region where approximately 2.2 million people live (Fort Wayne 2016). This region is considered part of the Great Lakes Megalopolis with an estimated population of 59 million people. Study subjects will be recruited from the Salus Research Categorized Database.

6 Trial Objectives and Purpose

6.1 Primary Objectives

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 to a placebo formulation.

6.2 Secondary Objectives

The secondary objectives are to assess the proof of concept (efficacy) of:

- KSL-W (30 mg dose) delivered in a chewing gum formulation compared to a placebo formulation in the change in plaque regrowth from baseline based on the QHT

- 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.

7 Trial Design

7.1 Study Measurements (Endpoints)

The primary endpoint is:

- Incidence of AEs including change from baseline in vital signs

The secondary endpoints are:

- Change from baseline in QHT (Day 4 QHT minus baseline QHT)
- QHT based on sub-scores from designated regions of the mouth (upper jaw, lower jaw, buccal and lingual surface

7.2 Overall 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. The study will evaluate the ability of APCG to reduce existing supragingival plaque. Plaque will be assessed using the QHT (Turesky et al-1970).

The OST and OHT will be examined. Changes from baseline, such as soft tissue erythema, ulceration and sloughing, will be noted and assessments will be made by the principal investigator or designee as to whether these events are related to treatment with APCG.

The study design is illustrated in Table 3 and is detailed below. The Study Event Schedule is presented in Table 4.

Table 3: 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 4: Study Events Schedule

	Study Visit/Day					
	Visit 1	**Visit 2**				**Visit 3**
	Screening (-16 to -1)	**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).

7.3 Measures Taken to Minimize/Avoid Bias

7.3.1 Randomization

The random assignment of subjects to the 2 study arms will be 1:1. There will be 2 evaluators at the study site to assess the QHT scores, and the evaluator assigned to each subject will remain with that subject throughout the study. The randomization schedule will be generated by an independent biostatistician not involved in any way with the conduct and analysis of the study. The randomization schedule will be provided to designated study personnel for preparation of the blinded product and for emergency unblinding for safety reasons if necessary.

7.3.2 Blinding

For this double-blind study, the investigator, study biostatistician, staff not involved in product preparation and study subjects will be blinded to the treatment assignments throughout the duration of the study. A study specific procedure explaining the blinding and unblinding plan will be developed and maintained by appropriate study team members.

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

7.3.3 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: Carrie Laurencot, PhD Acting-Director, Clinical Services Support Division

  Phone: 301-619-0317

7.3.4 Calibration Exercise and Repeatability of Plaque Assessments by Evaluator

The dental examiners (evaluators) must have completed the standard calibration exercise and repeatability procedure on the QHT prior to the conduct of this study. The statistical report containing the results of this exercise and procedure will be written prior to conduct of the study and maintained on file as documentation that all evaluators can conduct the QHT scoring in a consistent manner and any differences between evaluators would be negligible.

7.4 Investigational Product

Table 5 shows a description of the investigational product and the placebo to be used in this study. The active ingredient is KSL-W. The other materials contained in the product (CPC, an isomalt additive, peppermint powder, and sucralose) meet United States Pharmacopeia/National Formulary specifications and are listed on the Food and Drug Administration's (FDA) Inactive Ingredient Guide for oral formulations. Each tablet of gum is at the defined formulation. The placebo chewing gum will be identical in appearance and will differ only in the amount of active ingredient (KSL-W) and isomalt.

Table 5: Description of Investigational Product and Placebo

Product Name	**Antiplaque Chewing Gum**	**Placebo**
Dosage Form	Chewing gum	Chewing Gum
Unit Dose	30 mg	0 mg
Route of Administration	Oral	Oral
Physical Description	White to yellowish, round compressed tablet	White to yellowish, round compressed tablet
Manufacturer	Fertin Pharma	Fertin Pharma
Lot Number	3925-273	3925-267
Product Indication	Reduction of plaque and gingivitis	None

7.4.1 Investigational Product Packaging and Labeling

The APCG and placebo products are supplied in bulk. Each opaque plastic vial (Activ-Vial®) contains 20 pieces of gum and a desiccant. Each vial is labeled for human administration and includes the following statement: "Caution: New Drug – Limited by Federal (or U.S.) Law to Investigational Use." Figure 2 and Figure 3 display the representative vial labels for 30 mg KSL-W and Placebo, respectively.

Figure 2: Representative Bulk Antiplaque Chewing Gum Vial Label: KSL-W

Antiplaque Chewing Gum (APCG), 30 mg KSL-W, 20 pcs
Lot Number: 3925-273
Contains: 30 mg KSL-W Storage: 2-8°C
Caution: New Drug – Limited by Federal (or United States) law to investigational use.
MFG Date: 22Nov2012
Manufactured by: Fertin Pharma, Vejle, Denmark

Figure 3: Representative Bulk Antiplaque Chewing Gum Vial Label: Placebo

Antiplaque Chewing Gum (APCG), Placebo, 20 pcs
Lot Number: 3925-267
Contains: 0 mg KSL-W Storage: 2-8°C
Caution: New Drug – Limited by Federal (or United States) law to investigational use.
MFG Date: 19Nov2012
Manufactured by: Fertin Pharma, Vejle, Denmark

7.4.2 Investigational Product Storage

The study drug is manufactured in accordance with Good Manufacturing Practices (GMP) by Fertin Pharma. Fertin Pharma will ship the product to Salus Research under refrigeration (2-8°C or 35.6 - 46.4°F) in opaque plastic vials (Activ-Vial®). At the site, the gum will be stored at 2-8°C or 35.6 - 46.4°F). A Temperature log will be maintained at the site and checked during site visits by the sponsor's clinical study monitor.

The product may be removed from the temperature-controlled environment and maintained at room temperature conditions, defined as the prevailing temperature in a working area (approximately 20-25°C or 68-77°F), during certain periods during the study: preparation of dose administration at the clinical site, and packaging and storage for unsupervised doses while in the subjects' possession (unsupervised chews).

7.4.3 Investigational Product Preparation

Each of the APCG and placebo products will be provided as a ready-to-use piece of gum from the manufacturer. The product will be repackaged into a new vial for each subject. Each blinded vial will contain 14 pieces of gum, either active or placebo that will be prepared according to the randomization schedule in order to maintain the double-blind nature of the study. Preparation of the subject's vials with their assigned doses will be performed ahead of time at room temperature and then returned to refrigeration (2-8°C or 35.6 - 46.4°F) for storage until dispensed to the subject.

Approximately one (1) hour prior to dispensing, the subject's vial of blinded study product will be removed from refrigerated storage to allow time for the product to come to room temperature. For the first chew, the assigned study product will be dispensed to the subjects by designated study staff for supervised use at the site. For unsupervised use, enough investigational product will be dispensed to each subject for self-administration during the 4 day study period. Subjects

will be given 2 additional chewing gum tablets, to use if the product is inadvertently lost or misplaced. If the subject needs additional product (ie. more than 2 tablets) they will need to contact Salus Research. The subjects will be instructed on proper storage of the study product.

