

Signature Page for VV-TMF-00176 v4.0

Protocol Number: Protocol No. CRO-2020-CAR-ARG-ED_MOD April 2, 2024

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Reason for signing: Approved	[REDACTED]
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Colgate-Palmolive Co.

CLINICAL TRIAL PROTOCOL

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Approved

Investigator's Agreement

I understand that all documentation supplied to me by the sponsor concerning this study, which has not been previously published, will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

The study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the sponsor, and the IRB, except where necessary to eliminate an immediate hazard to the subjects.

I agree to monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority (ies) as required.

I understand that there is nothing in this document which is intended to limit my authority as a dentist to provide emergency care under applicable regulations.

I have read and approved this protocol. My signature confirms my agreement that the clinical study will be conducted in full compliance with the protocol and all applicable laws, regulations and regulatory requirements including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki and all applicable country-specific and local regulations. All required study information will be archived as required by regulatory authorities.

I have read, understood, and do agree to abide by all the conditions and instructions contained in this protocol, "A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children."

Protocol # CRO-2020-CAR-ARG-ED

Investigator Signature

Date

Investigator Name Printed

Sponsor Agreement

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

STUDY NO.: *CRO-2020-CAR-ARG-ED*

SPONSOR: Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

The signatures of the Sponsor's representatives below constitute the Sponsor's agreement:

- a) to all provisions of the protocol;
- b) to comply with ICH GCP Guidelines and all applicable country-specific and local laws, regulations and guidelines.



Maria E Ryan, DDS, PhD, Vice President, Chief Dental Officer
Oral Care Research & Development
Colgate-Palmolive Technology Center

1/29/2020
Date

COLGATE-PALMOLIVE

Clinical Study Protocol

Title: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Protocol No. CRO-2020-CAR-ARG-ED

IND # 140794

Investigational Medicinal Product (IMP) COL101 (arginine)

Indication Reduction in dental caries

Sponsor: Oral Care Research & Development
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Medical Director: Maria E Ryan, DDS, PhD
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Study Investigators: Details of participating Study Investigators, clinical study sites and other study personnel is contained in the Clinical Trials Master File and may be obtained from the Sponsor

PROTOCOL SYNOPSIS

Protocol Title:	A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children
Protocol Number:	CRO-2020-CAR-ARG-ED
Study Phase:	Phase II
Rationale for the Study:	Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia et al., 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and also creates an environment that disfavors cariogenic bacteria and their deleterious activities. The present study is intended to evaluate anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year in 10 to 14 year old children. The outcome of this study may lead to an alternative method of caries prevention.

Study Design:

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in Section 5 of this protocol. At each study site, each enrolled subject will be randomized in a 1:1:1:1 ratio into one of four parallel study groups.

Group 1 dentifrice	1.5% arginine
Group 2 dentifrice	4.0% arginine
Group 3 dentifrice	8.0% arginine
Group 4 dentifrice	0.24% sodium fluoride with no arginine

Subjects will be required to brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice for one year. Measurements for safety and product use compliance will be conducted after 3 months, 6 months, 9 months and 12 months of assigned product use. In addition, caries examinations using the International Caries Detection and Assessment System (ICDAS) will be conducted at Baseline and at the 6 months and 12 months' time points. All subjects will be monitored for adverse events (AEs) during the course of the study.

Objectives:

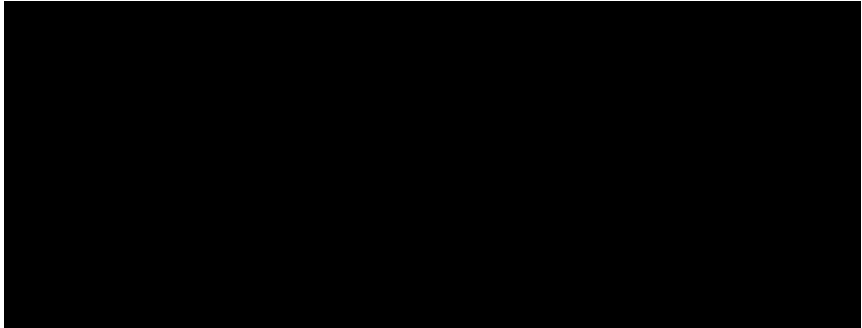
The objective of this study is to assess the safety and to evaluate the anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices containing 1.5%, 4% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10-14 year-old children over a one year period.

Main Endpoints:

Primary Endpoint: The primary efficacy endpoint will be the incremental subject-wise DMFS score after one-year of product use

Secondary Endpoints:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use.

- Clinically significant change in ICDAS severity scores between the baseline and the six-month and one-year examinations and between the six-month and one-year examinations.
 - Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6.
 - Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.
- 

Study Population:

Healthy school children 10 to 14 years of age with the presence of second permanent molars or evidence of erupting permanent second molars and evidence of previous caries experience.

Number of Subjects Planned:

2000 children (10-14 years of age) will be enrolled with the expectation that at least 1,800 subjects will complete the clinical trial at the end of a one-year period (10% annual attrition).

Number of Centers:

This study will be conducted by Study Investigators that are faculty from U.S. dental schools with standing approval from the Commission on Dental Accreditation and a Clinical Research Organization. Nine sites are planned.

Main Criteria for Inclusion:

- Healthy children 10-14 years of age of either sex. Subjects must be in good general health as evidenced by a review of their medical history
- Subjects must have presence of second permanent molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through.
- Subjects must have evidence of previous caries experience (DMFT >1).

	• Subjects must have two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth.
Test Products:	COL101 (arginine) dentifrices: 1.5%, 4.0%, and 8.0% arginine.
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Reference Therapy:	Positive control dentifrice: 0.24% sodium fluoride (1100 ppm F)
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Duration of Treatment:	For all dentifrices, subjects will be instructed to brush their teeth for two minutes twice daily using their assigned dentifrice for one year.
Efficacy Parameters:	Increments in Decayed Missing or Filled Surfaces (DMFS) over the one-year duration of the study. Caries threshold at the “moderate” cavitation caries level of ≥ 3 in the International Caries Detection and Assessment System (ICDAS).
Safety Parameters:	Safety will be assessed by an evaluation of all reported/observed adverse events during the course of the study and by hard and soft-oral tissue examinations conducted at Baseline, 3 months (± 1 month), 6 months (± 1 month), 9 months (± 1 month) and at 1 year (± 1 month).
Primary Objective:	The objective of the study is the estimation of the effectiveness on the reduction of caries of each of the three test products (1.5%, 4.0%, and 8.0% Arginine) relative to the positive control (0% arginine/sodium fluoride 0.24%).
Study Monitoring (Data Safety Monitoring Board):	The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. Specific for this trial, the incidence of caries progression in each of the Study Product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DMSB can recommend removal of individual

subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor.

Statistical Methods:

Efficacy of each of the four treatment groups will be estimated by the mean 1-year DMFS increment. Associated 95% confidence intervals will also be calculated. Generalized linear models will also be used to compare the DMFS increments statistically. Hard- and soft-tissue findings will be summarized by treatment group. Adverse events will be summarized by treatment group.

Approved

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LIST OF ABBREVIATIONS

ADA	American Dental Association
AE	Adverse Event
ANCOVA	Analysis of covariance
CRF	Case Report Form
CFR	Code of Federal Regulations

CPI	Community Periodontal Index
DMFS	Decayed Missing Filled Surfaces
DMFT	Decayed Missing Filled Teeth
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
ICCMS	International Caries Classification and Management System
ICDAS	International Caries Detection and Assessment System
ICH	International Conference on Harmonisation
IND	Investigational New Drug (Application)
IRB	Institutional Review Board

MRTD	Maximum Recommended Therapeutic Dose
NaF	Sodium Fluoride
NSAE	Non Serious Adverse Event

PSR	Periodontal Screening and Recording
SAE	Serious Adverse Event
US	United States
WHO	World Health Organization

1. INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

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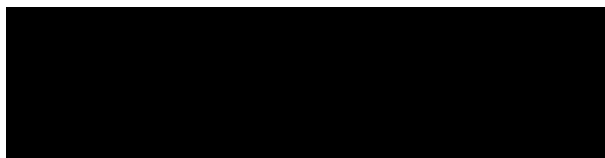
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Biostatistician:



2. INTRODUCTION AND BACKGROUND

Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia *et al.*, 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and creates an environment that disfavors cariogenic bacteria and their deleterious activities.

2.1. Rationale for the Study

The present study is intended to evaluate anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year. The outcome of this study may lead to an alternative method of caries prevention

2.2. Risk-Benefit Assessment

L-arginine is a semi-essential amino acid that can be obtained through dietary sources such as dairy products, beef, pork, soybeans, poultry, and granola among other sources. The normal intake of L-arginine from dietary sources is orders of magnitude higher than incidental ingestion from dentifrice. This amino acid is considered semi-essential because it can be synthesized *de novo* from glutamine, glutamate, and proline. Endogenous synthesis of arginine can, however, be insufficient e.g. during periods of growth, in inflammatory disease states or during infections.

L-arginine is generally recognized as safe (GRAS) by the US FDA when used in accordance with good manufacturing practice (21CFR 582.5145) and has been approved for use as a food additive permitted for direct addition to food for human consumption (21CFR 172.320 – amino acids). Although a Recommended Daily Allowance (RDA) has not been set, a Maximum Recommended Therapeutic Dose (MRTD) has been provided and set at 500 mg/kg body weight/day for L-arginine supplementation by the US FDA. The expected exposure to arginine from the use of dentifrice (maximum exposure, 2 yr old = 14 mg) is well below both the MRTD and the normal dietary intake.

Arginine has a good safety profile and is currently marketed in the United States (US) as an ingredient in dentifrice. Proven clinical benefits include the reduction of dentin hypersensitivity. There has been no observed pattern of adverse events (AEs) associated with its regular use.

2.3. Compliance Statement

The study will be conducted according to the protocol and in compliance with, International Council for Harmonization Good Clinical Practice (GCP) guidelines and other applicable local regulatory requirements and laws^{2,3}.

3. OBJECTIVES

The objective of this one-year study is to assess the safety and to evaluate the anti-carries efficacy of non-fluoride dentifrices containing 1.5%, 4% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10 to 14 year old children.

Approved

4. OVERALL DESIGN AND PLAN OF THE STUDY

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in [Section 5](#) of this protocol. At each study site, each enrolled subject will be randomized into one of four parallel study groups (1.5% arginine dentifrice, 4.0% arginine dentifrice, 8.0% arginine dentifrice or 0.24% sodium fluoride dentifrice with no arginine). Voluntary participants will brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice. Measurements for efficacy, safety and assessment of product use compliance will be conducted at baseline, 6 months (± 1 month) and 1 year (± 1 month). Additional safety evaluations including evaluation of oral soft and hard tissues, as well as and product use compliance assessment will be performed at 3 months and 9 months (± 1 month). All subjects will be monitored for adverse events (AE) during the course of the study.

Subjects who are discontinued cannot reenter treatment and will not be replaced. Adverse events will be monitored for up to 30 days following study conclusion, until the AE is resolved or it is determined by the Study Investigator and Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) to be stable.

4.1. Overview

4.1.1. Screening and Selection of Subjects

Candidates will be screened by a trained and calibrated study examiner to identify those subjects who meet the inclusion/exclusion criteria ([Section 5](#)) and the findings will be recorded on an Inclusion/Exclusion case report form (CRF). Parents or legal guardians of participating children will be informed about all aspects of the study and informed consent/assent forms will be completed by each participating subject and by their parent or legal guardian.

At each site, subjects who, in addition to meeting the inclusion criteria, assent to voluntarily participate and whose parents or legal guardian have signed the informed consent form will be enrolled.

4.1.2. Baseline Clinical Examinations of Soft and Hard Tissue

The following evaluations will be performed at Baseline:

Soft and Hard Tissues will be examined and abnormalities will be noted in corresponding CRFs.

The soft tissue structures examined will include the soft palate, hard palate, gingival mucosa, buccal mucosa, mucogingival folds, tongue, sublingual and submandibular areas, salivary glands, tonsillar and pharyngeal areas. Observations will be listed as “Normal” and “Abnormal” and abnormalities will be described.

The hard tissue structures examined will include assessing for enamel irregularities, tooth fracture, pathologic tooth wear, cavitated caries lesions, residual roots, faulty restorations

and implants. Observations will be listed as “Normal” or “Abnormal” and conditions noted as abnormal will be described.

The International Caries Detection and Assessment System (ICDAS) will be used to determine caries severity and the caries lesion activity and to establish subject eligibility^{4,5,6}. As the subjects are recruited, baseline caries examinations will be performed by trained and calibrated study examiners who will carry out the examinations according to ICDAS Criteria. All examinations will be conducted after subjects have brushed their teeth with water and, if necessary, brushed again and possibly flossed by the study examiner or study personnel.

