Official Study Title:

Trial of Nano-hydroxyapatite-Containing Toothpastes for Relief of Dentin Hypersensitivity

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EXHIBIT A

CLINICAL STUDY AGREEMENT BETWEEN

The University of Texas Health Science Center at San Antonio

AND

SANGI Co., Ltd, Tokyo, JAPAN 104-8440

Randomized Non-inferiority Trial of Nano-hydroxyapatite-Containing Toothpastes for Relief of Dentin Hypersensitivity

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OBJECTIVE

Dentinal hypersensitivity (DHS) is the incidence of short, sharp pain near the base of a tooth, which arises because of dentin being exposed to external stimuli by cervical erosion/abrasion or gingival recession, and which cannot be attributed to any other form of dental defect or pathology such as caries, broken or leaking restorations, or a chipped or cracked tooth. The objective of the present study is to determine whether or not the regular use of a nano-hydroxyapatite(nano-HAP)-containing toothpaste is non-inferior to the regular use of a potassium nitrate(KNO_3)-containing toothpaste in the relief of DHS. Non-inferiority would be declared if the mean percentage reduction of sensitivity for the nano-HAP toothpaste was no worse than the mean percentage reduction for KNO_3-containing toothpaste, within statistical variability, by a margin (Δ) of 20%(at 95% probability). Our null hypothesis is that the nano-HAP toothpaste is not similar to the KNO_3 toothpaste, using anon-inferiority margin of Δ = 20% for the primary outcome measure. Our choice of a non-inferiority trial design was based on the abundant and well-established evidence for the sensitivity relief efficacy of KNO_3 toothpaste and the expectation that non-inferiority of nano-HAP toothpaste to KNO_3 toothpaste would be sufficient to place nano-HAP toothpaste in the same class of quasi-drug as the KNO_3 toothpaste for the relief of DHS. A further study objective is to show whether or not, statistically, the regular use of a nano-HAP-containing toothpaste is significantly more effective in the relief of DHS than the regular use of a placebo toothpaste not containing nano-HAP.

SUMMARY OF STUDY DESIGN

This study is a double-blind, randomized, placebo-and positive-controlled, stratified parallel group clinical trial. A total of 192 patients diagnosed with DHS and meeting all necessary requirements for selection as subjects will be stratified into three balanced groups (64 per group) according to age, gender, and their mean sensitivity to cold air stimulus as scored on a Visual Analog Scale (VAS) at the time of baseline examination for final selection during the recruitment screening process. Males and females aged between 20 and 80 years will be enrolled. The three groups will be randomly assigned to use one of three test toothpastes having an identical base formulation but containing respectively either 0% nano-HAP (placebo), 15% nano-HAP or 5% KNO_3 (positive control). Subjects will be instructed to use their assigned test toothpaste as their sole oral hygiene product for the 8 weeks treatment duration. Subjects will be instructed to brush their teeth twice daily for 3 minutes, in the morning and before bed at night, applying on each occasion a one-inch strip of their assigned toothpaste on a soft-bristled toothbrush which will be supplied. Examination for DHS will include response to cold air, as the primary stimulus, and to tactile pressure, as a secondary stimulus, and will be conducted at the commencement of

recruitment screening (preliminary examination), then subsequently at baseline, 4 and 8 weeks. All dental examinations for data collection in all 192 subjects will be conducted by the same Clinical Examiner throughout the study. Subjects will be examined and queried on adverse events at each study visit.

POPULATION AND INITIAL SCREENING PROCEDURES

This study will be conducted at the clinical research facility of the school of dentistry of the University of Texas Health Science Center at San Antonio (UTHSCSA) following approval by the UTHSCSA Institutional Review Board (IRB). UTHSCSA IRB will also approve the Human Assurance Documents as well as perform the compliance assessment (study monitor). All documents for this study will be used with Japanese language superimposed and will be approved by the IRB. This study will be conducted according to the "Recommendations for Evaluating Agents for the Reduction of Dentinal Hypersensitivity" as proposed by the Council on Dental Therapeutics of the American Dental Association, and in compliance with International Conference on Harmonization (ICH) Good Clinical Practice Guidelines including ICH E6, the Abbreviated Requirements of the Investigational Device Exemption Regulations (21CFR Part 812), and with 21 CFR Parts 50, 54, and 56.