7.4.4 Investigational Product Accountability

The sponsor's representative is responsible for distributing the investigational product to the study site and has ultimate responsibility for accountability of study drug. The sponsor's representative has delegated the drug accountability responsibility for this product to the Principal Investigator. The Principal Investigator may delegate in writing this responsibility to another individual, but the Principal Investigator is ultimately responsible for the investigational product and its proper storage from the time the investigational product arrives at the study site until it is returned to the sponsor's representative or designee or is destroyed, as directed by the sponsor's representative. Drug accountability will be conducted once the site receives the investigational product. The Principal Investigator or designee, will maintain logs of storage, drug accountability by subject, including dispensed product, and product remaining before final disposition within Salus Research. In the event of a temperature excursion, the Principal Investigator should contact the Sponsor Representative, who will make the determination of the product's integrity and use.

Used investigational product will be collected by study staff during the supervised time (first chew) at the site on Day 0. For each of the unsupervised doses, subjects will be instructed to collect the used product in individually labeled bags (Figure 4) and return them to the site at Visit 3 (Day 4). A total of 11 bags of used investigational product will be returned at Visit 3. If a subject forgets to return the used product, they will be asked to make arrangements to return the used product bags to the site. Subjects will also be instructed to return any unused product resulting from missed doses. Unreturned used and unused product (missed dose) will be considered protocol deviations.

Used product and unused product will be verified by the sponsor's study monitor and then destroyed in accordance with site SOPs for destruction of study drug as directed by the sponsor's representative and as stipulated by institutional, state, and Federal regulations.

Figure 4: Example Label for Used Product Bags

Subject Number:

Date and Time of Chew:

Caution: New Drug - Limited by Federal (or United States) law to 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

7.5 Duration of Subject Participation

Each subject will participate for up to 21 days; screening, 4 days of treatment followed by 1 day for dental evaluation and end of study activities.

7.6 Dose-adjustment Criteria

For this study, dose adjustments will not be made other than to discontinue the use of study medication if the situation warrants.

7.6.1 Safety Criteria for Dose Adjustment or Stopping Doses

This section is not applicable.

7.6.2 Pharmacokinetic Criteria for Dose Adjustment or Stopping Doses

This section is not applicable.

7.6.3 Study Termination Criteria

The Principal Investigator, research monitor, sponsor's representative, the IRB and/or the United States Army Medical Research and Material Command (USAMRMC) Office of Research Protections, Human Research Protection Office or the FDA may stop or suspend the use of this product at any time.

7.7 Trial Treatment Randomization Codes

Subject ID numbers will be assigned in ascending numerical order as each subject signs the consent form. The Subject ID numbers will be assigned from one centrally located pre-printed list.

Each subject who meets the inclusion and exclusion criteria and is deemed fully eligible will be assigned a unique randomization number. The randomization numbers will be on the randomization list, generated by the independent unblinded biostatistician. The randomization numbers will be assigned to subjects sequentially as they are randomized at Visit 2.

7.8 Identification of Data to be Recorded on the Case Report Forms

All eCRF data will be transcribed from subject's source records. For more information on data handling, refer to section 16.

8 Selection and Withdrawal of Subjects

8.1 Recruitment of Subjects

Salus Research is located in Fort Wayne, Indiana. Salus Research expects to recruit from a subject population in the surrounding Fort Wayne area. Based on the site's vast experience with dental trials and database of potential participants, it is estimated that 35 subjects will need to be screened in order to obtain 26 subjects eligible for randomization.

The staff at Salus Research will be trained on the details of the protocol and will have the responsibility to identify potential study participants. A recruitment plan based on the inclusion/exclusion criteria of the study will be developed and submitted to the U.S. Investigational Review Board for approval. Salus Research will recruit subjects from their Salus Research Categorized Database of past study participants. After the IRB has approved the protocol and the study initiation visit has been completed, prospective subjects will be contacted by the study staff via telephone. These prospective subjects will be provided the study dates and, if interested, the inclusion and exclusion criteria from the protocol will be reviewed. Once this is complete and they are still interested, they will be scheduled for the Screening Visit.

8.2 Eligibility Screening

Each subject must satisfy all inclusion and exclusion criteria. During screening, the following assessments will be conducted: physical examination, urine drug screen, medical history, periodontal examination, OHT and OST examinations, oral hygiene check, plaque index measurement and vital sign measurements. Females of child-bearing potential must have a negative urine pregnancy test result at screening (14±2 days prior to randomization) in order to participate and must agree to use a reliable form of birth control throughout the duration of the study. The Principal Investigator or designee will make the final decision regarding the eligibility of the subject. Only eligible subjects will be given the investigational product.

8.2.1 Subject Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study:

I01 Males or females between 18 and 64 years of age (inclusive at time of screening)

I02 A negative urine pregnancy test (females of childbearing potential only)

I03 A negative urine drug test

I04 On a reliable form of birth control for at least 30 days prior to the start of the study and willing to use a reliable form of contraception for the duration of the study (Females of childbearing potential only), with reliable contraception defined as:

- Abstinence which has been the customary lifestyle of choice
- Oral contraceptive, either estrogen progesterone combined, or progesterone alone

- Injectable progesterone
- Implants of levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device or intrauterine system
- Double barrier method [condom or occlusive cap (diaphragm or cervical vault caps) plus spermicidal agent (foam, gel, film, cream, suppository)]
- Male partner sterilization at least 6 months prior to the female subject's entry into the study, and this male is the sole partner for that subject
- Post-menopausal for at least two years

I05 Good health, as determined by pertinent medical history, physical examination, and vital signs.

I06 A minimum of 20 natural teeth with 6 scorable surfaces per tooth

- Sufficient number of opposing posterior teeth to chew on both sides of the mouth as determined by the examining dentist
- Teeth that have gross caries, full crowns or extensive restorations on facial and/or lingual surfaces, orthodontic bands, and third molars are not included in the tooth count

I07 Subject must have refrained from all oral hygiene procedures 12 to 16 hours prior to screening visit.

I08 Plaque Index of 1.95 or greater (Turesky et al-1970)

I09 Willing to forgo any optional dental procedures during the study period, such as dental prophylaxis or teeth whitening.

I010 Ability to comprehend and a willingness to sign an informed consent, which includes the Authorization for the Release of Health Information document.

I011 Ability to access the internet to complete the drug compliance information

I012 Willingness to comply with all study procedures

8.2.2 Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

E01 Phenylketonuria

E02 Acute or chronic medical conditions, organ system disease, or medications that, in the principal investigator's opinion, would impair the subject's ability to participate

E03 TMD

E04 Self-reported allergy to sucralose or mint flavors

E05 Self-reported use of tobacco products including e-cigarettes

E06 Use of any type of anticoagulant medications (eg clopidogrel)

E07 Routine use of proton pump inhibitors

E08 Allergic to any component of the study drug

E09 Gross oral pathology, including widespread caries or chronic neglect, extensive restoration, pre-existing gross plaque or calculus, or soft or hard tissue tumor of the oral cavity

E010Orthodontic appliances or removable partial dentures that will compromise the ability of the potential subject to participate in the study

E011Periodontitis as indicated by periodontal pockets greater than 4 millimeters on more than one site

E012 Receipt of any investigational drug/test product within 30 days prior to study entry with study entry defined as Day 0, or currently participating in either the active or follow-up phase of any other investigational study or planning to participate in any other investigational study during participation in this trial