The severity criteria used in the ICDAS diagnostic system are as follows:

Code 0 Sound tooth surface

There should be no evidence of caries (either no or questionable change in enamel translucency after prolonged air drying (suggested drying time 5 s). Surfaces with developmental defects such as enamel hypoplasias; fluorosis; tooth wear (attrition, abrasion and erosion), and extrinsic or intrinsic stains will be recorded as sound. The examiner should also score as sound a surface with multiple stained fissures if such a condition is seen in other pits and fissures, a condition which is consistent with non-carious habits (*e.g.* frequent tea drinking).

Code 1 First visual change in enamel

Code 1: Pits and fissures

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air drying (approximately 5 s is suggested to adequately dehydrate a carious lesion in enamel) a carious opacity or discoloration (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel.

OR

When there is a change of color because of caries which is not consistent with the clinical appearance of sound enamel and is limited to the confines of the pit and fissure area (whether seen wet or dry). The appearance of these carious areas is not consistent with that of stained pits and fissures as defined in code 0.

Code 1: Smooth tooth surfaces

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air-drying a carious opacity (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel. This will be seen from the buccal or lingual surface.

Code 2 Distinct visual change in enamel

The tooth must be viewed wet. When wet there is a (i) carious opacity (white spot lesion) and/or (ii) brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel (Note: the lesion must still be visible when dry)

Code 3 Localized enamel breakdown because of caries with no visible dentin or underlying shadow

The tooth viewed wet may have a clear carious opacity (white spot lesion) and/or brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel. Once dried for approximately 5 s there is carious loss of tooth structure at the entrance to, or within, the pit or fissure/fossa. This will be seen visually as evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the fissure or pit, and although the pit or fissure may appear substantially and unnaturally wider than normal, the dentin is NOT visible in the walls or base of the cavity/discontinuity.

If in doubt, or to confirm the visual assessment, the WHO/CPI/PSR probe can be used gently across a tooth surface to confirm the presence of a cavity apparently confined to the enamel. This is achieved by sliding the ball end along the suspect pit or fissure and a limited discontinuity is detected if the ball drops into the surface of the enamel cavity/discontinuity.

Code 4 Underlying dark shadow from dentine from dentin with or without localized enamel breakdown

This lesion appears as a shadow of discolored dentin visible through an apparently intact enamel surface which may or may not show signs of localized breakdown (loss of continuity of the surface that is not showing the dentin). The shadow appearance is often seen more easily when the tooth is wet. The darkened area is an intrinsic shadow which may appear as grey, blue or brown in color. The shadow must clearly represent caries that started on the tooth surface being evaluated. If in the opinion of the examiner, the carious lesion started on an adjacent surface and there no evidence of any caries on the surface being scored then the surface should be coded '0'.

Code 5 Distinct cavity with visible dentine

Cavitation in opaque or discolored enamel exposing the dentin beneath.

The tooth viewed wet may have darkening of the dentin visible through the enamel. Once dried for 5 s there is visual evidence of loss of tooth structure at the entrance to or within the pit or fissure – frank cavitation. There is visual evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the pit or fissure and in the examiner judgment dentin is exposed.

The WHO/CPI/PSR probe can be used to confirm the presence of a cavity apparently in dentin. This is achieved by sliding the ball end along the suspect pit or fissure and a dentin cavity is detected if the ball enters the opening of the cavity and in the opinion of the examiner the base is in dentin. (In pits or fissures the thickness of the enamel is between 0.5 and 1.0 mm. Note the deep pulpal dentin should not be probed).

Code 6 Extensive distinct cavity with visible dentine

Obvious loss of tooth structure, the cavity is both deep and wide and dentin is clearly visible on the walls and at the base. An extensive cavity involves at least half of a tooth surface or possibly reaching the pulp.

Classification of the Tooth Profile, Surface Condition and Lesion Activity status in the ICDAS

Tooth Profile	
1	When a permanent or temporary filling is present, missing or defective
7	Not counted, unerupted teeth, congenitally missing or supernumerary teeth, teeth removed for reasons other than dental caries, and primary teeth retained in the permanent dentition
8	Trauma; poor prognosis (Not Counted)
9	When a tooth has been extracted due to caries

Surface Condition	
0	No filling, No sealant
1	Sealant (partial or complete)
2	Filling: when a permanent or temporary filling is present, missing or defective (e.g. composite, amalgam, crown, etc.)
3	Restoration: restored due to other reasons (e.g. cervical lesions, residual composite due to ortho or aligners, diastema closure, etc.)

Caries Lesion Activity Assessment (ICCMS Guide)⁶:

Code 0 Signs of Inactive Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located near the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing. Surrounding enamel has polished edges and may be shiny and hard and smooth when the ball-ended probe is moved gently across the surface.

Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning. The adjacent gingival tissue may show signs of inflammation or bleed upon probing.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.

A study examiner (dentist) will evaluate the condition of every surface of every tooth and will verbalize the findings to a trained recorder who will enter the data on to a CRF.

4.1.3 Subsequent Soft and Hard Tissue Examinations

Subsequent 6-month and 12-month clinical examinations will be conducted following the same examination criteria and procedures employed at baseline. Additional soft and hard tissue examinations will be conducted at 3 and 9 months for safety reasons. Examinations 3, 6 and 9 months will coincide with resupply of assigned toothpaste and toothbrush.

4.1.4 Calibration of Examiners

For each cohort, a didactic training session will be held to the participating examiners prior to the actual ICDAS clinical calibration session by a gold standard examiner (the Principal Investigator). This didactic session will include: 1) Review of ICDAS depicting the dental status examination criteria; 2) Evaluation of participating examiners' knowledge of the criteria; 3) Clinical Training with demonstration examinations; and 4) Practice Examinations of extracted teeth.

On training session day one, examiners from one cohort will see the first few qualifying screening subjects together and discuss their scores with the gold standard examiner and among each other. The calibration may start on day one or day two at the senior examiner's discretion. On calibration session (days 2 and 3) the participating examiners will conduct the examinations independently. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each permanent tooth surfaces will be scored. On day 3, approximately 3-5 willing subjects from calibration session (day 2) will be asked to return to the clinic for a repeat session. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each surface of permanent teeth will be scored.

Each tooth will be categorized into one of seven categories (0-6) based on its ICDAS score. Analyses will be performed at the tooth level and the subject level. Intra and inter-examiner reliability will be assessed using weighted kappa scores. A kappa score of 0.61

or higher will be considered substantial agreement for inter-examiner reliability. A kappa score of 0.81 or higher will be considered substantial agreement for intra-examiner reliability. If an examiner fails to achieve the said mark, the exercise may be repeated on some of the same subjects if they're willing to come back for future dates.

4.1.5 At-Home Product Use

After the baseline examinations are completed, dental study personnel (non-examiners) will give subjects tubes of their assigned dentifrice and adolescent size soft bristled toothbrushes. Subjects will be instructed to brush their teeth by applying a full ribbon of their assigned dentifrice to their assigned toothbrush head, and brush their teeth for 2 minutes twice daily. Subjects will also be requested to use no other dental products, such as other toothbrushes, mouth rinses or other dentifrices during the course of the study, however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with the dentist. Subjects that routinely use dental floss may continue to do so during the study period.

The assigned toothpaste and a new toothbrush will be re-supplied every three months.

4.1.6 Dental Treatment During the Study

Subjects will be instructed to continue regular visits to the dentist and routine dental treatment during the course of the study. In addition, at every scheduled study examination, subjects will receive a referral for dental care, if needed.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects meeting all criteria below will be included in the study:

1. Subject assent and parental/guardian informed consent for voluntary participation.
2. Willingness and ability to use the assigned products according to instructions, availability for all appointments and likelihood of completing the clinical trial.
3. Children ages 10-14 years at baseline.
4. Presence of permanent second molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through the mucosa.
5. Good general health as evidenced by a review of the medical history.
6. Subjects who, at study entry, have present two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth and previous caries experience (DMFT >1).

5.2. Exclusion Criteria

Subjects presenting any of the criteria below will be excluded from the study:

1. Presence of fixed or removable prosthetic appliance or orthodontic treatment involving more than four permanent teeth.
2. Use of medication that could increase the risk of developing dental caries, i.e. medications that reduces saliva flow and those with high sugar content.
3. Long-term antibiotic therapy.
4. Children with a confirmed diagnosis of cognitive and/or motor impairment.
5. Severe malocclusion.
6. Subjects who, at study entry, have present severe caries (ICDAS 5 or 6) on five or more teeth.
7. Evidence of moderate to severe periodontal disease.
8. Participation in any other clinical study within the 30 days preceding the start of the clinical study.
9. Known history of allergies or other adverse reactions to arginine, or oral care products, or their ingredients.

5.3. Withdrawal and Replacement of Subjects

A genuine effort will be made to determine the reason(s) why a subject fails to report to the scheduled examinations or has been dropped from the study. A subject will be dropped from the study if any of the following occurs:

1. Subject fails to report for the examinations.
2. Subject elects to terminate participation in the study.

3. Sponsor elects to terminate the study.
4. Subject experiences a serious adverse reaction to the test products. Withdrawal of the subject is at the discretion of the Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendation of the Medical Monitor). (See [Section 7.5.7](#) for SAE reporting procedures).
5. Subject is determined to be non-compliant by the Site PI in consultation with the Sponsor.

Subjects discontinued from the study for any reason will not be allowed to re-enter the study and will not be replaced. Subjects withdrawn due to AEs will receive follow-up as outlined in [Section 7.5.8](#)

5.4. Statistical Basis for Sample Size

The sample size requirement was determined based on the precision of the efficacy estimate for each treatment group. Details regarding this determination are provided in [Section 10.2](#) of this protocol.

5.5. Subject Identification, Randomization, and Blinding

Enrolled subjects at each study site will be assigned subject numbers specific to that site. An un-blinded biostatistician will generate a separate randomization listing for each study site, ensuring that the study biostatistician will remain blinded to the treatment assignments until the study has been completed. The randomization listings will be transferred to a designated un-blinded individual at each study site, who will manage randomized assignment, product dispensing and resupply. In addition to utilizing this information for the dispensing to treatment to enrolled subjects, this individual will also be on call to provide emergency un-blinding information for an individual subject if such a need should arise during the study. Each study site will maintain a list of all individuals who are privy to the randomization listing. At the conclusion of the study, after all data cleaning and statistical analyses have been programmed and completed (based on the blinded study data), the investigator at each study site will indicate that un-blinding can proceed. Un-blinding of the study data will not take place until this indication has been received from all study sites.

5.6. Un-blinding

If the Study Investigator determines that some event, such as a serious adverse event (SAE) has occurred and the treatment should be un-blinded for that subject, the Study Investigator should contact the Colgate Study Monitor. The Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendations of the Medical Monitor) will then make a decision about breaking the blind for the subject. The Colgate Study Monitor will then contact the study code un-blinder, and the subject will be un-blinded and documented accordingly.

6. STUDY PRODUCT

6.1. Identity

Study Product 1 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 1.5% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 2 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 4.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 3 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 8.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 4 (Control Product) Name: Dosage form: Manufacturer: Description:	Dentifrice 0.24% sodium fluoride (1100 ppm F) Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube

6.2 Packaging, Labeling, and Storage

The packaging and labeling will be performed by the sponsor according to all local legal requirements.

All supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to subjects, the study dentifrices will be stored in a securely locked area, only accessible to authorized personnel.

The study products will be coded and the identity of the products will be concealed.
The sponsor will provide the study dentifrices to the site.

Representative product labeling that will be placed on the outside box of each tube of toothpaste and on the tube of toothpaste itself can be found in Appendix IV.

6.3 Product Use Instructions

Subjects will be verbally instructed to brush their teeth twice daily (morning and evening before bed) for two minutes each time, using their assigned dentifrice and toothbrush. A timer will be provided to each participant as an aid to comply with 2-minute brushing. Subjects will also be instructed to dispense a full ribbon of toothpaste covering the full length of the toothbrush head for each tooth brushing. Study personnel will demonstrate this at the initial study visit. No oral hygiene products, other than the toothbrush and the dentifrice provided, should be used during the treatment period. Subjects that routinely use dental floss may continue to do so during the study period.

In addition to verbal product use instructions and essential information provided in product labels, subjects will be given written product use instructions to take home (Appendix V).

6.4 Study Product Dispensing

Kits containing dentifrices and toothbrushes shall be provided to the subjects every three months. All product dispensing and resupply will be handled by a study site individual unblinded to product assignment.

The initial distribution of the study products will occur at the examination facility after completion of the baseline examinations. Subsequent product dispensing will then take place every three months at the 3-month, 6-month and 9-month examination visits. Subjects will receive at each of these product resupply visits a new adolescent-sized, soft-bristled toothbrush and sufficient dentifrice will be dispensed to last until the next scheduled visit (one tube (4.7 oz tube) for every month) of product use.

Should additional dentifrice be required between routine deliveries, the subject will contact the study coordinator. The coordinator shall immediately ensure resupply via appropriate study personnel, preserving the double-blind design.

6.5 Study Product Accountability

The Sponsor will provide each study site with sufficient amounts of the study products.

The study site will confirm in writing receipt of all batches of study product.