Patients presenting to any of the dental school clinics, either with a primary complaint of tooth hypersensitivity or whom a clinician discovers to have a hypersensitive tooth or teeth during other routine dental treatment or examination will be screened to determine whether they meet study entry criteria.

Patients can be referred to the study Investigators by any of the dental school clinics or from surrounding private clinics. Initial screening of patients to confirm eligibility to participate in the study will be conducted by the Study Coordinator, and will include a medical history and information on medication use, and a review of the rest of the inclusion/exclusion criteria. 192 adult male and female patients, who are in good general health except for the symptoms of DHS, and who meet specific inclusion/exclusion criteria and the subsequent requirements of recruitment screening will be enrolled as subjects in the clinical study and randomized into the three test groups. The enrolment objective will be to have at least 57 subjects complete the study in each of the three test groups. Therefore to allow for about 10% dropout in each test group, 192 subjects (64 per group) will be enrolled. All relevant medical and non-medical conditions will be taken into consideration when deciding whether this protocol is appropriate for a particular subject. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate.

Inclusion Criteria

- Males or females between the age of 20 and 80 years, of any socio-economic status
- Diagnosed as having DHS, i.e. having at least one sensitive tooth with demonstrated cervical erosion/abrasion or gingival recession
- Showing a sensitivity response to both tactile and cold air stimulus delivered by a Yeaple probe and a one-second blast of cold air respectively (see detailed description below)
- Patients must be reliable, cooperative and of adequate intelligence to read and understand the rating scales and other study instructions
- Patients must be able to read, comprehend, and sign the informed consent form
- The teeth and sites to be tested should be on the buccal/labial surfaces of incisors, canines, premolars or molars where the affected sites are accessible
- Teeth selected for testing should have a plaque index of ≤ 2

Exclusion Criteria

- The sensitive tooth is associated with concomitant oral pain due to any other condition such as soft-tissue lesions, tooth-ache ascribable to dental caries, tooth fracture, or cracked tooth syndrome, or pain due to other surgical procedures or injuries.
- The sensitive tooth is associated with a periodontal abscess as diagnosed from an X-ray or clinical examination of the tooth
- The sensitive tooth is associated with mobility >1
- The sensitive tooth is associated with gum pain from gingivitis, occlusal trauma, thermal or chemical burns
- Patients having pain from periodontal-related causes but not DHS
- Previous professional desensitizing treatment
- Patients using medication which could interfere with the perception of pain
- Medical histories marked by chronic use of anti-inflammatory agents, daily analgesics, anticonvulsants, antihistamines, antidepressants, sedatives and/or other psychotropic drugs
- Pregnancy or breastfeeding
- Allergies and idiosyncratic responses to toothpaste ingredients
- Eating disorders or conditions associated with vomiting
- Systemic conditions that are etiologic or predisposing to DHS
- Excessive dietary or environmental exposure to acids
- The sensitive tooth was restored in the preceding three months
- The sensitive tooth is an abutment tooth for fixed or removable prostheses

- The sensitive tooth has extensive restoration or restorations extending into the test area
- Patients below 20 years or above 80 years of age
- Smokers

RECRUITMENT SCREENING AND STUDY PROCEDURES

Only patients who meet all initial screening criteria and provide written informed consent will be invited to proceed to recruitment screening for participation in the trial. Recruitment screening will consist of three steps, as described below: (1) a preliminary examination; (2) a 4-week washout period (for patients who meet the entry criteria during the preliminary examination); then (3) at the end of the washout period, evaluation and recording of each patient's baseline sensitivity level, as the basis for final subject selection.