E013 Participation in the Phase 1/2a antiplaque study

E014 Receipt of antibiotics within 30 days prior to study entry

E015 Need for antibiotic prophylaxis prior to invasive dental procedures

E016 Receipt of prescription antibacterial oral products (eg products containing chlorhexidine) within 30 days prior to study entry

E017 Pregnant or breast-feeding female

E018 An employee of the study site directly involved with the study

E019 Inability to comply with assigned treatment regimen

8.3 Subject Withdrawal Criteria

A subject may withdraw consent at any time during the study without penalty. The PI may discontinue the subject's activity without the subject's consent if any of these criteria is met:

- A subject fails to comply with study procedures
- A subject's safety or health may be compromised by further participation

8.3.1 When and How to Withdraw Subjects

A subject may end his or her participation in the study at any time. If a subject withdraws, the Principal Investigator will make a reasonable effort to determine the reason for the withdrawal from the study and to complete termination procedures as described in section 8.5.2 and section 8.5.4. Telephone calls, registered letters, and email correspondence are considered reasonable

effort. For subjects leaving the study, a targeted examination may be performed, if medically indicated and if permitted by the subject.

A subject may be withdrawn for an AE or SAE resulting in a safety concern. When a subject withdraws due to an AE or is withdrawn by the principal investigator due to an AE, the sponsor's safety office, the USAMRMC Clinical Services Support Division (CSSD), Product Safety Surveillance Branch (PSSB), must be notified within 72 hours (usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil). The Principal Investigator must follow specific policy regarding the timely reporting of AEs and SAEs to the US Investigational IRB as the IRB of record (section 11.5.1.2). In all cases, the Principal Investigator will make a reasonable effort to complete study termination procedures.

If a subject meets withdrawal conditions for a concomitant medication violation or noncompliance, this should clearly be stated in the source document and the study termination eCRF.

8.3.2 Data Collected for Withdrawn Subjects

All data collected up to the time of withdrawal will be reported. The reason for withdrawal will be specified in the eCRF.

8.3.3 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

8.3.4 Follow-up for Withdrawn Subjects

Salus Research will attempt to contact any subject who withdraws from the study in an effort to determine the reason for withdrawal as well as to schedule a visit to conduct the study termination procedures (Visit 3). Reasonable effort will be made to complete final study documents.

9 Treatment of Subjects

9.1 Study Visits

9.1.1 Screening (Day -16 to -1) – Visit 1

Potential subjects will arrive at Salus Research and the informed consent process will proceed. After the informed consent document and the Authorization for the Release of Health Information (HIPAA) document are signed, the following procedures will occur:

- Inclusion and exclusion criteria will be evaluated
- A medical history with demographic information will be collected
- Vital signs (diastolic and systolic blood pressure, heart rate, respiration rate and temperature) will be collected
- A physical examination will be performed
- A urine drug screen will be performed
- Females of childbearing potential will take a urine pregnancy test
- A periodontal exam will be performed. This exam will include a determination of the number of teeth, scorable surfaces and pocket depths around teeth
- An intraoral examination (OST and OHT) will be performed
- Oral hygiene check - Subjects must have refrained from oral hygiene procedures (flossing, brushing of teeth, mouth wash rinse) for 12 to 16 hours prior to the screening visit.
- Supragingival plaque will be assessed using the QHT. (A red food dye will be used to disclose plaque deposits.)
- Concomitant medications will be recorded

A subject is not considered enrolled in the study until it is determined that he or she satisfies all of the inclusion and exclusion criteria (section 8.3 and section 8.4).

9.1.2 Supervised Treatment, Study Day 0 (Baseline) – Visit 2

After the screening period, those subjects who are eligible for participation will return to the clinic for Visit 2 (Day 0 baseline). The following procedures will occur:

- The inclusion and exclusion criteria will be re-checked
- Vital signs (systolic and diastolic blood pressures, heart rate, respiration rate and temperature) will be measured
- Intraoral exam (OST and OHT) will be conducted
- Oral hygiene check: The subject will be asked to confirm that he/she did not perform any oral hygiene procedures (flossing, brushing of teeth, mouth wash rinse) for 12 to 16 hours prior to Day 0.
- Randomization (1:1)
- Supragingival plaque will be assessed using the QHT. (A red food dye will be used to disclose plaque deposits.)

- Licensed dental hygienist will polish teeth.
- The first chew will be administered under supervision in the clinic. The subject will be instructed to chew one tablet of gum for 20 minutes. Chewing should be balanced as equally as possible between both sides of the mouth.
- After chewing the gum for the designated time, the subject will be given a used product bag to store the chewed gum. The evaluator will inform the subject to label this bag with the time and date of the chew.
- After the chewing gum is stored in the used product bag, the subject will complete the start and stop times for chewing gum on the electronic diary information system (ePRO). The subject will enter this information while in the clinic.
- The study drug will be dispensed for unsupervised use. The subject will receive:
    - 13 gum tablets for their unsupervised use along with 13 individual used product collection bags.
    - Subjects will be given instructions for chewing the gum.
        a. The gum will be chewed for 20 minutes preferably after a meal or every 4 to 6 hours (3 times a day). Chewing will be balanced as equally as possible between both sides of the mouth for a maximum of 3 chews per day.
        b. After completing each 20 minute chew, subjects will store the used gum in the used product collection bags provided to them.
        c. Subjects will label each used product collection bag with the date and time of chew. (A separate bag will be used for each chew).
        d. After each chew, subjects will record the start and stop time of the chew on the electronic diary information system - ePRO (Instructions provided in Appendix D)
        e. Subjects will be informed that they must bring all of the used product collection bags back to the clinic for Visit 3
- Subjects will be told that no oral hygiene procedures of any kind (teeth brushing, flossing or mouth wash rinse) will be allowed while on study treatment (Day 0, 1, 2, 3 and 4).
- AEs from first chew will be collected.
- Concomitant medication will be recorded.

9.1.3 Unsupervised Treatment, Study Days 0, 1, 2, and 3

After the first supervised chew is completed, the subjects will be released from the clinic. There will be a total of 11 unsupervised, self-administered chews. The subjects will chew one tablet of the gum (study drug) for 20 minutes every 4 to 6 hours, preferably after a meal, for a maximum of 3 chews per day according to the schedule in Table 6.

Table 6: Schedule for Unsupervised Chews:

Time[a]	Day 0	Day 1	Day 2	Day 3
After Breakfast [b]	N/A	1	1	1
After Lunch	1	1	1	1
After Dinner	1	1	1	1
Total Chews per Day	2	3	3	3

[a] Gum will be chewed for 20 minutes preferably after a meal 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.

[b] First chew takes place in the clinic.

After completing each 20 minute chew, the subject will store the used gum in the used product collection bags provided to them. The subject will record the date and time of chew on the individual collection bags as instructed. A separate bag will be used for each chew. Subjects will record their chewing gum start and stop times on the electronic diary system (ePRO) after each chew.