The study site will administer/dispense study product only to subjects included in this study according to the procedures established in this study protocol. Each subject will be given only the dentifrice assigned to him/her. Each dispensed tube of dentifrice will be documented in the dispensing log.

All supplies must be accounted for at the end of the study. The study site must maintain accurate and adequate records, including dates dispensed, quantities received, subject dispensed to, date returned by the subject, amount returned by the subject, date returned to the sponsor and/or destroyed at the study site.

At the end of the study, no remaining supplies are to be in the study site's possession. The study monitor will procure and document that all remaining study supplies are properly discarded by the site.

6.6 Product Use Compliance

Subjects will be expected to return previously dispensed study dentifrice (empty, partially used or unused tubes of dentifrice included) to the site at each of the pre-established product resupply events and exchanged for new supply to last until the next scheduled visit (Appendix XV). Unused study dentifrice will also be collected at the site at the end of study participation. The study site will weigh all tubes of toothpaste at the time of dispensing and weigh the tubes when returned, maintaining a log of the gathered information on a subject per subject basis. For each individual, the amount of toothpaste used will be estimated by weight at each of the tube return/collection time points and compared to the expected use based on projection of using "two ribbons" per day. A timer will be provided to each participant as an aid to comply with 2-minute brushing.

6.7 Concomitant Medications

Any medication used during the study period, other than the study dentifrices specified in the protocol, is considered a concomitant medication. All concomitant medications must be recorded at the beginning of every study visit through completion of a health questionnaire.

7 SAFETY

7.1. Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. The DSMB will include clinical research scientists and statistician not otherwise connected with the study that, collectively, have extensive experience in the management of clinical trials and in the conduct and monitoring of randomized clinical trials and will be competent in applying this experience to the study of children with dental caries. The DSMB will elect a chair under rules they define in their organizational meeting and review and approve a DSMB Charter provided by the Sponsor. The DSMB will have access to un-blinded safety and effectiveness outcome data during the trial that will be provided by an un-blinded data manager. Specific for this trial, the incidence of caries progression in each of the study product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DSMB can recommend removal of individual subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor. The DSMB will meet at least every three months throughout the trial and distribute a report summarizing any safety concerns or serious adverse events that have occurred since the last three-month exam. This report will be submitted to the IRBs of each study site (or Central IRB), the Study Investigators and the Sponsor. Each report should contain an open section containing materials for blinded staff, and a closed section of treatment comparisons. Every precaution will be taken to maintain the blind from Study Investigators, study examiners, statisticians and the Sponsor. Interim conference calls may also be scheduled at the discretion of the board, Study Investigators or the Sponsor.

7.2. Stopping Rules

If an investigational product-related serious or unexpected AE occurs and it is determined to be an unacceptable risk to the health and safety of other investigational product recipients by the Study Investigator, Colgate Study Monitor, Medical Monitor, and DSMB, administration of investigational product will be discontinued until a thorough review of the events is undertaken by the Study Investigators, institutional review board (IRB) of record, and Colgate Monitor (who represents the recommendation of the Medical Monitor). The study may be resumed with the concurrence of the Medical Monitor (via Colgate Study Monitor), Study Investigators, and the US Food and Drug Administration (FDA).

7.3. Subject Safety Measures

Study subjects that have cavitated lesions (ICDAS 5/6) at their screening examinations will be referred to their dentist of record for necessary treatment. If the subject does not have a dentist, the study site will provide the names of three local dentists to the subject's parent/guardian.

7.4. Rescue Therapy

Any randomized subject that experiences pain, swelling, abscess or caries progression resulting in frank cavitation (ICDAS 5/6) during any follow up visit will be referred to their dentist of record for appropriate dental treatment. If the subject does not have a dentist, the study site will refer the subject to a local dentist or a dental school clinic.

7.5. Adverse Events (AEs)

Illnesses present at entry to the study are considered pre-existing conditions and will be documented on the Health Questionnaire (sample included as Appendix VII). AEs will be followed for up to 30 Days, until it resolves or is determined by the Study Investigator and the Medical Monitor (through the Colgate Study Monitor) to be stable.

All AEs must be reported and documented as described below.

7.5.1 Definitions

Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined by the ICH Guideline for Good Clinical Practice (ICH GCP) as follows:

Adverse Event: Any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include any clinically significant deterioration of a subject's medical status, after being enrolled in the study and signing an Informed Consent form. The AE may involve any organs or systems and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change from baseline, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring after the first administration of study medication is an adverse event. All such occurrences must be recorded and reported accordingly, whether they appear causally related to the study medication, or not.

Serious Adverse Event: Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening adverse event
- Inpatient hospitalization, or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience 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 important 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.

7.5.2 Assessment of Adverse Events

Volunteered, observed, and elicited AEs will be recorded. This includes those the subject reports spontaneously, those the study examiner observes, and those the study examiner elicits in response to open-ended questions at the times indicated on the Schedule of Study Activities, [Section 8.1](#).

All clinical complaints, symptoms, or signs that meet the adverse event definition will be recorded on the Adverse Events case report form (Appendix XIII) using a recognized medical term or diagnosis that accurately reflects the event. Source documentation should be maintained that allows for clear identification of each adverse event and the following parameters required for the CRF:

- AE description
- Date of onset
- Date of resolution
- Outcome
- Severity
- Seriousness
- Relationship to study drug (causality)
- Actions taken

Adverse events will be assessed by the investigator or designee for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification of the sponsor.

For CRF data collection purposes, the outcome of all adverse events recorded on the Adverse Event form should be reported within two (2) weeks of the study completion. The Investigator will include this information in the Site Report providing a line listing using the Periodic/End of Study Report Form (Appendix XIV) and attaching the individual adverse event form for each case reported. However, the Investigator is responsible for following all

adverse events until resolution or until no longer of clinical concern, and providing these data to the Sponsor.

When protocol duration, is six (6) months or longer, a Periodic/End of Study Report Form must be completed and included as part of your Site Report every six (6) months for the duration of the protocol.

7.5.3 Serious Adverse Events (SAEs)

Federal law defines an SAE as any event, occurring at any dose, which suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, an SAE can be described as one or more of the following:

- **Fatal:**

This includes deaths that appear to be completely unrelated to study product (e.g., car accident). If a subject dies during the study and an autopsy is performed, autopsy results will become part of this subject's CRF. Possible evidence of organ toxicity and the potential relationship of the toxicity to the study product will be of particular interest. The autopsy report should distinguish the relationship between the underlying diseases, the study product's side effects, and the cause of death.

- **Life-threatening:**

A life-threatening AE is any adverse event during which the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered a life-threatening event though drug-induced hepatitis can be fatal.

- Permanently or significantly disabling
- Requiring/prolonging inpatient hospitalization
- A congenital anomaly/birth defect

AEs that fall outside of these categories are not considered serious.

7.5.4 Severity

Regardless of the classification of an AE as serious or not, its severity must be assessed according to the following categories:

Mild:	does not interfere with routine activities
Moderate:	interferes with routine activities
Severe:	impossible to perform routine activities

Note that a severe AE need not be serious and that an SAE need not, by definition, be severe.

7.5.5 Relationship to Study Product

The study examiner will assess the relationship between the study product and the AE.

The following definitions are used to determine the relationship between the study product and the AE.

Definite: (must have four of the following)

This category applies to those AEs that the study examiner feels are incontrovertibly related to study product. This relationship may be considered definite if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose and recurs with re-exposure to study product (Note: this is not to be construed as a requirement to re-expose the subject; however, a category of definitely related can only be used when recurrence is observed);
- follows a known pattern of response to study product;
- is associated with toxic levels of the study product in the blood or positive results on drug sensitivity tests (e.g., skin test).

Probable: (must have 3 of the following)

This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to study product. This relationship may be considered probable if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the study product, yet the event is clearly related to the study product (e.g., tardive dyskinesia);
- follows a known pattern of response to study product.

Possible: (must have two of the following)

This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the study product appears unlikely, but cannot be ruled out with certainty. This relationship may be considered possible if or when the adverse event:

- follows a reasonable temporal sequence after administration of the study product;
- could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- follows a known pattern of response to study product.

Unlikely: (must have two of the following)

In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study product. This may be considered unlikely if or when the adverse event:

- does not follow a reasonable temporal sequence after administration of the study product;
- could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- does not follow a known pattern of response to study product;
- does not reappear or worsen when the study product is re-administered.

Not related:

This category applies to those AEs that, after careful consideration, are clearly and incontrovertibly due to causes other than the study product (e.g., disease or environment).

7.5.6 Recording Adverse Events (AEs)

All AEs, regardless of relationship to study product, must be recorded on the Adverse Events CRF. All AE reports should contain the date the AE occurred, a brief description of the event, time of onset, duration of event, intensity, treatment required, relationship to study product, study product action taken, outcome, and whether the event is classified as serious.

7.5.7 Reporting Non Serious Adverse Events (NSAEs) and Serious Adverse Events (SAEs)

The Study Investigator must complete the Report of Adverse Event when an AE is identified. The Study Investigator must report any NSAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 72 hours of the event. The Study Investigator will provide the NSAE Report to Central IRB within 1 month of the event. The Colgate Study Monitor will then report the NSAEs to the DSMB within 1 month of discovering the event.

The Study Investigator must report any SAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 24 hours of the event. The Study Investigator will provide SAE Report to Central IRB no later than 2 weeks (10 business days) of the event. The Colgate Study Monitor will then report the SAEs to the DSMB within 5 days of discovering the event.

The Study Investigator must also follow local IRB guidelines for Adverse Event reporting. The Study Investigator may be asked to submit substantiating data, such as diagnostic test reports, to the Colgate Study Monitor.

The Study Investigator and the Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) will review each Serious Adverse Event Report and evaluate the relationship of the event to study product.

Based on the Investigator and Sponsor's assessments of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new AE related to arginine raises concern over the safety of continued administration of the study product to subjects, the Sponsor will take immediate steps to notify the Federal Food and Drug Administration (FDA) and all investigators participating in clinical trials with arginine.

Further action that may be required includes the following:

- Modification of the protocol
- Discontinuation or suspension of the study
- Modification of the existing consent/assent form and informing current study participants of new findings
- Addition of any newly identified arginine-related AEs to the list of expected AEs.

7.5.8 Follow-Up of Adverse Events (AEs)

The Investigator must continue to follow all SAEs and those non-serious events possibly related to study product until they resolve or until the Study Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

Any SAE occurring within 30 days after the end of the study and considered to be at least possibly caused by the study product, and therefore a possible adverse product reaction, must be reported as above.

7.5.9 Reporting Safety Information

The Study Investigator must promptly report to the Colgate Study Monitor, Central IRB, his or her Institutional Review Board (IRB), according to the specific guidelines of that IRB, all unanticipated problems involving risks to subjects. The Clinical Study Monitor will provide all unanticipated problems involving risks to subjects to the DSMB. This includes death from any cause and all SAEs associated, or possibly associated, with the use of the study product.

7.5.10 Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis, only in the event of an emergency. The Study Investigator or other physician in attendance in such an emergency must contact the Colgate Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Study Investigator will decide, in consultation with the Colgate Monitor (who consults with and represents the recommendations of the Medical Monitor), whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be recorded.

8. STUDY CONDUCT

8.1. Schedule of Study Activities

Assessment	Baseline	3 Month (±1 Month)	6 Month (±1 Month)	9 Month (±1 Month)	12 Month (±1 Month)
Informed Consent/Assent	X				
Baseline Medical History/ Concomitant Medications	X				
Hard and Soft Tissue Examinations	X	X	X	X	X
Conformance with Entry Criteria	X				
Caries Examination	ICDAS	Visual Monitoring for Safety	ICDAS	Visual Monitoring for Safety	ICDAS
Medical History Update/Concomitant Medications		X	X	X	X
Visit Form (Continuance)		X	X	X	X
Dentist Notice/Referral (when Necessary)	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X
Randomization, Study Group Assignment and Initial Toothpaste and Toothbrush Supply	X				
Study toothpaste and toothbrush re-supply		X	X	X	
Collection of previously dispensed study toothpaste and toothbrush		X	X	X	X
Assessment of Product Use Compliance		X	X	X	X
Periodic/End of Study Report Form for Non-interventional Studies on Humans			X		X

8.2. Observations by Visit

8.2.1 Baseline Examination

- Obtain parental written informed consent and participant assent
- Verify conformance with entry criteria (inclusion/exclusion criteria).
- Medical history/concomitant medications
- Hard and soft tissue evaluation
- ICDAS Caries Examinations

- Randomization
- Adverse Events
- Dentifrice and toothbrush distribution and written and oral instructions for use
- Dentist Notice/Referral (if necessary)

8.2.2 3 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- Adverse Events
- Dentifrice and brush collection and resupply
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)

8.2.3 6 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- ICDAS Caries Examinations
- [REDACTED]
- Adverse Events
- Dentifrice and brush collection and resupply
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)
- Periodic/End of Study Report Form for Non-interventional Studies on Humans

8.2.4 9 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- Adverse Events
- Dentifrice and brush collection and resupply
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)

8.2.5 12 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- ICDAS Caries Examinations
- [REDACTED]
- Adverse Events

- Dentifrice and brush collection
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)
- Periodic/End of Study Report Form for Non-interventional Studies on Humans

8.2.6 Follow-Up Procedures

Subjects will be followed for AE resolution, as defined in [Section 7.5.8](#)

8.3. Site / Study Termination

If the Sponsor, or the Investigator discovers conditions arising during the study that indicate that the study should be halted, it must be terminated after appropriate consultation between the study Sponsor, project manager, and Investigator. Conditions that may warrant termination include, but are not limited to:

- * The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- * Failure of the Study Investigator to enter subjects at an acceptable rate.
- * Insufficient adherence to protocol requirements.
- * A decision on the part of the sponsor to suspend or discontinue development of the study product.