(1) Preliminary Examination for Recruitment

Patients eligible for recruitment screening will report to the clinical research facility having refrained from 1) oral hygiene procedures or use of chewing gum for 8 hours, and 2) eating or drinking for 4 hours, except for drinking water, prior to the visit. The examination will include checking the patient's medical history and medication use, and a thorough oral examination by the Clinical Examiner, with evaluation of sensitive teeth. Tooth sensitivity will be assessed by a positive response to tactile and cold air stimuli, and the entry criteria for parameters assessed at this preliminary examination for recruitment will be 1) a positive response to tactile stimulus using a Yeaple probe at 30g force (standardized application for every subject), and 2) a VAS score of 30mm or more assessed using a one-second cold air blast from a standard dental unit air syringe. (The procedures for each of these tests are described below).

(2) Washout Period

Only patients who meet the entry criteria in the preliminary examination will proceed to the washout period. They will be assigned to use a toothpaste not containing either fluoride, hydroxyapatite or KNO_3, with an adult soft-bristled toothbrush, for a period of four weeks. The toothpaste and toothbrush will be used in place of the patient's normally used toothpaste and toothbrush, and will be supplied by the Sponsor. The patient will be instructed, after wetting the brush, to apply one inch (2.5cm) of the supplied toothpaste per brushing and to brush for 3 minutes by the scrubbing method twice daily, in the morning and last thing before bed at night, rinsing out the toothpaste with 10ml of water for 10 seconds after brushing. Patients will be asked to return to the clinical research facility for assessment at 4 weeks.

(3) Final Selection : Baseline Sensitivity Measurement

As for the preliminary examination for recruitment, patients reporting for baseline examination will be required, after brushing their teeth with the supplied toothpaste and toothbrush on the morning of the visit, to have refrained from 1) any other oral hygiene procedures or use of chewing gum, and 2) eating or drinking, except for drinking water, prior to the visit. The baseline examination will assess tactile and cold air sensitivity. (The procedures for each of these tests are described below). For each patient eligible to participate in the study, one or more hypersensitive teeth that satisfy the tactile and cold air hypersensitivity enrolment criteria will be identified for evaluation throughout the study. For each assessment visit, including the baseline examination, sensitivity must be triggered by application of a tactile stimulus and a cold air blast stimulus, and the level of sensitivity recorded.

For each patient completing the washout period, the result obtained according to the selection criteria at the preliminary examination for recruitment shall be compared with the result obtained at baseline examination. Only patients who 1) show a worsening of DHS or 2) maintain the same level of DHS over the duration of the washout period shall be selected and enrolled as subjects to participate in the trial, i.e. only patients who at the baseline examination meet the qualifying criteria, namely a Yeaple value of 30g or less and a VAS score in response to cold air stimulus of 30mm or more, will be accepted as subjects. As shown in the section explaining tactile stimulus, however, though the Yeaple criterion for acceptance in the study will be sensitivity at a pressure of 30g or less, in carrying out the baseline examination, the Clinical Examiner will apply pressure starting from a load of 10g, and increasing by increments of 10g, up to a maximum of 80g.

Test Products

The test products shall contain respectively 0% nano-HAP (placebo), 15% nano-HAP, and 5% KNO_3 (positive control).

Randomization/Allotment to Test Product Groups

A total of 192 subjects diagnosed with DHS and who have met all necessary requirements for selection as subjects in the trial will be stratified into three balanced groups according to age, gender and VAS score in response to cold air stimulus at the time of baseline examination for final selection of subjects eligible to participate in the trial (64 per group). One of the three test products shall be randomly assigned to each of the three groups. The 0% and 15% nano-HAP-containing toothpastes and the 5% KNO_3 toothpaste shall be randomly coded as either A, B, or C by the manufacturer or Sponsor, and the code shall not be disclosed until all statistical analysis is complete.