9.1.4 Treatment, Study Day 4 – Visit 3

After 4 days of treatment, subjects will return to the clinic for Visit 3. The following procedures will occur at Visit 3:

- Subjects will return all used product bags and any unused product. Site Staff will collected used/unused product bags.
- Vital signs (diastolic and systolic blood pressures, heart rate, respiration rate and temperature) will be measured.
- A brief, symptom-oriented physical examination will be performed
- Females of child-bearing potential will take a urine pregnancy test
- Subjects will be asked to verify that he/she has refrained from all oral hygiene procedures (teeth brushing, flossing or mouth wash rinse) since their last chew.
- An intraoral exam (OST and OHT) will be performed.
- Supragingival plaque will be assessed using the QHT. (A red, food dye will be used to disclose plaque deposits on the teeth).
- AEs will be assessed.
- Concomitant medications will be recorded.

- Subject will be discharged from the study. (Subject will be allowed to brush their teeth just prior to leaving the research center is discharged from the study.)

9.4 Concomitant Medications

This protocol places no restrictions on rescue medications.

9.5 Procedures for Monitoring Subject Compliance

The first chew will be administered by the study staff and the chewing will be supervised at the clinic. Subject compliance will be monitored through supervision of the first dose, controlled distribution of product and collection of used product.

For unsupervised dosing, each subject will be provided with bags to collect the used product. Each bag will contain the used product of one chew. The bags (11 total) will be labeled to record product usage. Subjects will return the used product bags to the research center at Visit 3. Subjects will record the start and stop time of each chew on the electronic diary information system.

10 Proof of Concept Assessments

10.1 Supragingival Plaque

Supragingival plaque will be assessed at screening, Day 0 (baseline) and Day 4 using the QHT (Turesky et al-1970). The scoring index is shown below in Table 7 and the calculation is provided in Appendix B.

Table 7: Quigley Hein-Turesky Plaque Index Scores

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin of the tooth
2	A thin continuous band of plaque (up to one mm) at the cervical margin of the tooth
3	A band of plaque wider than one mm but covering less than one-third of the crown of the tooth
4	Plaque covering at least one-third but less than two thirds of the crown of the tooth
5	Plaque covering two-thirds or more of the crown of the tooth

10.1.1 Proof of Concept Measurement (Endpoints)

Two proof of concept endpoints will be assessed based on the QHT. The change in plaque regrowth from baseline as well as the change in plaque regrowth based on sub-scores from specific regions of the upper jaw, lower jaw, buccal and lingual surface.

10.2 Methods/Timing for Assessing, Recording, and Analyzing Proof of Concept Measurements (Endpoints)

The QHT will be measured on Day 0 after randomization. The Day 0 score will be designated as the baseline score. The QHT is measured again on Day 4 after the subjects have completed 4 days of treatment with study drug. The change from baseline to Day 4 in the QHT will be defined as the difference, KSL-W minus placebo.

Proof of concept measurements will also include the change from baseline in plaque regrowth based on sub-scores from specific regions of the upper jaw, lower jaw, buccal and lingual surface based on the QHT.

Refer to Section 12 for statistical details.

11 Safety Assessment

Safety monitoring will be conducted throughout the study; therefore safety concerns will be identified by continuous review of the data by the Principal Investigator, clinical staff, the Sponsor's Clinical Monitor, Research Monitor, and United States Army Medical Material Development Activity (USAMMDA) Clinical Services Support Division (CSSD) Product Safety Surveillance Branch (PSSB). The following data will be monitored: vital signs, physical examinations, and intraoral (OHT and OST) examination.

Study Safety Management: The IRB, Research Monitor, and Principal Investigator will review any safety concern. A data safety monitoring board (DSMB) is not required for this study.

Research Monitor: The Research Monitor will function as an independent safety advocate for subjects per AR 70-25 and DoD Instruction 3216.02. An independent Research Monitor is required to review all unanticipated problems involving risk to subjects or others, SAEs, and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum the Research Monitor should comment on the outcomes of the event or problem and, in the case of a SAE or death, comment on the relationship to participation in the study. The Research Monitor should also indicate whether he/she concurs with the details of the report provided by the Principal Investigator. Reports for events determined by either the Principal Investigator or Research Monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to US Investigational Review Board and/or USAMRMC ORP and USAMRMC CSSD PSSB (sponsor safety office).

USAMMDA Clinical Services Support Division: CSSD is responsible for coordinating and integrating the review of safety data regarding The Surgeon General (TSG)-sponsored products. The PSSB reviews each SAE report for medical consistency, accuracy, and completeness and follows each event until it is satisfactorily resolved. USAMMDA Safety Pharmacovigilance (PVG) physician, as delegated by the Sponsor, evaluates all safety cases and provides the final determination on relatedness to the product, and whether expedited reporting is warranted, per current FDA regulation and guidance.

11.1 Specification of Safety Measurements (Endpoints)

11.1.1 Vital Signs

Vital sign 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.

11.1.2 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.

11.1.3 Intraoral Examination

11.1.3.1 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.

11.1.3.2 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.

11.2 IND Safety Reporting

The following terms, as defined by 21 CFR 312.32, apply to IND safety reporting.

11.2.1 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.

11.2.2 Solicited Adverse Event

This section is not applicable.

11.2.3 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.

11.2.4 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.

11.2.5 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 within 5 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.

11.3 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 DENTIST/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.

11.3.1 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 potentially life-threatening as defined in Table 8. Refer to the FDA guidance for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials in Appendix C for further guidance in the assignment of severity.

Table 8: Severity Assessment Scale

Category	Grade	Description
Mild	1	Mild symptoms: No interference with routine activities (Minimal level of discomfort)
Moderate	2	Moderate symptoms: Moderate interference with the patient's routine activities (Moderate level of discomfort)
Severe	3	Severe Symptoms: Considerable interference with the patient's daily activities, unable to perform routine activities (Significant level of discomfort)
Potentially Life-threatening	4	Urgent intervention indicated Hospitalization or ER visit for potentially life-threatening event

The severity assessment criteria may be used for any symptom not included in the grading scale. Any grade 4 (potentially 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 8 will be followed; however, if a subject is evaluated in an emergency room setting for nonlife threatening illness or symptoms (ie, 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.

11.4 Recording Adverse Events

11.4.1 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 2 - Day 0) through Visit 3 - Day 4.

11.4.2 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 a 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 as defined in section 11.5.1.1.

11.5 Reporting Adverse Events

The Principal Investigator will report all AEs to the sponsor's safety office (USAMRMC CSSD) and the U.S. Investigational Review Board/or the USAMRMC ORP in the appropriate safety, annual, and/or final reports. After appropriate data cleaning and query resolution between the clinical site, sponsor's clinical monitor, and clinical data manager, SAEs from the clinical database will be reconciled with the sponsor's SAE database. Annual and final study report data will be provided by the ClinSmart Data Management Group.

11.5.1 Reporting Serious and Unexpected Adverse Events

Contact information for reporting SAEs is provided in Table 9.