9. DATA HANDLING AND RECORD KEEPING

9.1. Data Quality Assurance

Colgate Study Monitors will conduct a site visit to verify the qualifications of the Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

An Investigator's meeting will be held to introduce the Investigators and their key personnel to the study protocol, CRFs, procedures, and regulatory requirements.

The Study Investigator is required to prepare and maintain adequate and accurate case histories, designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRFs for this study must be consistent with the subject's source documentation (i.e., medical records).

9.2. Case Report Forms (CRFs) and Source Documentation

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

In this clinical trial visit forms, confirmation of enrollment, randomization, study group assignment, log of product dispensing, data from soft tissue and hard tissue examinations, data from caries examinations, and administration of [REDACTED] will be captured on electronic case report forms (eCRFs). Direct data entry into eCRFs will be captured and stored in Veeva Vault Clinical Suite. Paper case report forms (paper CRFs) will be used to capture all other data that will not be directly entered into the Veeva system, such as report of adverse events and documentation of product use compliance. Paper CRFs will be retained as original source documents and will be scanned and uploaded to the Veeva Vault Clinical Suite.

Veeva Vault is a cloud-based Content Management System (CMS) developed by Veeva Systems. The Vault Clinical Suite includes Vault eTMF and Vault CTMS. Vault Clinical enables increased compliance of clinical processes, inspection readiness, and permits a unified and connected view of clinical operations business functions. In addition, Veeva Vault produces secure and compliant audit trails in accordance with the FDA 21 CFR Part 11 Electronic Records, Electronic Signatures, and Eudralex Annex11: Computerized Systems regulations. All data collected from the web based EDC hosted on a private Google Cloud Platform (GCP) cloud will be verified before being sent through encoded HTTP POST requests to the Veeva Vault cloud hosted on Amazon's Web Services cloud (AWS).

A study coordinator, designated by the study center Investigator will be responsible for overseeing management principles including validated data entry at the point of data generation, data storage in one comprehensive relational database and data security.

9.3. CRF Fields as Database Entry Sources

CRFs should be considered the only source for database entry. Data should not be entered on any other form. Should an AE occur that requires clinical laboratory or electrocardiogram (ECG) data, the original printout should be attached to the Adverse Event CRF.

9.4. Direct Access to Source Data

During the course of the study, the Colgate Study Monitors will make site visits to review protocol compliance, compare CRFs and individual subject's medical records/study records, assess product accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records/study records will be performed in a manner to ensure that subject confidentiality is maintained.

Reviewing the CRFs for completeness and clarity, and cross-checking with source documents will be required to monitor the progress of the study. Moreover, regulatory authorities and/or the Sponsor's clinical quality assurance group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

9.5. Documentation of Consent, Privacy Notice and Storage of Study Documents

All informed consent/assent forms and privacy notices will be administered in either English or Spanish, whichever is most appropriate, and will be kept as source documentation. Informed Consent/Assent forms will be stored in a secure locked room designated for research charts storage in the clinical site. The Study Investigator will provide each subject's parent with a clear and understandable Privacy Notice (Appendix I-A presents the Sponsor's standard privacy notice) regarding the processing in connection with the study of personal data (i.e., any information relating to an identified or identifiable individual) by the Study Investigator, Sponsor and other persons involved in the study. The Study Investigator will obtain parental signature to this privacy notice. The original signed copy of the privacy notice for each subject participating in the study will be retained in the Investigator's study records. Each subject's parent will be given a copy of the privacy notice and the privacy notice will be referenced in and form a part of the overall study informed consent/notice process.

A baseline privacy notice is included in this protocol for that purpose. Any deviation to the privacy notice as regards processing by the Sponsor (including its vendors, monitors and other representatives) must be agreed with the Sponsor. In addition, The Study Investigator is responsible for ensuring that all study subjects' parents receive a copy of the privacy notice, and that the privacy notice includes any local requirements regarding data security and privacy laws and regulations applicable to the study and the subjects. Should the privacy notice provided by the Sponsor fail to meet any applicable local requirements, the Study Investigator is responsible for amending the privacy notice to bring it into compliance with local applicable regulations and the Study Investigator agrees to indemnify and be liable to the Sponsor for any damages resulting from such non-compliance. Subjects' study charts will be stored in a secure locked room designated for research charts storage in the clinical site.

The chart room is a limited- access area and only delegated study personnel will have access to the study charts and subjects' data.

9.6. Archiving Study Records

Essential documents should be retained for a minimum of 5 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or for at least 5 years since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local regulations.

Approved

10. STATISTICAL METHODS

10.1 Study Objectives and Hypotheses

10.1.1 Primary Study Objective

The primary objective of the study is the estimation of the effectiveness of the three test products (1.5%, 4.0%, and 8.0% Arginine) each relative to the positive control (0% arginine/sodium fluoride 0.24%).

Toward this end, the following null hypothesis will be considered for each of the three test products (1.5%, 4.0%, and 8.0% Arginine) in the analysis of the data:

- H_0 : There is no difference between the anti-caries efficacy of the test product and that of a dentifrice containing 0% arginine/ sodium fluoride 0.24% (1100 ppm F).

These hypotheses will each be tested through a comparison of the mean caries DMFS increments for the respective dentifrices. The secondary efficacy endpoints, counts of clinically significant changes in ICDAS severity (progression and regression) and caries lesion activity scores between the baseline and the 6-month and one-year examinations and between the 6-month and one-year examinations will also be compared among the four dentifrices. The analysis methods are described in [section 10.6](#).

10.2 Sample Size Considerations

The sample size determination was based on the expected half width of the 95% confidence interval for the one-year DMFS increment for each treatment group. Based on past data we expect a standard deviation of approximately 3.0. Using the normal approximation and 450 subjects per group at one year, the confidence interval half-width would be ± 0.28 . These estimates will provide data to be used in planning the next (pivotal) study.

10.3 Randomization

Separate randomization listings for each study site will be provided. Within each randomization, subjects will be assigned to each of the 8.0% arginine/0 ppm F dentifrice, 4.0% arginine/0 ppm F dentifrice, the 1.5% arginine/0ppm F dentifrice and the 0% arginine/ sodium fluoride 0.24% (1100 ppm F), in a 1:1:1:1 ratio.

10.4 Analysis Populations

Analysis populations for this study are as follows:

- Intent to Treat (ITT): The ITT population will consist of all subjects randomized and dispensed treatment.
- Safety: The Safety population will consist of all randomized subjects who received at least one administration of the study treatment

- **Per-Protocol (PP):** The PP population will consist of those subjects in the ITT population who completed all study examinations, and who experienced no serious protocol violations.

For the purpose of this determination, serious protocol violations:

1. Subject fails to report for examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.
4. Subject is treated with medications that may affect the parameters under investigation during the study.

All analyses performed on the ITT population will be based on treatments as randomized. Analyses performed on both the Safety and PP populations will be based on treatments actually received. Analyses performed to investigate safety will be performed on the Safety population. Analyses to investigate efficacy will be performed on both the ITT and PP populations; however, the primary efficacy analyses will be those based on the PP population.

10.5 Planned Interim Analyses

No interim analysis is planned for this study.

10.6 Final Analysis Plan

10.6.1 Procedures for Handling Missing, Unused, and Spurious Data

All analyses performed on the Safety and PP populations will be based on data as observed. For the ITT population, multiple imputation methodology will be employed to impute missing values for subjects who have missed visits, or who have dropped out of the study. Multiple imputation will be implemented using baseline subject characteristics to randomly impute each data point five times. The five complete data sets will be analyzed and then combined to incorporate both the estimated within and between data set error terms.

10.6.2 General Statistical Considerations

Data summaries for continuous variables will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

Baseline values for all parameters will be the most recent value prior to the first administration of study treatment.

10.6.3 Analyses for Efficacy

Based on the caries assessments performed on each tooth surface at each examination, subject-wise DMFS and DMFT scores will be calculated.

The primary efficacy endpoint will be the incremental subject-wise DMFS score after one year of product use.

Secondary efficacy endpoints will include:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use;
- Incremental subject-wise DMFT scores after 6-months and after one year of product use.
- Clinically significant change in ICDAS severity scores between the baseline and the six-months and one-year examinations and between the six-months and one-year. Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6. Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.

A score summary of all efficacy endpoints will be provided at each assessment time point.

The analysis of the primary endpoint (DMFS increment) will consist of the estimation of the mean and 95% confidence interval for each treatment group. This will allow the sponsor to make an informed decision on the choice of the treatment to pursue in a pivotal study.

The analyses of the secondary efficacy endpoints will consist of the preparation of descriptive summaries, which will include 95% confidence intervals.

Although the study is not powered to detect differences among the treatment groups, statistical models will still be implemented for the primary and secondary efficacy endpoints. Generalized linear models (GLIM) will be used for all analyses. For analyses of DMFS and DMFT increments, we anticipate that a normal error term will be appropriate. For counts of clinically significant changes, Poisson regression will be the most appropriate GLIM with the number of teeth at risk as the offset. This model is appropriate for analysis of progression or regression although the number of teeth at risk will differ. For changes in activity scores the GLIM will be in the form of a multinomial logistic regression with four categories (0 at both times, 0 to 1, 1 to 0 and 1 at both times) that compares the distributions among the treatment groups. All statistical tests will be performed using a two-tailed 5% significance level. 95% confidence intervals for the differences between treatments will also be calculated based on the models. In addition, the models will yield estimates of the pooled within group variance which can be used for planning further studies.

Analyses as described above will be performed on both the PP population, and the ITT population.

Listings of data will be provided for DMFS scores and for all efficacy endpoints.

10.6.5 Analyses for Safety

A summary of the hard- and soft-tissue findings will be provided, showing the incidence of findings in each treatment group.

Adverse events will be summarized by treatment group.

Data listings will be provided for all adverse event data, and for all soft- and hard-tissue findings.

10.6.6 Modifications to Statistical Methodology

Any modifications made to the analysis methodology described here will be clearly presented and explained in an amendment.

11. ETHICS, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1. Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Study Investigators abide by the principles of the GCP guidelines of the ICH. Also, the study will be carried out in accordance with local legal requirements.

The Study Investigator confirms the above by signing this study protocol.

11.2. Informed Consent/Assent

Before being enrolled in the study, informed consent will be obtained from the parent or legal guardian of each subject and assent will be obtained from the subjects according to the regulatory and legal requirements of the state. The consent and assent forms must be signed and dated and retained by the Study Investigator as part of the study records.

Should a protocol addendum be made, the consent/assent forms may be revised to reflect changes in the protocol.

The Study Investigator will not undertake any investigation specifically required by the protocol until valid consent/assent has been obtained.

11.3. Approval of Study Protocol

Before the start of the study, the study protocol and/or other appropriate documents will be submitted to the IRB and/or the authorities, in accordance with local legal requirements.

The Sponsor and the Study Investigator must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study.

11.4. Amending the Protocol

This protocol is to be followed exactly. Alterations and amendments must be written, receive approval from all persons who approved the original protocol, and receive FDA and IRB approval prior to implementation. Administrative changes (not affecting the patient benefit/risk ratio) may be made by the clinical monitor without any further approvals. All amendments will be distributed to all protocol recipients with instructions to append them to the protocol.

11.5. Confidentiality

All records of subject participation in this study are confidential and these records are available only to the investigator, specifically trained site personnel, supervising dentist/examiner, potentially the Sponsoring Company, Ethics/Institutional Review Board (IRB), the Food and Drug Administration of the United States (FDA) or other local regulatory agency. The results of this study may be published in a scientific journal or a government public clinical database. If any publication occurs, only the subject's study number/ID, gender and/or age may be used. They will agree to verify, by letter, that they participated in this study, if called upon to do so.

In addition, the identity of participating subjects must be protected. Only investigators (and specifically trained clinical site staff) will collect and have access to a subject's private information (e.g., name, medical records, etc.). Investigators will assign a study number to

subjects which will be used to conceal their identity on all case report forms and other documents prior to their sharing with the broader study team, including the sponsor. Documents that identify the subject by name (e.g., the signed informed consent form or health questionnaire) will not be transferred or submitted to the sponsor, and will be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate national or local authorities or to sponsor personnel to verify subject, product safety and study compliance.

Parents or legal guardians of participating subjects will be asked to review a participant privacy notice (Appendix I-A) and will be given a copy of the accepted and signed notice.