Clinical Procedures

Immediately following the baseline sensitivity examination, each patient who qualifies to become a subject in the trial will be given and make the first use of his/her allotted test toothpaste, under the supervision of the Study Coordinator, after the latter has confirmed and recorded the weight of the tube. During the next 8 weeks, subjects will be required to brush their teeth twice daily with their allotted test product, as instructed, and not to take any food or drink for at least 30 minutes after brushing except for drinking water. A diary covering the duration of the study will be provided to each subject to (1) keep a record of number of times of brushing each day, and (2) record the name of any medication taken during the study period. All subjects will be asked to maintain their normal dietary habits. However, the use of oral hygiene products that are not related to this clinical trial, such as mouthwash and prescription medicine, along with dental clinic visits, dental treatment, professional plaque removal, whitening, use of pain relievers or commercial hypoallergenic products as well as use of narcotics, anti-inflammatory drugs, conventional analgesics, anticonvulsants, antihistamines, antidepressants, sedatives and other psychotropic drugs shall be prohibited throughout the course of the study.

Each subject will be given an appointment 4 weeks and 8 weeks after the baseline examination, for post-treatment sensitivity assessment. On the day of each sensitivity assessment, subjects shall be prohibited, after morning tooth-brushing, from (1) the use of any other oral hygiene procedures or chewing gum and (2) from eating or drinking, except for drinking water, prior to the examination. The same sensitivity scoring procedures and restrictions used at baseline will be repeated for the examinations at 4 and 8 weeks. To ensure standardization, all dental examinations in all the 192 subjects will be performed by the same Clinical Examiner throughout the study. Subjects will be instructed to bring their allotted test toothpaste for weighing and their diary for inspection at the time of each assessment visit, and at the 4 week visit each subject will be given a fresh tube of his/her allotted test toothpaste whose weight has also been confirmed and recorded. This information will be used for monitoring adherence to the protocol. At each visit, subjects will also be interviewed with respect to the occurrence of adverse events and the use of concomitant medications.

EFFICACY AND SAFETY ASSESSMENT PROCEDURES

Application of the Stimulus to Trigger Sensitivity

Before stimulus application, all psychological and physiological factors that may alter the subject's degree of perception (for example—anticipation) should be controlled to the extent possible by standardization of procedure, training of the subject, demonstration of

the stimulus, and environmental controls (for example—noise, room temperature) including familiarization of the subject with the entire system.
DHS will be triggered by two stimuli, spaced at least 10 minutes apart to prevent the stimuli affecting each other. The two stimuli will be applied in the following order: first tactile, then cold air blast. If considered necessary, in the Clinical Examiner's judgement, each stimulus may be applied twice and/or a fake test included (in which no stimulus is delivered) to ensure that the subject is not responding erroneously.[A1]

Cold Air Stimulus

Assessment of cold air sensitivity will be conducted using air delivered from a standard dental unit air syringe at room temperature (~70°F±3°F)(~21°C±2°C) and a pressure of 60psi (± 5psi). The air will be directed perpendicular to the exposed root surface of the sensitive tooth for one second from a distance of approximately one centimeter, and to prevent false results, the sensitive tooth to be tested will be isolated from the adjacent teeth (mesial and distal) using cotton rolls held in place by the examiner's gloved fingers.[A2] Assessment of sensitivity will be carried out using VAS.[A3] Within 2 minutes from application of the stimulus, the Clinical Examiner shall ask the subject to record the intensity of the sensitivity he/she experienced, using the VAS scale. (See explanation below).

Tactile Stimulus

Tactile sensitivity will be assessed using the Model 200A Yeaple Electronic Force Sensing Probe (Yeaple Research, Pittsford, NY). The probe will be calibrated prior to use. The explorer tip of the Yeaple probe will be placed adjacent to the exposed dentin on the buccal/labial surface of the sensitive tooth, predominantly at the cement-enamel junction (CEJ). The explorer tip will be applied perpendicular to the tooth surface, starting from a load of 10g, and increasing its pressure by increments of 10g, up to a maximum of 80g, for all sensitivity examinations except the preliminary screening for recruitment, which shall be conducted using a standard pressure of 30g for all patients.