Table 9: Study Contacts for Reporting Serious Adverse Events

Sponsor's Safety Office	US Army Medical Research & Material Command ATTN: MCMR-UMR 1430 Veterans Drive Fort Detrick, MD 21702-5009 Fax: 301-619-7790 Telephone: 301-619-1106 Email: usarmy.detrick.medcom-usammda.mbx.sae-reporting@mail.mil
Institutional Review Board	U.S. Investigational Review Board 6400 S.W. 72nd Court Miami, Florida 33143 Telephone: 786-473-3095 Fax: 305-374-1789 Email: rmvf1550@aol.com *AND*
USAMRMC Office of Research Protections	Human Research Protection Office US Army Medical Research and Material Command, ATTN: MCMR-RPH 504 Scott Street Fort Detrick, Maryland 21702-5012 Fax: 301-619-7803 Telephone: 301-619-2165 Email: usarmy.detrick.medcom-usamrmc.other.hrpo@email.mil
Research Monitor	Armand L. Balboni, JD, MD, PhD CPT, MS, USA Deputy Director, Division of Regulated Activities and Compliance (DRAC) USAMMDA 1430 Veterans Drive Fort Detrick. MD 21702 Telephone: 301-619-2956 Fax: 301-619-2304 Email: armend.l.balboni.mil@mail.mil

11.5.1.1 Reporting to the Sponsor

All SAEs and unexpected AEs must be reported promptly (within 24 hours) to the sponsor's representative as per 21 CFR 312.64, whether or not the event is considered related to study product. All notification will be provided to the sponsor's safety office, the PSSB, Clinical Services Support Division (CSSD), USAMMDA, USAMRMC. Further, the investigator should comply with relevant study site SOPs on reporting SAEs.

The information that the investigator will provide to the USAMRMC CSSD, PSSB is specified in Table 10. The sponsor's representative may request additional information for purposes of the study.

Table 10: SAE Information to be Reported to the Sponsor's Safety Office

Notification Method	Information to be Provided
Email or Telephone (within 24 hours)	IND number, sponsor study number, name of the investigational product, and investigator name and contact number
	Subject identification number
	SAE term, description, onset date, date of investigational product administration, severity, relationship, and subject's current status
AND	
Email or Fax	Cover sheet or letter
	Adverse event case report form
	Sponsor approved Serious Adverse Event Report Form
	Concomitant medication case report form or a list of concomitant medications
	Medical record progress notes including medical history/pertinent laboratory/diagnostic test results

NOTE: When submitting SAE reports via email, the subject line of each email notification will read as follows:
SAFETY REPORT – IND # _____, Sponsor Study #_____, Subject# _____, Event term: _____

In order to comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 calendar days, investigators must submit additional information as soon as it is available on the SAE electronic Case Report Form/SAE Report Form. The sponsor's representative will report unexpected SAEs associated with the use of the drug to the FDA as specified at 21 CFR 312.32 (c).

Investigators must follow all relevant regulatory requirements as well as specific policy regarding the timely reporting of SAEs to the research monitor and US Investigational Review Board and/or the USAMRMC ORP.

Reporting to the sponsor's representative does not fulfill the investigator's duty to report all unanticipated problems involving risk to human subjects or others to the IRB. The Principal Investigator will notify US Investigational Review Board and/or the USAMRMC ORP, and the Research Monitor.

11.5.1.2 Reporting to the IRB

Unanticipated problems involving risk to subjects or others, SAEs related to participation in the study, and all subject deaths should be promptly reported by telephone, email, or fax to US Investigational Review Board and/or USAMRMC ORP. The IRB contact information is provided in Table 9. A complete written report should follow the initial notification.

Investigators are required to forward safety information provided by the sponsor's representative to the IRB.

11.5.1.3 Reporting to ORP HRPO

The Principal Investigator must comply with the following minimum reporting requirements. Specific reporting requirements for the protocol will be included in the HRPO Approval Memorandum. Failure to comply could result in suspension of funding.

1. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (E.G. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to subjects.
2. All unanticipated problems involving risk to subjects or others must be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Material Command, ATTN: MCMR-UMR, 1430 Veterans Drive, Fort Detrick, Maryland 21702-5009.
3. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by US Investigational Review Board (IRB), Salus Research, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.
4. A copy of the continuing review approval notification by the US Investigational Review Board (IRB of Record) must be submitted to the HRPO as soon as possible after receipt. For greater than minimal risk research, a copy of the continuing review report approved by the IRB must also be provided. Please note that the HRPO also conducts random audits at the time of continuing review. Additional information and documentation may be requested at that time.
5. The final study report, including any acknowledgement documentation and supporting documents, must be submitted to the HRPO when available.
6. The knowledge of any pending compliance inspection/visit by the FDA, DHHS Office of Human Protections (OHRP), or other government agency concerning this research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any regulatory agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements, must be promptly reported to the HRPO.

11.5.2 Reporting Additional Immediately Reportable Events to the Sponsor's Safety Office and IRB of Record and/or the USAMRMC ORP

11.5.2.1 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.

11.5.2.2 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.

11.5.2.3 Pending Inspections/Issuance of Reports

The knowledge of any pending compliance inspection/visit by the FDA, Office for Human Research Protections (Department of Health and Human Services), or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to US Investigational Review Board and/or the USAMRMC ORP HRPO and the sponsor's representative.

11.5.3 IND Annual Report to the FDA

The Principal Investigator will be responsible for the preparation of a detailed annual synopsis of clinical activity, including AEs, for submission to the sponsor's representative (USAMMDA). Each annual report will summarize IND activity for 1 year beginning approximately 3 months before the IND FDA anniversary date. The sponsor's representative will notify the Principal Investigator of the due date with sufficient time for the Principal Investigator to assemble the required information.

11.5.4 Final Report

A final study report will be prepared in accordance with "Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" and ICH E3 Guideline "Structure and Content of Clinical Study Reports" and provided to the sponsor's representative for review and approval. The sponsor's representative will use this report to prepare the final clinical study report for submission to the FDA.

The principal investigator will report all AEs to the sponsor's safety office (USAMRMC CSSD, PSSB) and the IRB of Record (US Investigational Review Board) in the appropriate safety,

annual, and/or final reports. After appropriate data cleaning and query resolution between the clinical site, sponsor's clinical monitor, and clinical data manager, SAEs from the clinical database will be reconciled with the sponsor's SAE database.

12 Statistics

Detailed statistical procedures, listings, table shells and figures will be provided in a separate statistical analysis plan (SAP) written shortly after protocol approval but before any subject enrollment. The SAP will be finalized before study close-out and database lock. The following key statistical components will be considered and a detailed description will be documented in the SAP:

- Primary and secondary measurements and how they will be measured,
- Statistical methods and tests that will be used to analyze the measurements,
- Strategy that will be used if the statistical test assumptions are not satisfied,
- Indication of whether the comparisons will be one-tailed or two-tailed (with justification of the choice) and the level of significance to be used,
- Identification of whether any adjustments to the significance level or the overall p-value will be made to account for any planned or unplanned subgroup analyses or multiple testing,
- Specification of potential adjusted analyses and a statement with which covariates or factors will be included,
- Planned exploratory analyses and justification of their importance, and
- Any subgroup effects with biological justification and support from within and outside the study.

12.1 Description of Statistical Methods

The primary objective of this Phase 2 study is:

- to assess the safety and tolerability of KSL-W (30 mg dose) delivered in a chewing gum formulation compared to placebo after multiple doses over a 4 day treatment period.

The secondary proof of concept (efficacy) objectives are:

- to assess the change in plaque regrowth from baseline in the WHT of KSL-W (30 mg dose) compared to placebo after multiple doses over a 4 day treatment period
- to assess the treatment related changes from baseline using the sub-scores of the QHT.