11.6. Advertising

No newspaper, radio, or television advertising will be used for recruitment purposes. If needed, a flyer may be created to recruit participants. If used, the flyer will be approved by an Institutional Review Board prior to posting or dissemination.

11.7. New Findings

Subjects will be informed of any significant new findings related to study products or procedures when they become known during the course of this clinical research study. Such information may affect the subject's decision to continue participation in the study.

11.8. Publication Policy

Colgate discourages any individual investigator from publishing his/her own results independently. An investigator shall not publish any data (poster, abstract, paper, etc.) without having received permission in advance from Colgate-Palmolive. The above procedure also applies to information on prematurely discontinued and other non-completed studies. Results from the investigator shall not be made available to any third party by the investigating team outside the publication procedure as set out above. Colgate-Palmolive will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

12. REFERENCES

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6. ICCMS™ Guide for Practitioners and Educators, 2014 <https://www.iccms-web.com/uploads/asset/59284654c0a6f822230100.pdf>
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APPENDIX I

**PARENTAL/LEGAL GUARDIAN CONSENT TO PARTICIPATE
IN A CLINICAL RESEARCH STUDY
AND
AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH
INFORMATION
AND
ASSENT FORM FOR CHILD PARTICIPANTS AGES 10 TO 14**

Sponsor / Study Title: Colgate-Palmolive / “A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine in each comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.”

Protocol Number: CRO-2020-CAR-ARG-ED

**Principal Investigator:
(Study Doctor)** «PiFullName»

Telephone: «IcfPhoneNumber»

Address: «PiLocations»

Taking Part in this Study is Voluntary

Your son or daughter is invited to voluntarily participate in a one-year clinical research study.

Before agreeing to your child’s participation in this research study, it is important that you read this form. This form, called a consent form, describes the purpose, procedures, benefits, risks and discomforts expected from participation in this research study. It also describes your right to withdraw consent for your child to participate in this research study at any time. No promises or guarantees can be made as to the results of this research study. Please ask as many questions as you want in order to decide whether you want your child be in this research study. This consent form may contain words that you do not understand. Please ask the research study doctor or the research study staff to explain any words or information that you do not clearly understand.

Please review the rest of this document for more details about this study and the things you should know before making a decision about whether to allow your child to participate in this study.

Why is this Study Being Done?

The purpose of the study is to compare the effectiveness in reducing tooth cavities of a commercially available fluoride toothpaste to non-fluoride dental toothpastes containing arginine (a safe and essential amino acid that is naturally found in saliva and produced by the human body). The use of the study product in this study is investigational which means it has not been approved by the United States Food and Drug Administration (FDA).

How Many People Will Take Part?

If you decide to allow your son/daughter to participate, know that he/she will be one of about 2,000 (two thousand) participants in the study. The study will be conducted simultaneously in many sites across the United States and Puerto Rico.

What Will Happen During the Study?

In order to be in this study your child must meet the following criteria.

1. Your son/daughter must be in the age range of 10 to 14 years and in good general health and absent of allergies.
2. The study examiner must find that conditions of your child's teeth and gums are satisfactory for the study and meet other teeth criteria that will be considered. This includes a prior experience with cavities, the current presence of tooth changes consistent with early cavities.

During your child's initial examination, the study doctor will evaluate your child's teeth and gums. If your child qualifies for the study, he/she will be assigned, using a procedure similar to flipping a coin, to one of four study groups. You, your child or the study doctor will not know to which toothpaste your child will be assigned to use for the one (1) year duration of the study. Every three (3) months, your child will be provided with toothpaste and a new toothbrush and he/she will be expected to return the previously dispensed tubes of toothpaste (no matter if full or empty). During the course of the study your child will be asked to not use any other oral hygiene products; however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with your child's dentist.

Your child will be examined every three (3) months for one (1) year.

Examination 1 (Screening)

You will be asked to read, sign and date this consent form and also fill out some other documents about the study. Your child will be provided with an assent form providing him/her with the opportunity to choose if he/she wants to participate in the study.

The study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study doctor will also check his/her teeth to see if there are any cavities.

After this examination, it will be decided if your child can be in this study.

Examination 2 (Baseline)

This examination may take place the same day of the screening examination. A study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study doctor will also check his/her teeth to see if there are any cavities. Your child will be asked to brush his/her teeth with water before he/she sees the study doctor.

Your child will also be given a short questionnaire for him or her to share how he or she feels about his/her oral health and his/her self-perception about oral function, social and emotional well-being. Similar questions will be asked after six (6) months and after twelve (12) months of assigned study product use.

Your child will be given the first supply of toothpaste and a toothbrush to take home. Your child will be instructed to brush his or her teeth twice per day (morning and evening) for two minutes each time, once in the morning and once before going to bed and not to use any other toothpastes, mouth rinses or other toothbrushes.

Your child will be asked to return the tubes of toothpaste provided (empty or not) at the next scheduled examination.

If the study doctor finds a cavity you will be notified and you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one. During this study, the investigator will not treat any abnormal issues in the mouth and will not fill cavities.

Examinations after three (3, 6, 9 and 12) months of study product use

A study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The same procedures as in the Examination 2 (Baseline) described above will be followed. After six (6) months and after twelve (12) months of assigned study product use, your child will be asked to complete the short questionnaire.

What are the Risks of Taking Part in the Study?

The risk of your child includes the possibility that the study product assigned may not prevent cavities as well as the fluoride. Your child will not be permitted during the study to receive fluoride treatments or sealants. There may be irritation caused by the dental examinations. Risks from the study product are expected to be the same as those for any currently marketed toothpaste. These include minor oral irritation and peeling skin in some sensitive individuals.

The risks associated with minor and rare irritations from dental examinations will be minimized by having trained and licensed oral care professionals conduct the oral examination, following standard clinical procedures.

There is a risk of possible loss of confidentiality while maintaining all research observations and data. There may be risks which are currently unknown.

Any significant findings will be communicated to you and, when necessary, will include a referral to a dentist or a note to his/her dentist. We encourage you inform your child's regular dentist of his/her participation in this study. If your child experiences any problems, you should contact the study doctor at the telephone number listed on page one of this form.

Discomfort with questionnaires

Some people feel uncomfortable when answering questions about the [REDACTED]. Though it is always better to have fully completed questionnaires, your child does not need to answer any questions that make him/her feel uncomfortable.

What are the Potential Benefits of Taking Part in the Study?

It is expected that your child will receive a direct dental benefit from participation in this study. Although it cannot be guaranteed for every child, a cavity reduction benefit is expected from all toothpastes in the study. Your child's teeth and gums will be monitored by examinations every three (3) months. Any significant findings will be communicated to you and, if necessary, will include a referral to a dentist or a note to his/her dentist. Participation in this clinical study does not replace the need for your son or daughter to visit his or her dentist on a regular basis. The results of this study may help the sponsor improve the study product and help dental professionals provide proper advice to their patients.

How will your Child's Information be Protected?

Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information may be disclosed if required by law. No information which could identify your child will be shared in publications about this study.

Organizations that may inspect and/or copy your child's research records for quality assurance and data analysis include groups such as the study doctor and his/her study staff, Advarra IRB, Colgate Palmolive, the U.S. Food and Drug Administration (FDA), and any state or federal agencies who may need to access your medical and/or research records (as allowed by law).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Will my Child's Information be used for Research in the Future?

Information collected from your child for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify your child will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

Alternatives to Participation

This research study is for research purposes only. The only alternative is to not participate in this study.

Will there be a Cost or Payment to Participate?

There is no cost to you or your child for the oral examinations and the use of toothpaste, toothbrush or any other study related product.

«Compensation»

Your child may receive an incentive for participation in the clinical study consisting of _____ (SITE TO DETERMINE IF APPLICABLE, ETC).

Who will Pay for my Child's Treatment if he/she gets Injured?

In the event of physical injury resulting from your child's participation in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your child's health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

Whom To Contact About This Study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
Study Subject Adviser
Advarra IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046

- or call **toll free:** 877-992-4724
- or by **email:** adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00040997.

Can my Child Withdraw from the Study?

Your child's participation is voluntary, and you may refuse to participate and/or withdraw your child at any time without penalty or loss of benefits to which your child would otherwise be entitled up to the point of withdrawal. Your child's study dentist has the right to withdraw your child from the study at any time if he or she feels that it is in your child's best interest or if your child fails to comply with the terms of the study.

Your child's participation may be terminated by the study doctor without regard to your consent in circumstances when the study doctor feels it may not be beneficial to your child.

You will be told about new information that may affect your child's health, welfare, or willingness to stay in the study.

Study Sponsor

This clinical research study is sponsored by the Colgate-Palmolive Company. The Study Site will receive financial support and material for this study. The study staff and study doctor have no financial interest in the Colgate-Palmolive Company.

Informed Consent Statement

I have read the contents of the consent form and have listened to the verbal explanation given by the study doctor. My questions concerning this study have been answered to my satisfaction. I hereby give voluntary consent for my child to participate in this study. Signing and dating this consent document does not waive my or my child's rights nor does it release the study doctor, study staff, institution, or sponsors from their responsibilities. I will receive a copy of this signed and dated consent document.

I voluntarily agree for my child to participate in this study. I understand that I will be been given a copy of this consent form after signing and dating it.

CHILD'S NAME _____

Signature of Parent or Legal Guardian

Print Name of Parent or Legal Guardian

Date

I attest that the requirements for informed consent from the research study described in this form have been satisfied, that I have discussed the research study with the participant's parent or legal guardian and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Signature of Person Obtaining Consent

Printed Name of Person Obtaining Consent

Date: _____

SPONSOR'S PRIVACY NOTICE

In addition to the informed consent that explains the clinical study in which your child may participate in, this authorization gives you additional detailed information about how your child's health information will be protected. By signing and dating this document you are allowing Colgate Palmolive Co. to disclose personal health information to outside organizations or people involved with the processing of this study.

What personal health information is collected and used in this study and might be shared?

1. Name, address and telephone number
2. Medical history
3. Current medications
4. Procedures performed in this study such as: Oral health exams and stress related proteins

Why is your personal information being used?

So the study staff may contact you during the study. Your child's health information is used to ensure your child's safety while selecting participants for the study. Results and data are collected for the advancement of medicine, dentistry and clinical care.

Which of our personnel may use or disclose your child's personal health information?

The following individuals and organizations may use or disclose your child's personal health information for this research study:

1. The study doctor and associated study staff
2. The Institutional Review Board
3. Safety and Regulatory departments at Colgate Palmolive Co.
4. Authorized members of the clinical site who may need your information in the performance of their duties associated with this research (for example, to provide treatment, ensure integrity of the research, accounting, scheduling etc.)

Who outside Colgate Palmolive Co. or the study doctor might receive your child's personal health information?

1. Institutional Review Board

2. Food and Drug Administration (your child will be identified only by his/her first name and last initial)

How long will Colgate or the Clinical Site be able to use or disclose your child's personal health information?

Your authorization for this specific study does not expire however the information may not be re-used or re-disclosed for another purpose other than the research described in this document unless you give written permission to do so. In California and any other state that requires an expiration date, the Authorization will expire in 50 years after you sign and date this authorization document. The Institutional Review Board may grant permission to the study doctor or others to use your child's information for another purpose after ensuring that appropriate privacy safeguards are in place. The Institutional Review Board is a committee whose job it is to protect the safety and privacy of research participants. Results of tests and procedures are done solely for this research study and will not be included in your child's dental record.

Will you be able to access your child's records?

You will be able to access your child's dental record when the study is completed. During the study you will not have access to prevent knowledge of study results from affecting the reliability of the study. Should an emergency or need for care arise that would require your child's treating physician or dentist to know this information the records would be provided.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your child's personal information for research but you must do so in writing to the study doctor at the address provided on the first page in your parental informed consent. Even if you withdraw your permission, the study doctor may still use your child's personal information that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission to use your child's personal health information that means your child will also be withdrawn from the research study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. By signing and dating this document I am permitting Colgate Palmolive Co or the Study Site to use and disclose personal health information collected about my child for research purposes as described above. I will receive a signed and dated copy of this form. I am not giving up any of my legal rights by signing and dating this form.

CHILD'S NAME _____

Signature of Parent or Legal Guardian
Guardian

Print Name of Parent or Legal

Date

Signature of Person Obtaining
Authorization

Printed Name of Person Obtaining
Authorization

Date: _____

ASSENT FORM
FOR CHILD PARTICIPANTS AGES 10 TO 14 YEARS

Sponsor / Study Title: Colgate-Palmolive / “A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine in each comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.”

Protocol Number: CRO-2020-CAR-ARG-ED

Principal Investigator: «PiFullName»
(Study Doctor)

Telephone: «IcfPhoneNumber»

Address: «PiLocations»

You are invited to join in a research study that is described below:

WHAT IS THIS STUDY ABOUT?