The explorer tip will be drawn slowly across the tooth surface in a distal to medial direction for approximately 3-5 seconds, to ensure application of the stimulus across all exposed tubules. The interval between applications shall be 60 seconds. The subject will be asked to say "yes" at the point where he/she feels the pressure is uncomfortable, and at that time point the Clinical Examiner will apply the explorer tip again at the same load for confirmation, and the load at which the subject again says "yes" will be recorded.[A4]

Visual Analog Scale (VAS)[A3]

VAS will be used within 2 minutes of stimulus application to evaluate the intensity of sensitivity on each measurement occasion: preliminary examination for recruitment, baseline examination, and examination after 4 and 8 weeks. The VAS scale, which must be explained to the subject, consists of an unmarked horizontal straight line, 100mm long, drawn on a sheet of paper, with the beginning and end representing no pain and maximum pain respectively. Following stimulus application as described above, the Clinical Examiner shall ask the subject to draw a vertical mark on the line, indicating how much pain he/she just felt, with "no pain" being on the far left of the scale at 0mm and "pain as bad as it can be," i.e. the maximum pain the subject could experience, being on the far right at 100mm.The distance between 0mm and the mark made by the subject shall then be measured in mm by the Clinical Examiner and recorded as the subject's VAS score, i.e. his/her indicated level of pain.

Calibration of the Clinical Examiner

To ensure standardization and repeatability in all sensitivity assessment procedures, including the manufacturers' instructions, as well as to provide accurate interpretation and analysis of the sensitivity response, the Clinical Examiner will be calibrated on the sensitivity assessment techniques described above, for both the Yeaple probe and delivery of cold air stimulus. The calibration will be conducted by a benchmark calibrator who is experienced in sensitivity assessment using cold air and the Yeaple probe. The method of calibration will be determined by the benchmark calibrator. This will be done using about 10 patients attending the clinic and diagnosed as having DHS. The sensitivity evaluation data collected during calibration will be recorded, and the agreement between the Clinical Examiner and benchmark calibrator for objective evaluation of sensitivity (inter-examiner) and between the Clinical Examiner's own repeated sensitivity evaluations (intra-examiner) will be evaluated using Bland-Altman plots and intra-class correlation coefficients. Midway during the trial, duplicate examinations will be carried out on 10% of the study subjects to confirm maintenance of repeatability by the Clinical Examiner. Calculations of agreement between the Clinical Examiner and the calibrator and between the Clinical Examiner's own repeated measures will clearly educate the Clinical Examiner on the importance of keeping to one standard to maintain repeatability in the sensitivity assessment procedures.

Oral Soft and Hard Tissue Assessment

At the time of each sensitivity assessment, the Clinical Examiner shall visually examine each subject's oral cavity and perioral area using a dental light and dental mirror. This examination will include an evaluation of the soft and hard palate, gingival mucosa, buccal

mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands, and the tonsillar and pharyngeal areas.

Adverse Events

Information concerning any adverse events will be obtained by the Clinical Examiner from the subjects at the time of sensitivity assessment. All observed or voluntarily reported adverse events regardless of test group or suspected causal relationship with a test product shall require immediate notification within 24 hours to the IRB and the Sponsor or its designated representative, during a reporting period beginning from the time that the subject first provides informed consent, which is obtained prior to the start of the clinical study, i.e. prior to the subject undergoing any study-related procedure and/or receiving any test product, through to and including 30 calendar days after the last administration of the test product. Any adverse event occurring any time after the reporting period must be promptly reported to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the Sponsor or its designated representative. The Principal Investigator is required to assess causality, and for all adverse events, sufficient information should be obtained by the Principal Investigator to try to determine the causality of the adverse event. For adverse events with a suspected causal relationship to a test product, follow-up by the Principal Investigator is required until the event or its sequelae are resolved or stabilized at a level acceptable to the Principal Investigator, and the Sponsor concurs with that assessment.