The study will evaluate the following:

- KSL-W and placebo adverse event frequencies, incidences and rate estimates will be displayed side by side by affected body system, severity and relationship to study drug
- The estimated mean difference (KSL-W minus placebo) in the change in plaque regrowth from baseline to Day 4 in the QHT and the estimated standard deviation of these reductions

- The estimated means, standard deviations of the total score and sub-scores of the QHT, by visit (baseline, Day 4), and by study arm (KSL-W, placebo)
- The estimated effect of evaluator on the QHT index

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. The study biostatistician will remain blinded until database lock. Summaries of continuous variables will include the sample size, mean, median, standard deviation, and the minimum and maximum scores. Summaries of categorical variables will include the number and percentage of subjects that presented each value of the variable. Unless specifically noted to the contrary in the SAP, all analyses will be based on data as observed, with no imputation of missing data. Analyses will be performed using SAS, release 9.3 or later.

12.1.1 Analysis Addressing the Primary and Secondary Study Objectives

12.1.1.1 Safety (Primary)

All AEs 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. Verbatim AE terms will be shown in a table listing. Incidence rates (in events per patient-week) will be estimated as the number treatment emergent AEs divided by the total number of patient-weeks of follow-up. 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.

12.1.2.1 Proof of Concept Analyses (Secondary)

The QHT whole mouth average, determined at baseline and Day 4, will be the average of scores from surfaces evaluable for QHT. In order to qualify for this study each subject must have at least 20 teeth with 6 evaluable surfaces per tooth.

An analysis of covariance (ANCOVA) model will be applied to each subject's change in plaque regrowth from baseline in the QHT score (baseline minus Day 4) for subjects in the primary analysis population (FAS defined in section 12.8 below). The primary model will include study arm (KSL-W, placebo) and the baseline QHT score.

Estimates and 95% confidence bounds on all model parameters will be summarized, and the estimated mean study arm difference from the final ANCOVA model will be presented along with its standard error and 95% confidence bound. A 2-tailed p-value for this difference will also be presented as a further descriptive summary.

The estimated mean difference together with the error standard deviation from the primary ANCOVA model will be used to forecast success of future studies based on the average power for detecting a KSL-W improvement in the QHT reduction as a function of the future study sample size.

Secondary analyses involving the change in plaque regrowth will include a full model with the baseline QHT score, study arm, evaluator and all interactions of these terms. This model will be used to assess the overall effect of evaluator on the results, and any study arm difference in the slope terms of the baseline QHT score.

In addition to the model interaction evaluations described above, the assumption of equal error variance across the design will be checked using scatter plots and the estimated study arm standard deviations. The linearity assumption of mean reduction in QHT versus baseline QHT will be checked using scatter plots.

12.1.2 Multiple Endpoints

There will be only one primary assessment for this study.

12.1.3 Other Analyses

Demographic assessments will be summarized by study arm. Frequencies and proportions will be presented for categorical scales. Sample means, sample standard deviations, minima, maxima will be presented for continuous scales.

Descriptive summaries (sample means, sample standard deviations, minimum, maximum) of the total score and sub-scores of the QHT, by visit (baseline, Day 4), and by study arm (KSL-W, placebo) will be summarized using both the FAS and .per-protocol subjects cohorts.

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 end of study evaluation time points will be summarized.

The efficacy analyses described for the analysis in section 12.1.1 will also be performed using the per protocol population defined in section 12.8.

12.1.4 Subgroup Analysis

There are no planned subgroup analyses for this study.

12.2 Planned Enrollment and Reason for Sample Size

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 the phase 2a study will apply to this study having 4 treatment days.

12.3 Level of Significance to be Used

While formal p-value comparisons of the study arms based on the ANCOVA model results will be generated and summarized (2 tailed, p = 0.05), these will be considered only as descriptive summaries 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) reduction from baseline, and the estimated error standard deviation from the final ANCOVA model. This information will be critical to assess the chances for a successful demonstration of KSL-W efficacy from future phase 3 studies, utilizing QHT as a function of the sample size of these studies.

12.4 Statistical Criteria for the Termination of the Trial

There are no statistical criteria for study termination in this clinical trial.

12.5 Interim Analysis and Stopping Rules

No interim analyses are planned.

12.6 Accounting for Missing, Unused, and Spurious Data

Non-analyzable data will be documented.

12.7 Procedures for Reporting Deviations from the Original Statistical Plan

Any deviation(s) from the original statistical plan as indicated in the protocol will be described in an amendment to the protocol and the SAP. Deviations from the SAP will be documented in accordance with study site SOPs. Non-analyzable data will be documented.

12.8 Selection of Subjects to be Included in Analyses

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.

The Per Protocol Population (PP) is a subset of FAS and consists of all subjects with no major protocol violations such as: 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 during the study period. Analysis of the PP will be according to the treatment actually received by the subject.

The Safety Population consists of all randomized subjects receiving at least one dose of study medication, and summarized on the basis of treatment received. All AE summaries will be based on the safety population.

13 Direct Access to Source Data/Documents

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject. Representatives of USAMRMC, the sponsor's representative, the IRB of Record and/or the USAMRMC ORP, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied medical and research records.

13.1 Study Monitoring

Study monitoring will be the responsibility of ClinSmart CRO with oversight by USAMRMC CSSD Clinical Oerations Branch. Upon successful approval of the protocol and establishment of the regulatory file, ClinSmart CRO will establish a clinical monitoring plan. To ensure that the investigator and the study staff understand and accept their defined responsibilities, the clinical monitor will maintain regular correspondence with the site and may be present during the course of the study to verify the acceptability of the facilities, compliance with the investigational plan and relevant regulations, and the maintenance of complete records. As needed, the clinical monitor may witness the informed consent process or other applicable study procedures to assure the safety of subjects and the investigators' compliance with the protocol and GCPs.

Monitoring visits will be scheduled to take place at the initiation of the study, during the study at appropriate intervals, and after the last subject has completed the study. A report of monitoring observations will be provided to the Principal Investigator (for corrective actions) and USAMRMC CSSD. USAMRMC CSSD Operations Branch may conduct co-monitoring and/or sponsor monitoring visits as part of their oversight.

13.2 Audits and Inspections

Authorized representatives of the sponsor, the FDA, the independent ethics committee or IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guideline of the ICH, and any applicable regulatory requirements.

The investigator should contact the sponsor's representative and ORP HRPO immediately if contacted by a regulatory agency about an inspection.

13.3 Institutional Review Board

As the IRB of record, U.S Investigational Review Board along with ORP HRPO will serve as the responsible IRBs and will review the protocol, informed consent, and progress reports on a continuing basis in accordance with all applicable regulations, including Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. The ORP HRPO will provide a second review.

The Principal Investigator must obtain IRB approval for the study. Initial IRB approval and all materials approved by the IRB for this protocol, including the patient consent form and recruitment materials, must be maintained by the protocol physician and made available for inspection.

The Principal Investigator will be responsible for preparing and submitting continuing review reports per institution and IRB requirements. The Principal Investigator or a designee will submit the approved continuing review reports and the US Investigational Review Board approval notifications to ORP as soon as the documents are available.

14 Quality Control and Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor's representative may conduct quality assurance audits. Refer to section 13.2 for more details regarding the audit process.