We would like to find out if new toothpastes can prevent cavities as well as a fluoride toothpaste. If you qualify for the study and you agree to participate in the study, you will be assigned to one of four (4) study groups. The toothpaste to be assigned to you will be determined using a procedure similar to flipping a coin. You will not know what toothpaste you will be assigned to use. During the study, which will last one (1) year, you will be asked to brush your teeth with the toothpaste assigned to you and not use any other toothpastes or mouth rinses; however, you should continue with treatment and checkups with your regular dentist.

If you decide to participate, you will be one of about 2,000 (two thousand) other children participating in the study.

WHAT WILL HAPPEN TO ME IN THIS STUDY?

If you decide that you want to be in this study, you will be examined by the study doctor six (6) times in the one (1) year-long study. Here is what will happen at each of these examinations:

First Examination (Screening)

You will be asked to read, sign and date this form and also fill out some other documents about the study. Your parents will also need to sign and date a permission form.

A study doctor will look at your lips, cheeks, tongue and all other areas inside of your mouth. The study doctor will also check your teeth to see if you have any cavities.

After this examination, the study doctor will decide if you can be in this study.

Second Examination (Baseline)

This second examination may happen the same day as the first examination. You may be asked to brush your teeth with water before you have this more detailed second examination. If the study doctor wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

If the study doctor decides that you will be in the study, you will be given a toothbrush and the toothpaste assigned to you. You will be asked to brush your teeth for two (2) minutes, two (2) times a day, once in the morning and once before going to bed. You will be asked not to use any other toothpastes or mouth rinses.

You will be asked to return the tubes of toothpaste provided (empty or not) at your next scheduled examination.

If the study doctor finds a cavity, you will be asked to see your regular dentist or if you don't have one, the study dentist will recommend one.

Examinations three (3), four (4), five (5) and six (6)

You will be examined again every three (3) months after you start brushing with the toothpaste and the toothbrush that you will be given. During these examinations, the study doctor will look at your lips, cheeks, tongue and all other areas inside of your mouth. The study doctor will check your teeth to see if you have any cavities. Sometimes you may be asked to brush your teeth with water before you see the study doctor. If the study doctor wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

You will be asked to return the tubes of toothpaste provided (empty or not) at your next scheduled examination.

If the study doctor finds a cavity, you will be asked to see your regular dentist or if you don't have one, the study dentist will recommend one.

CAN ANYTHING BAD HAPPEN TO ME IN THIS STUDY?

We will try to be as careful as we can during the examinations but there is a chance that something could happen such as getting a sore spot in your mouth. There is also the possibility that the study product assigned to you may not prevent cavities as well as the fluoride getting a cavity and irritation caused by the dental examinations. Risks from the study product are expected to be the same as those for any currently marketed toothpaste. These include minor oral irritation and peeling skin in some sensitive individuals. We encourage you inform your parent/legal guardian or regular dentist of your participation in this study.

Discomfort with questionnaires

Some people feel uncomfortable when answering questions about the [REDACTED]. Though it is always better to have fully completed questionnaires, you do not need to answer any questions that make you feel uncomfortable.

WHAT IS GOOD ABOUT BEING IN THIS STUDY?

You may have a cavity reduction from the toothpaste you use in the study. Your mouth and teeth will be checked every three (3) months. You will be told if you have any problems in your mouth and you may be asked to see your dentist. The results of this study may help the company paying for the study to improve their toothpaste products and help dentists provide proper advice to their patients.

WHAT DO I HAVE TO TELL THE STUDY EXAMINER ABOUT?

If you choose to join this study, the study examiner may ask you questions about your health and medicines that you may be taking. We ask that you tell the study doctor about your health and answer any questions the best you can.

You also need to tell your parents or legal guardian and the study doctor if you do not feel well after your examinations.

DO I HAVE TO BE IN THIS STUDY?

You do not have to be in this research study if you do not want to. You can say “yes” or you can say “no”. You can stop later if you change your mind. No one will be angry with you if you say “no”. Your regular doctor and dentist will still take care of you.

WHO CAN I TALK TO ABOUT THE STUDY?

You can ask questions about the study at any time. If you feel sick, you or your mom or dad can call the study doctor.

STATEMENT OF ASSENT

DO YOU WANT TO PARTICIPATE?

☐
☐

Yes, I will be in this study.

No, I do not want to do this.

If you have any questions about the study, you may ask the study staff at any time. Your parent/legal guardian will be given a copy of the consent letter that has telephone numbers of people to call when you have questions. If you want to be in this study, read the next paragraph and sign and date in the space below.

I agree to participate in this research study. I may decide to stop at any time without hurting my chances of being in future dental studies.

Child's Name (Please Print)

Child's Signature

Date

Signature of Study Personnel Obtaining Assent

Date

Printed Name of Study Personnel Obtaining Ass

Approved

APPENDIX II

FORMULATIONS

CONTROL DENTIFRICE

This product is a commercially-available dentifrice of the Colgate-Palmolive Company under the commercial name Colgate Ultra Brite Anti-cavity Fluoride Toothpaste which is in compliance with the OTC Anti-caries Drug Monograph. It contains 0.24% sodium fluoride (1100 ppm F) in a silica base.

TEST DENTIFRICE 1

[1.5% Arginine in a calcium base]

This is a dentifrice containing 1.5% arginine in a calcium base.

TEST DENTIFRICE 2

[4.0% Arginine in a calcium base]

This is a dentifrice containing 4.0% arginine in a calcium base.

TEST DENTIFRICE 3

[8.0% Arginine in a calcium base]

This is a dentifrice containing 8.0% arginine in a calcium base.

APPENDIX III

PRODUCT LABEL INFORMATION

Caution: New Drug - Limited by Federal (or United States) law to investigational use. Not for sale.

Protocol Number: CRO-2020-CAR-ARG-ED

Product Code _____ Subject # _____

Brush your teeth twice daily (morning and evening) for two minutes each time. Apply a full ribbon of toothpaste on the toothbrush head. Use only the toothpaste and toothbrush provided.

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study

For study-related questions call:

Dr. _____ at phone number (____) ____-____.

In case of emergency call:

Dr. _____ at phone number (____) ____-____.

APPENDIX IV

PRODUCT USE INSTRUCTIONS

Important Product Information

Colgate Palmolive Sponsored Clinical Study (Protocol Number: *CRO-2020-CAR-ARG-ED*)

Caution:

For Investigational Use Only. Not for sale.

- Brush your teeth twice daily in the morning and in the evening before bed
- Brush for two minutes each time. Use the timer as aid.
- Apply a full ribbon of toothpaste on the toothbrush head just like it was demonstrated at the beginning of the study.
- Use only the toothpaste and toothbrush provided.
- The study products are only for your use.

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study

For study-related questions call:

Dr. _____ at phone number (____) ____-____.

In case of emergency call:

Dr. _____ at phone number (____) ____-____.

APPENDIX V

INITIAL SCREENING FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

The following questions will be answered based upon Investigator/Examiner/Study Personnel discretion:

1. Has the parental/ legal guardian provided informed consent for voluntary participation of the child and has the child provided written assent?	Yes	No
2. Is the subject in good general health?	Yes	No
3. Is the child willing and able to use the assigned products according to instructions, available for all appointments and likely to complete the study?	Yes	No

If any answer to any questions 1-3 is 'NO', the subject is ineligible for study. Dismiss subject and complete question 13 below. If the subject is eligible, continue to questions 4-13.

4. Is the subject undergoing orthodontic treatment, wears intraoral appliance?	Yes	No
5. Does the subject use medications that could increase the risk of developing soft tissue irritations?	Yes	No
6. Is the subject taking long-term antibiotic therapy or have a condition which would require an antibiotic prior to a dental procedure?	Yes	No
7. Does the child have cognitive and/or motor impairment?	Yes	No
8. Does the subject have severe malocclusion?	Yes	No
9. Does the subject appear to have evidence of moderate to severe periodontal disease?	Yes	No
10. Is the subject participating in any other clinical study within 30 days preceding the start of the clinical study?	Yes	No
11. History of allergies or other adverse reactions to arginine or oral care products, or their ingredients?	Yes	No
12. Are you pregnant and/or currently breastfeeding?	Yes	No N/A
13. IS THE SUBJECT ELIGIBLE FOR ENTRY INTO STUDY?	Yes	No

Please note any additional observations (if applicable)

Text

APPENDIX VI

CONTINUATION FORM (REVIEW ELIGIBILITY CRITERIA)

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

The following questions will be answered based upon Investigator/Examiner/Study Personnel discretion:

1. Does the parental/ legal guardian <u>still</u> consent for voluntary participation of the child and does the child <u>still</u> assent to participate?	Yes	No
2. Is the subject in good general health?	Yes	No
3. Is the child still willing and able to use the assigned products according to instructions, available for all appointments and likely to complete the study?	Yes	No

If any answer to any questions 1-3 is 'NO', the subject is ineligible for study. Dismiss subject and complete question 13 below. If the subject is eligible, continue to questions 4-13.

4. Has the subject undergone orthodontic treatment, or currently wears an intraoral appliance?	Yes	No
5. Does the subject use any new medications that could increase the risk of developing soft tissue irritations?	Yes	No
6. Is the subject currently taking long-term antibiotic therapy or have a condition which would require an antibiotic prior to a dental procedure?	Yes	No
7. Does the child have cognitive and/or motor impairment?	Yes	No
8. Does the subject have severe malocclusion?	Yes	No
9. Does the subject appear to have evidence of moderate to severe periodontal disease?	Yes	No
10. Has the subject participated in any other clinical study since enrollment?	Yes	No
11. History of allergies or other adverse reactions to arginine or oral care products, or their ingredients?	Yes	No
12. Are you pregnant and/or currently breastfeeding?	Yes	No N/A
13. IS THE SUBJECT ELIGIBLE TO CONTINUE WITH THE STUDY?	Yes	No

Please note any additional observations (if applicable)

Text

APPENDIX VII

HEALTH QUESTIONNAIRE

Name: _____ today's date: (mm/dd/yyyy) _____

Date of Birth: (mm/dd/yyyy) _____

Name of Physician: _____ Phone#: _____

Date of last visit: (mm/dd/yyyy) _____

Phone #: _____ Home ☐ Cell ☐

Email: _____

Home Address: _____

Are we allowed to contact you? Phone ☐ Cell ☐ email ☐

☐ By checking this box YOU are providing consent to be contacted by the clinical site

Emergency contact Name: _____ Phone#: _____

Your current physical health is: ___ Good ___ Fair ___ Poor

Have you ever had any serious operations? ☐ Yes ☐ No

If yes, please explain: _____

Are you currently under the care of a physician? ☐ Yes ☐ No

If yes, please explain: _____

Please check if you have been treated for or told that you have:

☐ Abnormal bleeding	☐ Anemia
☐ Hemophilia	☐ AIDS
☐ Blood transfusion	☐ Arthritis
☐ Ulcers/Colitis	☐ Glaucoma
☐ Heart problems	☐ Drug addiction
☐ Epilepsy/Seizures	☐ Skin problems
☐ Asthma or Hay fever	☐ Blood Disorders
☐ Chemo/Radiation therapy	☐ Cancer/Tumor
☐ Diabetes/abnormal blood sugar	☐ Kidney/Liver disease
☐ Difficulty breathing	☐ Hepatitis /Jaundice
☐ Lung problems	☐ Emphysema
☐ High/Low blood pressure	☐ Rheumatic fever

Please describe any of the above conditions:

Do you have a history of allergies to whitening oral care products, personal care consumer products, or their ingredients?

If yes, please fill explain: _____

Do you take any medications? If yes, please fill out following:

List any prescription or over the counter medications which you are taking:

Name of Medication	Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy)	Amount taken	How often	Reason

DENTAL HISTORY

Name of your dentist: _____ Phone#: _____

How often do you visit your Dentist? _____

Date of last visit: (mm/dd/yyyy) _____

WOMEN ONLY

Please answer the following:

Are you pregnant? ☐ Yes ☐ No

If yes, list due date (mm/dd/yyyy) _____;

Are you currently nursing or breastfeeding? ☐ Yes ☐ No

I understand that the information that I have given today is correct to the best of my knowledge. I also understand that this information will be held in the strictest of confidence, and it is my responsibility to inform this office of any changes in my medical status. I understand that my participation in this study is voluntary and that I can drop from the study at any time.