STATISTICAL PROCEDURES:

Product Efficacy Data Analysis:

Efficacy outcomes: The primary efficacy outcome will be the decrease in cold air stimulus sensitivity (VAS score) from baseline to 8 weeks. The secondary efficacy outcome will be the increase in tactile stimulus force from baseline to 8 weeks. Additional outcomes will include changes in cold air stimulus sensitivity and tactile stimulus force from baseline to 4 weeks.

(1) Data Analysis for Efficacy of the Primary Evaluation Item

Comparisons among the three groups for differences in the primary and secondary efficacy outcomes at each time point will be analyzed using analysis of covariance; because of the stratified randomization, age, gender, and baseline VAS cold air sensitivity will be included as covariates. Pre-planned post-hoc comparisons include: 1) pair-wise comparisons of the test product and the positive control against the placebo, to demonstrate effectiveness and 2) 95% confidence intervals (CI) for the ratio of means for the nano-HAP test product to the positive control to demonstrate non-inferiority of the test product with the positive control. Non-inferiority will be demonstrated if the lower

bound of the 95% CI falls within the 20% non-inferiority margin. If the data are log-normally distributed, then the analyses will be done on the log-transformed data. If the 95% CI for the difference between the test paste and the positive control is transformed back to the original scale, the back-transformed CI is a 95% CI for the ratio of means. If data are normally distributed, the 95% CI will be computed using Fieller's theorem, and the other condition that must be met to show non-inferiority is that the reference (i.e. positive control) mean must be significantly different from zero using a one-sided test. A 5% significance level will be used for all tests. From the results obtained for the placebo and positive control groups, it will be confirmed whether the non-inferiority margin used in the trial (20%) was appropriate or not.

(2) Data Analysis for the Efficacy of the Secondary Evaluation Item

Repeated measures analysis of covariance will be used for comparison between the 4-week and 8-week outcomes within each group. Interactions of the treatment effect with age, gender, and tactile sensitivity will be examined to evaluate significance of differential effects of the treatment by patient characteristics.

Sample Size Calculation

Based on data from prior studies, [A2, A5, A6] the coefficients of variation (the ratio of the standard deviation to the mean (SD/Mean)) at 8 weeks in cold air stimulus sensitivity and tactile stimulus force are estimated to be 0.500 and 0.400, respectively. [A7] Based on this COV, the power and sample size for non-inferiority t-tests from a parallel-groups design is calculated with the statistical hypotheses expressed in terms of mean ratios (Treatment Mean / Reference Mean) instead of mean differences. Using the software PASS 2019, v19.0.1, the sample size for Non-Inferiority Tests for the Ratio of Two Means is calculated from R Package of Chow [A8] by inputting the following information;

Option	Value
Design Tab	
Solve For:	Sample Size
Higher Means Are:	Better (H1: R > 1 - NIM)
Power:	0.80
Alpha:	.050
Group Allocation:	Equal (N1 = N2)
NIM (Non-Inferiority Margin):	0.2
R1 (Actual Ratio):	1.0
COV (Coefficient of Variation):	0.5 0.4

The following results were generated by the software.

Non-Inferiority Tests for the Ratio of Two Means

Numeric Results for a T-Test

R = Treatment Mean / Reference Mean

Higher Means are Better

Hypotheses: H0: $R \leq 1$ - NIM vs. H1: $R > 1$ - NIM

Target Power	Actual Power	N1	N2	N	-NIM	Bound R0	R1	COV	Alpha
0.80	0.80419	38	38	76	-0.200	0.800	1.000	0.400	0.050
0.80	0.80557	57	57	114	-0.200	0.800	1.000	0.500	0.050

The highlighted numbers are the sample sizes if primary outcome measure is based on cold air (green) or tactile stimuli (yellow). The sample sizes were calculated for nano-HAP (N1) and KNO_3 (N2) groups. (By default the placebo group will have the same sample size).

Report Definitions

Target power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.

Actual power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.

N1 and N2 are the number of items sampled from each population.

N is the total sample size, N1 + N2.

-NIM is the magnitude and direction of the margin of non-inferiority. Since higher means are better, this value is negative and is the distance below one that is still considered non-inferior.