Auditing of the clinical trial may be conducted at any time during the study to ensure continued compliance with regulations, policies and procedures. Auditing will be undertaken, as needed, by independent personnel designated by the Quality Office, USAMMDA. Audit findings will be documented in a formal audit report that will detail the conduct of the audit and summarize the observations noted.

15 Ethics

15.1 Ethics Review

This study will be conducted under an IRB approved protocol. The study is to be conducted by scientifically and medically qualified persons. The IRB will determine whether the benefits of the study are in proportion to the risks. The rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 CFR Part 50 and the Belmont Principles.

15.1.1 Review/Approval of Study Protocol

Before a clinical study can be initiated, the study protocol and other required documents will be submitted to the following departments in the order listed for review and/or approval, with the final review by the FDA:

- Integrated Product Team
- Sponsor's Representative Team (Senior Regulatory Affairs Advisor; Division of Regulated Activities and Compliance, USAMMDA)
- Commander, Subordinate Command, if applicable
- IRB
- Office of Research Protections, Human Research Protection Office (ORP HRPO)
- Sponsor's Representative (acting for The Office of the Surgeon General of the Army)
- USAMRMC Commanding General, if applicable

Enrollment in this protocol may not begin until all approvals have been obtained and the formal authorization letter is received by the Principal Investigator from the sponsor's representative.

15.1.2 Protocol Modifications

All modifications to the protocol and supporting documents (informed consent, study-specific procedures, SOPs, recruitment materials, etc) must be reviewed and approved prior to implementation. Any protocol amendment will be agreed upon and approved by the sponsor's representative prior to submission to the IRB and/or the ORP and prior to implementation of said change or modification. Any modification that could potentially increase risk to patients must be submitted to the FDA prior to implementation. The informed consent document must be revised to concur with any amendment as appropriate and must be reviewed and approved with the amendment. Any patient already enrolled in the program will be informed about the revision and asked to sign the revised informed consent document if the modification directly affects the individual's participation in the program. A copy of the revised, signed, and dated informed consent document will be given to the patient. All original versions of the informed consent

document will be retained in the subject's medical record and a copy will be retained in the protocol regulatory file.

15.1.3 Protocol Deviation Procedures

All subject-specific deviations from the protocol (eg, failure to return for follow-up visits) are to be documented. The Principal Investigator or designee will be responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study-specific procedure. Deviations will be reported annually in the continuing review report to the IRB and/or the ORP and, if appropriate, in the final study report. Action taken in response to the deviation, and the impact of the deviation will be assessed by the Principal Investigator or sub-investigator and recorded as significant or nonsignificant.

Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study, the deviation will be reported immediately to the sponsor's representative, IRB and/or the ORP.

15.2 Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal and DoD human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guideline and the CFR. The Principal Investigator confirms this by signing this study protocol and FDA Form 1572.

15.2.1 Confidentiality

HIPAA requires that researchers obtain the subject's permission (HIPAA Authorization) to use and disclose health information about the subject that is either created by or used in connection with this research. The information includes the entire research record and supporting information from the subject's medical records, results of laboratory tests, and both clinical and research observations made during the individual's participation in the research.

In this research, the subject's health information will be collected and used to conduct the study; to monitor the subject's health status; to measure effects of the investigational product; to determine research results, and possibly to develop new tests, procedures, and commercial products. Health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. After the study ends, each subject has the right to see and receive a copy of his/her information.

Representatives of the OTSG as the IND sponsor, USAMRMC as the sponsor's representative, the IRB and/or the ORP, the DoD, and the FDA are eligible to photocopy and review records related to this protocol as a part of their responsibility to protect the participants of this protocol. In addition, these representatives are eligible to witness the applicable study procedures to assure the safety of subjects.

No personal identifier will be used in any publication or communication used to support this research study. The subject's identification number will be used in the event it becomes necessary to identify data specific to a single subject.

15.2.2 Compensation for Participation

The compensation for participation amounts are provided in Table 11.

Table 11: Compensation for Study Subjects

Visit(s)	Amount Per Visit ($)*
Screening	25-
Each Randomized Subject	200-
Total Compensation	225-

*Compensation will be given in the form of gift cards.

15.2.3 Medical Care for Research-Related Injury

All non-exempt research involving human subjects shall, at a minimum, meet the requirement of 32 CFR 219.116(a)(6).

If a subject is injured because of participation in this research and is a DoD healthcare beneficiary (eg, active duty in the military, military spouse or dependent), the subject is entitled to medical care for that injury within the DoD healthcare system, as long as the subject remains a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at Army hospitals or clinics.

If a subject is injured because of participation in this research and is not a DoD healthcare beneficiary, the subject entitled to medical care for that injury at an Army hospital or clinic; medical care charges for care at an Army hospital or clinic will be waived. The subject is also entitled to care for that injury, but such care for that injury at other DoD (non-Army) hospitals or clinics may be limited by time, and the subject's insurance may be billed. It cannot be determined in advance which Army or DoD hospital or clinic will provide care. If the subject obtains care for research-related injuries outside of an Army or DoD hospital or clinic, the subject or the subject's insurance will be responsible for medical expenses.

15.3 Written Informed Consent

The informed consent process and document will be reviewed and approved by US Investigational Review Board, USAMRMC ORP and Sponsor's representative prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with the United States Code of Federal Regulation, Title 21, Part 50 (21 CFR 50). The consent document indicates that by signature, the subject permits witnessing of applicable study procedures by the sponsor's representative, as well as access to relevant medical records by the sponsor's representative and by representatives of the FDA. The sponsor's representative will submit a copy of the initial IRB and sponsor's representative-approved consent form to the FDA

and will maintain copies of revised consent documents that have been reviewed and approved by US Investigational Review Board and ORP.

A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for that subject. This consent document must be retained by the investigator as part of the study records. Each subject will receive a copy of the signed informed consent document. The investigators or their designees will present the protocol in lay terms to individual subjects. Questions on the purpose of the protocol, protocol procedures, and risks to the subjects will then be solicited. Any question that cannot be answered will be referred to the PI. No subject should grant consent until questions have been answered to his/her satisfaction. The subject should understand that the study product is an investigational drug and is not licensed by the FDA for commercial use, but is permitted to be used in this clinical research. Informed consent includes the principle that it is critical the subject be informed about the principal potential risks and benefits. This information will allow the subject to make a personal risk versus benefit decision and understand the following:

- Participation is entirely voluntary,
- Subjects may withdraw from participation at any time,
- Refusal to participate involves no penalty, and
- The individual is free to ask any questions that will allow him/her to understand the nature of the protocol.
- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US law.

Should the protocol be modified, the subject consent document must be revised to reflect the changes to the protocol. If a previously enrolled subject is directly affected by the change, the subject will receive a copy of the revised informed consent document. The approved revision will be read, signed, and dated by the subject.

16 Data Handling and Recordkeeping

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator, the medical record and the research records will be considered the source documents for the purposes of auditing the study. The source documents will be retained at the site.

For this study, an EDC database system will be used for the collection of the study data in an electronic format. The EDC database system will be designed based on the protocol requirements, the approved eCRF layouts and specifications, and in accordance with 21 CFR Part 11. The eCRF layouts and specifications define and identify the applicable source data that will be collected and captured into the EDC database system. The applicable source data will be electronically transcribed by the site designee onto the eCRF (data entry screens) in the EDC database system. The investigator is ultimately responsible for the accuracy of the data transcribed on the eCRF. Data monitoring will be performed in the EDC database system by the study monitor and the designated Data Management group.