Signature _____

Date (mm/dd/yyyy) _____

APPENDIX VIII
ORAL SOFT TISSUE ASSESSMENT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

<u>AREA</u>	<u>NORMAL</u>	
1. Lips	YES _____	NO _____
2. Soft Palate	YES _____	NO _____
3. Hard Palate	YES _____	NO _____
4. Gingival Mucosa	YES _____	NO _____
5. Buccal Mucosa	YES _____	NO _____
6. Mucogingival Folds	YES _____	NO _____
7. Tongue	YES _____	NO _____
8. Sublingual and Submandibular areas	YES _____	NO _____
9. Salivary glands	YES _____	NO _____
10. Tonsillar and Pharyngeal areas	YES _____	NO _____

If answer to any of questions 1-10 is "NO", please explain or add a comment:

Signature, Examiner

Date

APPENDIX IX

ORAL HARD TISSUE ASSESSMENT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

	Absent	Present	If Present, please specify findings
Enamel Irregularities	☐	☐	
Tooth Fracture	☐	☐	
Pathologic Tooth Wear	☐	☐	
Cavitated Lesion	☐	☐	
Active Non-Cavitated Lesion	☐	☐	
Residual Root	☐	☐	
Faulty Restoration	☐	☐	
Implant	☐	☐	

Signature, Examiner

Date

APPENDIX X

UPDATED HEALTH QUESTIONNAIRE VISIT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

1. Were there any unexpected or serious reactions since the previous examination? YES NO

If yes, describe _____

2. Was any treatment prescribed for the above? YES NO

If yes, describe _____

3. Was any dental treatment received since the previous examination? YES NO

If yes, describe _____

4. Was any new medication (including OTC products) prescribed for subject since previous examination? YES NO

If yes, describe dose, duration and reason _____

Name of Medication	Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy)	Amount taken	How often	Reason

5. Do any of the responses to Questions 1-4 warrant exclusion of this subject's data from the statistical analysis? YES NO

If yes, explain _____

Signature, Examiner

Date

APPENDIX XI

SAMPLE CARIES EXAMINATION FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Caries

Study Name:

Subject #:
Initials:

Visit Date:
Gender:

Visit
DOB:

UPPER TEETH																					
Tooth	2			3			4			5			6			7			8		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																					
M																					
D																					
V																					
P																					

Tooth	9			10			11			12			13			14			15		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																					
M																					
D																					
V																					
P																					

LOWER TEETH																											
Tooth	16			17			18			19			20			21			22			23			24		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																											
M																											
D																											
V																											
L																											

Tooth	25			26			27			28			29			30			31		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																					
M																					
D																					
V																					
L																					

Calculations

ICDAS Mean:					
DT	MT	FT	DMF-T	Total T	
DS	MS	FS	DMF-S	Total S	

Examiner:
Version:
Reason Comment:

Approval Date:
Reason:

Classification of the Tooth Profile, Surface Condition and Lesion Activity status in the ICDAS

Tooth Profile	
1	When a permanent or temporary filling is present, missing or defective
7	Not counted, unerupted teeth, congenitally missing or supernumerary teeth, teeth removed for reasons other than dental caries, and primary teeth retained in the permanent dentition
8	Trauma; poor prognosis (Not Counted)
9	When a tooth has been extracted due to caries

Surface Condition	
0	No filling, No sealant
1	Sealant (partial or complete)
2	Filling: when a permanent or temporary filling is present, missing or defective (e.g. composite, amalgam, crown, etc.)
3	Restoration: restored due to other reasons (e.g. cervical lesions, residual composite due to ortho or aligners, diastema closure, etc.)

Caries Lesion Activity Assessment (ICCMS Guide):

Code 0 Signs of Inactive Lesions

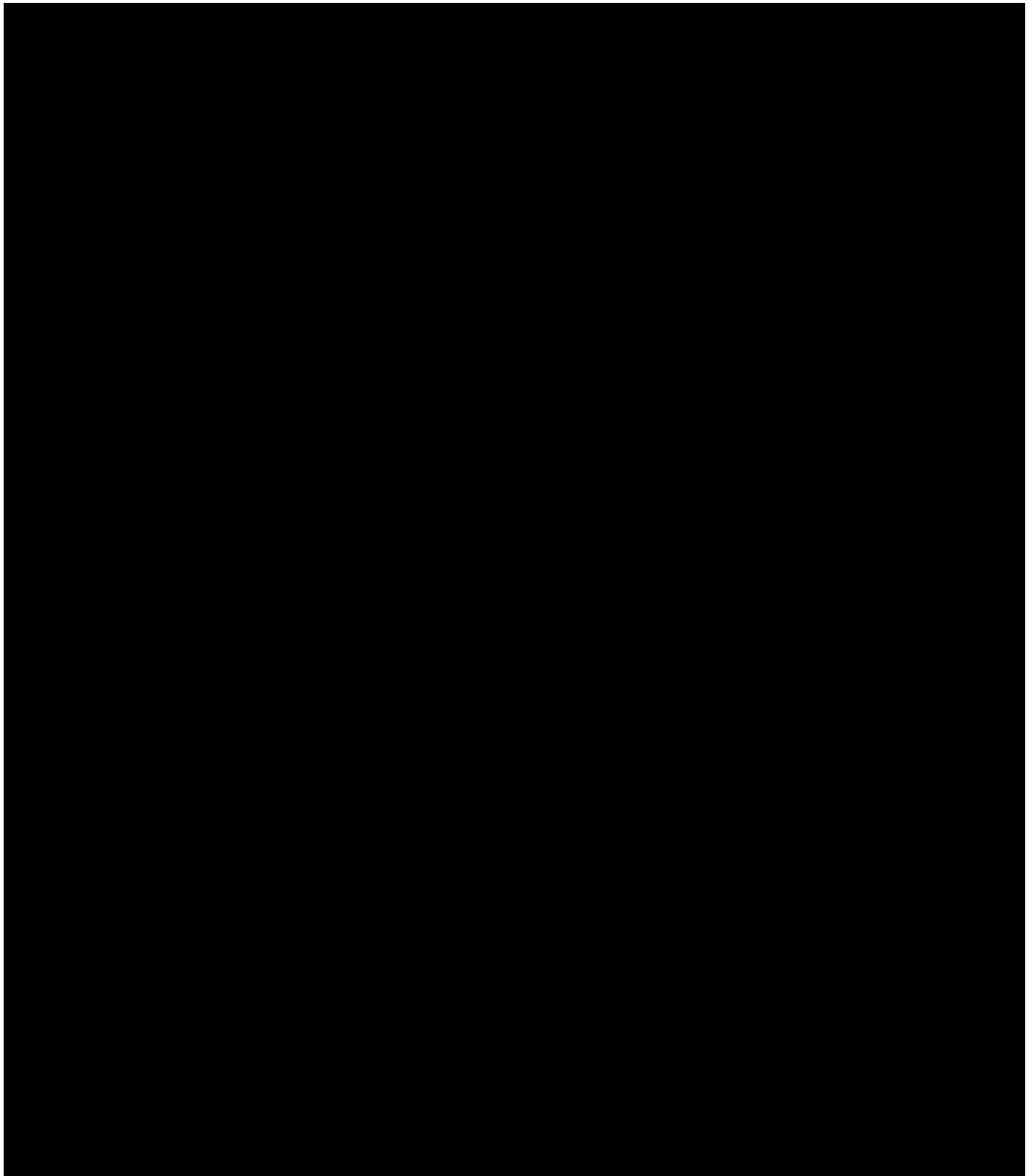
For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located at some distance from the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

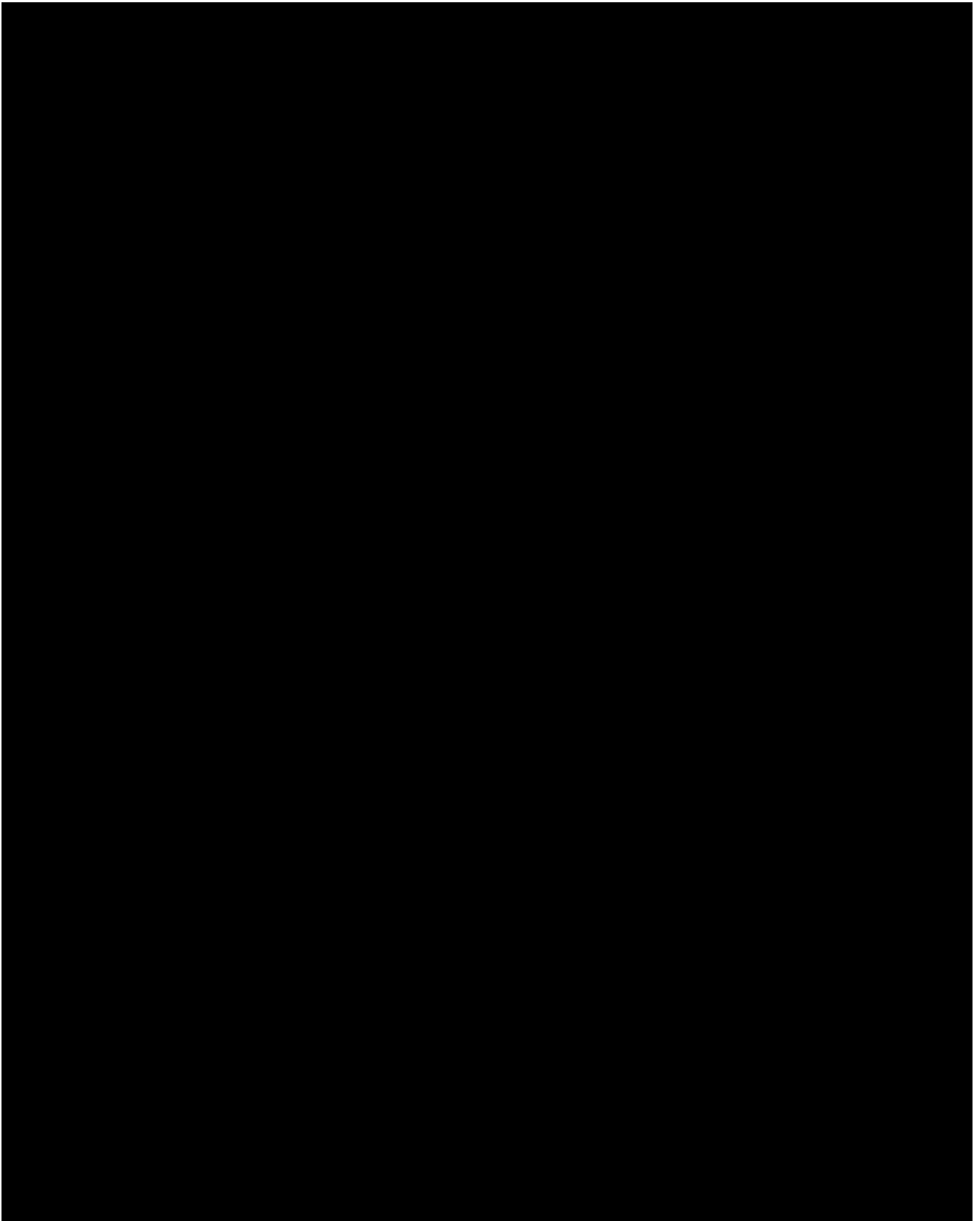
For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing.

Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.





APPENDIX XIV

REPORT OF ADVERSE EVENT

Instructions: Refer to the General Instructions & Supplemental Guidance pages for specific details on completing sections of the form. Additional pages may be added, if necessary, to report all information.

Awareness date – Colgate-Palmolive:		Awareness Date- Investigator:	
1) Study Information			
Protocol #:		Centre Name:	
Study Title:		Investigator:	
Indication /Objective of Protocol:		Address:	
Study Type: ☐ Clinical Trial (Interventional) ☐ Consumer ☐ Panel ☐ Phase II Clinical Trial ☐ Other Clinical ☐ Other Specify		Tel.: Fax:	
Study Originator/Monitor:		Email:	
Contact #		Health Care Professional : ☐ Yes ☐ No Specify occupation:	

2) Subject Information			
Subject's ID #: Initials:	Gender	Age/(Age Group): Or Date of Birth:	Weight
	☐ Male ☐ Female	- -	☐ LB ☐ KG
If subject is pregnant, how many months?			

3) Reporter Information (Complete only if different from Investigator named above)	
Sender/Reporter Name:	
Address	Country:
Email:	Telephone: Fax:
☐ Healthcare Professional Specify occupation:	☐ Non-Healthcare Professional

4) Phase of study the earliest event (s) occurred during:

☐ After consent ☐ Pre-randomization ☐ Randomization: no product ☐ Randomization: product exposure
☐ Baseline ☐ 3-Month ☐ 6-Month ☐ 9-Month ☐ 12-Month ☐ Other:

5) Study products (Please indicate if Test product, Blinded Product, Comparator (control product) was used by subject)

Product Name	Lot No/ Batch No/ Serial No (If MOCD)	Route of administration	Dosage & Frequency	Start Date (DD-MMM- YYYY)	Stop Date (DD-MMM- YYYY)	Action taken with Product
				- -	- -	
				- -	- -	
				- -	- -	
				- -	- -	

6) Adverse Event/Reaction Information

Adverse Events (AEs)	Start Date of AEs (DD-MMM- YYYY)	Stop Date of AEs (DD-MMM- YYYY)	Seriousness Criteria	Causality	Outcome
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	

Death (dd/mmm/yyyy):	Autopsy: ☐ YES ☐ NO ☐ Unknown
Cause of death if known:	Outcome:

Describe event (s)/reactions(s) in detail:

Protocol status of subject:		
☐ Subject continued in protocol ☐ Unrelated ☐ Unable to assess Subject continued in protocol	☐ Subject discontinued from protocol ☐ Unrelated ☐ Unable to assess Subject discontinued from protocol	
Was the subject treated for the event(s)/reaction(s) (Medical Intervention)? ☐ YES ☐ No If yes, please specify or describe:		
Event/Reaction abated after study product(s) stopped or dose reduced?		
☐ YES	☐ NO	☐ N.A.
Event/Reaction reappeared after study product(s) reintroduced?		
☐ YES	☐ NO	☐ N.A.