R0 is the corresponding bound to the non-inferiority margin and equals 1 - NIM.

R1 is the mean ratio (treatment/reference) at which the power is computed.

COV is the coefficient of variation on the original scale.

Alpha is the probability of rejecting a true null hypothesis.

Summary Statements

Group sample sizes of 38 in the first group and 38 in the second group achieve 80% power to detect non-inferiority using a one-sided, two-sample t-test. The margin of non-inferiority is 20%. The true ratio of the means at which the power is evaluated is 1.000. The significance level (alpha) of the test is 0.050. The COV of both groups are assumed to be 0.400.

With a sample size of at least 57 subjects per group completing the study, a non-inferiority test of means using two one-sided tests achieves 80% power at a 5% significance level for cold air stimulus sensitivity when the true ratio of the means is 1.000 and the non-inferiority limit of the mean ratio is 20%. Because the COV for tactile stimulus force is smaller, the study will have higher power for that outcome. To allow for 10% dropout, the study will enroll 64 subjects per group (192 subjects in total). Sample size calculations were performed using PASS 2019 (Kaysville, UT).

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment sample size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
10%	38	38	76	43	43	86	5	5	10
10%	57	57	114	64	64	128	7	7	14

Definitions

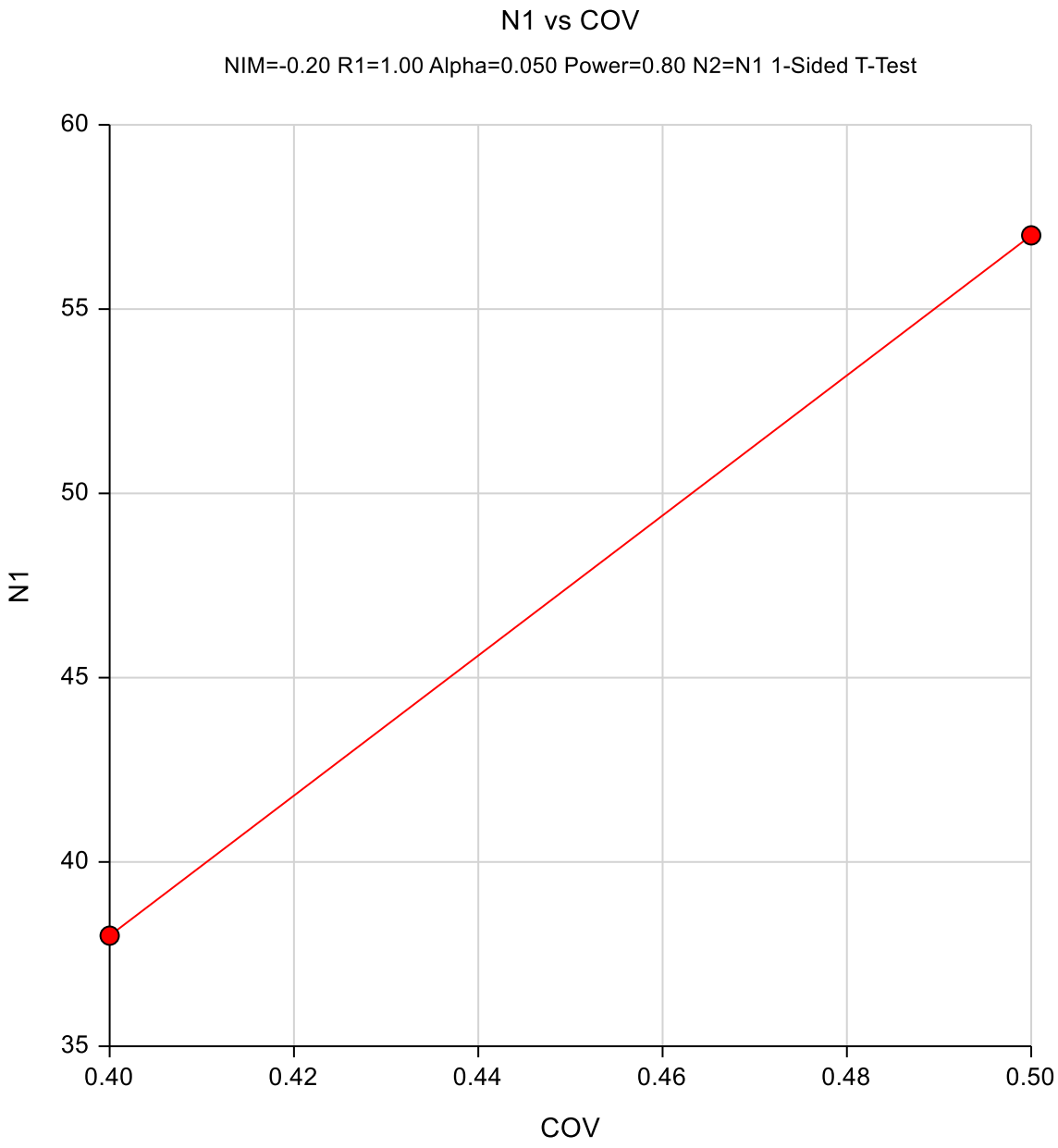
Dropout Rate (DR) is the percentage of subjects who are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e. who will be treated as "missing").