A detailed data management plan will be written and approved by the study team and the Principal Investigator prior to study start, with approval by the sponsor's data manager in the USAMMDA CSSD. All updates to the data management plan must be approved before study close-out and database lock.

16.1 Inspection of Records

The sponsor's representative or designee will be allowed to conduct site visits at the investigation facility for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

Subjects' health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. The informed consent document indicates that by signature, the subject permits access to relevant medical records by the sponsor and its representatives, U.S. Investigatonal Review Board and by representatives of the FDA in order to audit or monitor the study data.

Upon a subject's termination from the trial, completed eCRFs will be ready and available for on-site review by the sponsor's representative or the designated representative within 14 days after receipt of the subject's data.

16.2 Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved for 2 years following the discontinuance of the investigational product for investigation. If it becomes necessary for the sponsor's representative or designee or the FDA to review any documentation relating to the study, the investigator must permit access to such records.

Completed, monitored eCRFs will be stored in a secure location by the sponsor's representative or designee. A copy of each completed eCRF will be retained by the investigator.

The Principal Investigator will be responsible for retaining sufficient information about each subject, ie, name, address, telephone number, driver's license number and subject identifier in the study, so that the sponsor's representative, the IRB of record, the FDA, employees of USAMRMC, or other regulatory authorities may have access to this information should the need arise.

It is the policy of the USAMRMC that data sheets are to be completed for all subjects participating in research (Form 60-R, Volunteer Registry Data Sheet). The data sheets will be entered into this Command's Volunteer Registry Database. The information to be entered into this confidential data base includes the subject's name, address, and Social Security Number; study title; and dates of participation. The intent of this data base is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure research subjects are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years. The Volunteer Registry Database is a separate entity and is not linked to the study database.

17 Publication Policy

All data collected during this study will be used to support this IND. All data may be published in the open medical or military literature with the identity of the subjects protected. Anyone desiring to publish or present data obtained during the conduct of the study will conform to Salus Research policies and then forward the publication for review to the Commander, USAMMDA or designee and usarmy.detrick.medcom-usamrmc.list.clearances@mail.mil prior to submission.

18 List of References

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19 Appendices

Appendix A. Study Personnel Roles and Responsibilities – Salus Research

Study Staff	Responsibility
Jeffery L. Milleman, DDS, MPA	Principal Investigator; Examiner
Kimberly R. Milleman, RDH, MS	Sub-Investigator; Examiner
Kirstin K. Battershell, RN, MBA	Senior Clinical Coordinator; Vital Signs; Urine Drug Screen, Urine Pregnancy Test
Julie E. Wygant	Front Desk; Recruiting
Brian T. Marks Kara K. Wygant	Study Product Preparation
Kaylie S. Wills	Randomization
Abigale L. Yoder	Informed Consent; Medical History & Demographics Collection
Jack L. Lowe	Recorder
Justin M. Bute	Product Distribution; Product Use Instructions; Supervised Use; Evaluate Compliance
Holly M. Scott, RDH, BS	Dental Polishing (Supervised Dental Hygienist)
Dental Hygienist	Dental Polishing (Independent Contractors)

Appendix B. Quigely Hein Index and Calculation Example

Quigely Hein Index (modified)

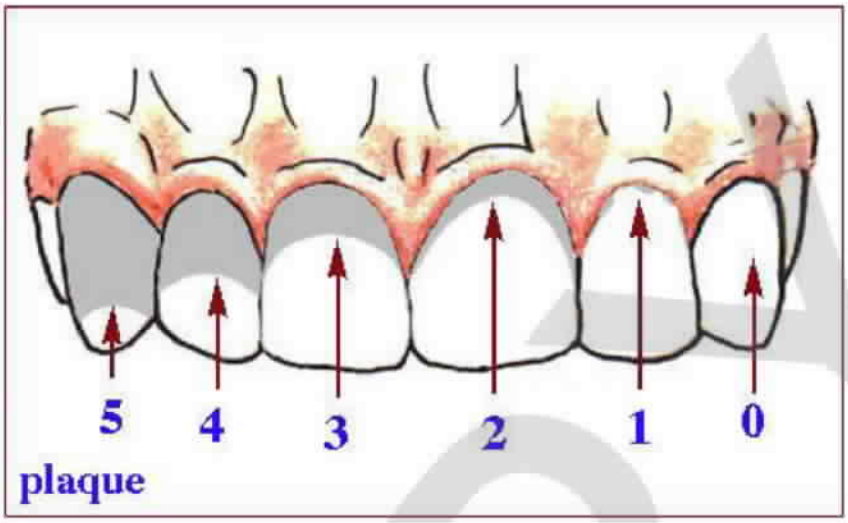
- Quigley Hein Index -
(Modified by Turesky et al, 1970)

Guest editor: Kaban Moslehzadeh

This index is the same as the Quigley Hein Index except the criteria has been modified. As Quigley Hein Index, a score of 0 to 5 is assigned to each facial and lingual nonrestored surface of all the teeth except third molars, as follows

The Plaque Index System

Scores	Criteria
0	No plaque
1	Separate flecks of plaque at the cervical margin of the tooth
2	A thin continuos band of plaque (up to one mm) at the cervical margin of the tooth
3	A band of plaque wider than one mm but covering less than one-third of the crown of the tooth
4	Plaque covering at least one-third but less than two-thirds of the crown of the tooth
5	Plaque covering two-thirds or more of the crown of the tooth



An index for the entire mouth is determined by dividing the total score by the number surfaces (a maximum of 2 x 2 x 14 = 56 surfaces) examined.

CALCULATION EXAMPLE:

Assuming nonrestored upper jaw and lower jaw surfaces are examined and the scores are stored in the following two tables:

Upper jaw	Buccal surface score	Lingual surface score
25	2	2
22	1	3
21	3	2
11	0	1
12	0	0
13	1	2
14	1	3

15	2	2
17	5	3
Total	**15**	**18**

Lower jaw	Buccal surface score	Lingual surface score
47	4	5
44	3	5
43	2	3
42	2	3
41	2	4
31	2	3
32	0	2
33	0	2
34	0	0
Total	**15**	**27**

Index	=	**Total score / The number surfaces examined**
		((15 + 18) + (15 + 27)) / 36 = 2.1

The index for the entire mouth is 2.1.

Appendix C. Guidance for Industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf

Appendix D. ePRO Electronic Diary Information

Each subject will record the start and stop times for chewing gum on the ePRO Electronic Diary Information System. This data will be collected via the internet. The subject will receive three emails per day containing a link to the respective ePRO form. Each form will be identified by "Day" and "Time of Chew". For example, for Day 1, the forms will be identified as: Day 1 – Chew 1 (morning), Day 1 – Chew 2 (afternoon), Day 1 Chew 3 (evening). Over the course of the study there will be a total of 12 forms (one for each chew) to be completed.

The subject will open the email and click the link to the ePRO form. On the form, the subject will enter the start and stop times for each chew and "submit" this information in real time.