N1, N2, and N are the evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.

N1', N2', and N' are the number of subjects that should be enrolled in the study in order to end up with N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' always rounded up. (See references A7, pages 52-53, or A8, pages 32-33.)

D1, D2, and D are the expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Chart Section



Criteria for Test Aborting and Drop-out

Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the Principal Investigator or Sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort shall be made to document subject outcome, if possible. The Principal Investigator should inquire about the reason for withdrawal, and request that the subject return all unused

test product, and return for a final visit, if applicable, and should also follow-up with the subject regarding any unresolved adverse events.
If a subject withdraws from the trial and also withdraws his/her consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.
The Principal Investigator may discontinue a subject's participation if, in the opinion of the Principal Investigator, the subject is no longer a suitable candidate for the study. Possible reasons for such discontinuation include, but are not limited to:

- Adverse event
- Deviation from the protocol
- Missed appointment(s)
- Subject no longer meets eligibility criteria
- Use of antibiotic therapy or other prohibited medication during the study period

Criteria for Inclusion of Subjects as Appropriate for Efficacy Analysis

- Usage rate of toothpaste was 80% or more
- No evidence of events or activity likely to impair the reliability of the examination results, such as loss of diary records, etc.
- Subject has complied with the required restrictions during the examination period

Period of Data Storage :

The Principal Investigator agrees that all basic documentation used in the study (informed consent forms, Case Report Forms (CRFs) and all other relevant documents) shall bear superimposed Japanese translation, for reference purposes only, to be provided in advance by the Sponsor, and that the Sponsor shall have access to copies of all such documentation, if it so requests, upon completion of the study. To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Principal Investigator agrees to keep records including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment abrogation. The records shall be retained by the Principal Investigator according to ICH guidelines and local regulations, or as specified in the Clinical Study Agreement, whichever is the longer period.
If the Principal Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor must be notified in advance. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor.

The Principal Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

Schematization of Test Design

	1st Visit	2nd Visit	4 weeks	3rd Visit	4 weeks	4th Visit	4 weeks	5th Visit
Initial Screening: selection of candidates eligible for recruitment screening and receipt of candidates' informed consent	○							
Recruitment Screening: ①Preliminary examination: selection of candidates eligible to proceed to washout period		◎						
②Washout period(4 weeks)			⟷					
③Baseline measurement: final selection of subjects eligible to participate in the trial				◎				
Subject enrolment				○				
Randomization / assignment to groups				○				
Use of test toothpaste (4 weeks)				○	⟷			
Examination/measurement after 4weeks						◎		
Use of test toothpaste (another 4 weeks)							⟷	
Examination/measurement after 8 weeks								◎
Record-keeping in diary (8 weeks)					⟷	⟷	⟷	

References

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