7) Subject Medical History: ☐ None ☐ Unknown <i>(Provide the medical history including pre-existing medical conditions)</i>

8) Other Medications/ Products used simultaneously: ☐ None ☐ Unknown					
Other Medications/ Products	Start Date (DD-MMM- YYYY)	Stop Date (DD-MMM- YYYY)	Indication	Dosage & Frequency	Route of administration
	-	-			
	-	-			
	-	-			
	-	-			

9) Laboratory data & other test procedure(s) relevant to the AE/AER(s)		
Test	Date (dd/mmm/yyyy)	Result (Specific value, normal, abnormal, clinically significant)

Investigator/Designee Signature: 	Date (dd/mmm/yyyy):

Approved

APPENDIX XIV

Periodic/End of Study Report Form for Non-interventional Studies on Humans (Colgate-Palmolive 105362)

Section A: Study Information	
Study Title:	Study Type: Clinical ☐ Phase II ☐ Consumer ☐ Panel ☐ Other ☐ Specify if selecting Other:
Protocol #:	Ref #:
Indication/Objective of Protocol:	
Primary Study Product/PDM#:	
Study Start Date (dd/MMM/yyyy):	State where study was conducted:
Investigator Name:	Study Originator Name:

Investigator/ Designee Signature: _____ Date dd/mmm/yyyy: _____

Section B: Report Type

Check applicable report type

☐ Periodic Report

☐ End of Study report

Were any adverse events/reactions reported during the study? If 'Yes' is checked, please complete section C

☐ Yes ☐ No

Section C: Adverse Event/Reaction Information

Protocol #:

Investigator Name:

Complete the table below *only* if an adverse event/reaction was reported during the study.

Case ID No.	Study Site Aware Date	Subject Information			Study Product Information			Adverse Events/Reactions			Other Products Used	Outcome with Date	Comments
		ID No.	Age/Date of Birth	Gender	Product Name	Dose & Frequency	Duration of Use	Description	Causality	Serious (Yes/No)			

Note: If needed attach additional pages of Section C to document all events/reactions reported during the study.

APPENDIX XV

CLINICAL PRODUCTS RETURN LOG SHEET

Organization _____

Principal Investigator _____

Date	Subject #	Product Code	1)Tube Before Use (Weight_g)	2)Tube After Use (Weight_g)	Weight Difference 1) – 2)

Print Name of Person Weighing Products

[Signature][Date]

APPENDIX XVI
REFERRAL/NOTICE FORM

Patient Name: _____ Patient DOB: _____

Patient Referred By: _____

- ☐ We did not find any condition that needs immediate treatment, but we recommend that you visit your dentist every 6 months
- ☐ During your next visit to the dentist you should let him/her know that you may have a dental problem
- ☐ You should visit the dentist as soon as possible
- ☐ You should visit the dentist for an emergency visit

Comments:

Doctor Signature: _____

Date: _____

Signature Page for VV-TMF-00176 v3.0

Protocol Number: Protocol No.CRO-2020-CAR-ARG-ED_MOD June 6, 2023

Reason for signing: Approved	[REDACTED]
Reason for signing: Approved	[REDACTED]
Reason for signing: Approved	[REDACTED]
Reason for signing: Approved	Name: Domenick Zero Role: Principal Investigator Date of signature: 14-Jul-2023 15:28:36 GMT+0000
Reason for signing: Approved	Name: Maria Ryan Role: Executive Approver Date of signature: 14-Jul-2023 15:38:38 GMT+0000

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Colgate-Palmolive Co.

CLINICAL TRIAL PROTOCOL

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Superseded

Investigator's Agreement

I understand that all documentation supplied to me by the sponsor concerning this study, which has not been previously published, will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

The study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the sponsor, and the IRB, except where necessary to eliminate an immediate hazard to the subjects.

I agree to monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority (ies) as required.

I understand that there is nothing in this document which is intended to limit my authority as a dentist to provide emergency care under applicable regulations.

I have read and approved this protocol. My signature confirms my agreement that the clinical study will be conducted in full compliance with the protocol and all applicable laws, regulations and regulatory requirements including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki and all applicable country-specific and local regulations. All required study information will be archived as required by regulatory authorities.

I have read, understood, and do agree to abide by all the conditions and instructions contained in this protocol, "A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children."

Protocol # CRO-2020-CAR-ARG-ED

Investigator Signature

Date

Investigator Name Printed

Sponsor Agreement

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

STUDY NO.: *CRO-2020-CAR-ARG-ED*

SPONSOR: Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

The signatures of the Sponsor's representatives below constitute the Sponsor's agreement:

- a) to all provisions of the protocol;
- b) to comply with ICH GCP Guidelines and all applicable country-specific and local laws, regulations and guidelines.



Maria E Ryan, DDS, PhD, Vice President, Chief Dental Officer
Oral Care Research & Development
Colgate-Palmolive Technology Center

1/29/2020
Date

COLGATE-PALMOLIVE

Clinical Study Protocol

Title: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Protocol No. CRO-2020-CAR-ARG-ED

IND # 140794

Investigational Medicinal Product (IMP) COL101 (arginine)

Indication Reduction in dental caries

Sponsor: Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

Medical Director: Maria E Ryan, DDS, PhD
VP and Chief Dental Officer
Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

Study Investigators: Details of participating Study Investigators, clinical study sites and other study personnel is contained in the Clinical Trials Master File and may be obtained from the Sponsor

PROTOCOL SYNOPSIS

Protocol Title:	A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children
Protocol Number:	CRO-2020-CAR-ARG-ED
Study Phase:	Phase II
Rationale for the Study:	Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia <i>et al.</i>, 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and also creates an environment that disfavors cariogenic bacteria and their deleterious activities. The present study is intended to evaluate anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year in 10 to 14 year old children. The outcome of this study may lead to an alternative method of caries prevention.

Study Design:

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in Section 5 of this protocol. At each study site, each enrolled subject will be randomized in a 1:1:1:1 ratio into one of four parallel study groups.

Group 1 dentifrice	1.5% arginine
Group 2 dentifrice	4.0% arginine
Group 3 dentifrice	8.0% arginine
Group 4 dentifrice	0.24% sodium fluoride with no arginine

Subjects will be required to brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice for one year. Measurements for safety and product use compliance will be conducted after 3 months, 6 months, 9 months and 12 months of assigned product use. In addition, caries examinations using the International Caries Detection and Assessment System (ICDAS) will be conducted at Baseline and at the 6 months and 12 months' time points. All subjects will be monitored for adverse events (AEs) during the course of the study.

Objectives:

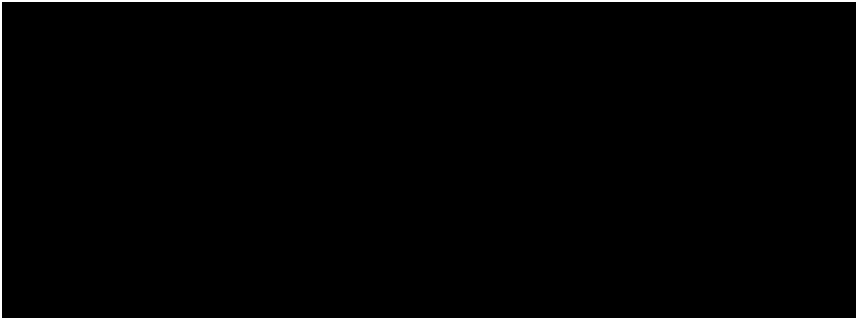
The objective of this study is to assess the safety and to evaluate the anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices containing 1.5%, 4% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10-14 year-old children over a one year period.

Main Endpoints:

Primary Endpoint: The primary efficacy endpoint will be the incremental subject-wise DMFS score after one-year of product use

Secondary Endpoints:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use.

- Clinically significant change in ICDAS severity scores between the baseline and the six-month and one-year examinations and between the six-month and one-year examinations.
 - Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6.
 - Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.
- 

Study Population:

Healthy school children 10 to 14 years of age with the presence of second permanent molars or evidence of erupting permanent second molars and evidence of previous caries experience.

Number of Subjects Planned:

2000 children (10-14 years of age) will be enrolled with the expectation that at least 1,800 subjects will complete the clinical trial at the end of a one-year period (10% annual attrition).

Number of Centers:

This study will be conducted by Study Investigators that are faculty from U.S. dental schools with standing approval from the Commission on Dental Accreditation and a Clinical Research Organization. Nine sites are planned.

Main Criteria for Inclusion:

- Healthy children 10-14 years of age of either sex. Subjects must be in good general health as evidenced by a review of their medical history
- Subjects must have presence of second permanent molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through.
- Subjects must have evidence of previous caries experience (DMFT >1).

	• Subjects must have two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth.
Test Products:	COL101 (arginine) dentifrices: 1.5%, 4.0%, and 8.0% arginine.
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Reference Therapy:	Positive control dentifrice: 0.24% sodium fluoride (1100 ppm F)
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Duration of Treatment:	For all dentifrices, subjects will be instructed to brush their teeth for two minutes twice daily using their assigned dentifrice for one year.
Efficacy Parameters:	Increments in Decayed Missing or Filled Surfaces (DMFS) over the one-year duration of the study. Caries threshold at the “moderate” cavitation caries level of ≥ 3 in the International Caries Detection and Assessment System (ICDAS).
Safety Parameters:	Safety will be assessed by an evaluation of all reported/observed adverse events during the course of the study and by hard and soft-oral tissue examinations conducted at Baseline, 3 months (± 1 month), 6 months (± 1 month), 9 months (± 1 month) and at 1 year (± 1 month).
Primary Objective:	The objective of the study is the estimation of the effectiveness on the reduction of caries of each of the three test products (1.5%, 4.0%, and 8.0% Arginine) relative to the positive control (0% arginine/sodium fluoride 0.24%).
Study Monitoring (Data Safety Monitoring Board):	The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. Specific for this trial, the incidence of caries progression in each of the Study Product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DSMB can recommend removal of individual

subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor.

Statistical Methods:

Efficacy of each of the four treatment groups will be estimated by the mean 1-year DMFS increment. Associated 95% confidence intervals will also be calculated. Generalized linear models will also be used to compare the DMFS increments statistically. Hard- and soft-tissue findings will be summarized by treatment group. Adverse events will be summarized by treatment group.

Superseded

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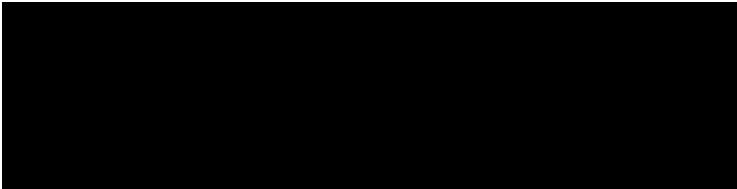
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LIST OF ABBREVIATIONS

ADA	American Dental Association
AE	Adverse Event
ANCOVA	Analysis of covariance
CRF	Case Report Form
CFR	Code of Federal Regulations
CPI	Community Periodontal Index
DMFS	Decayed Missing Filled Surfaces
DMFT	Decayed Missing Filled Teeth
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
ICCMS	International Caries Classification and Management System
ICDAS	International Caries Detection and Assessment System
ICH	International Conference on Harmonisation
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MRTD	Maximum Recommended Therapeutic Dose
NaF	Sodium Fluoride
NSAE	Non Serious Adverse Event
PSR	Periodontal Screening and Recording
SAE	Serious Adverse Event
US	United States
WHO	World Health Organization

1. INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

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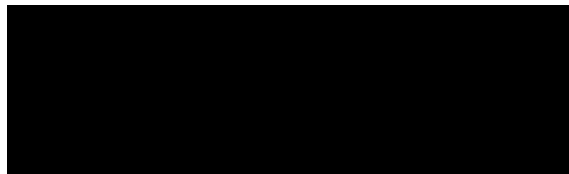
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Biostatistician:



2. INTRODUCTION AND BACKGROUND

Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia *et al.*, 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and creates an environment that disfavors cariogenic bacteria and their deleterious activities.

2.1. Rationale for the Study

The present study is intended to evaluate anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year. The outcome of this study may lead to an alternative method of caries prevention

2.2. Risk-Benefit Assessment

L-arginine is a semi-essential amino acid that can be obtained through dietary sources such as dairy products, beef, pork, soybeans, poultry, and granola among other sources. The normal intake of L-arginine from dietary sources is orders of magnitude higher than incidental ingestion from dentifrice. This amino acid is considered semi-essential because it can be synthesized *de novo* from glutamine, glutamate, and proline. Endogenous synthesis of arginine can, however, be insufficient e.g. during periods of growth, in inflammatory disease states or during infections.

L-arginine is generally recognized as safe (GRAS) by the US FDA when used in accordance with good manufacturing practice (21CFR 582.5145) and has been approved for use as a food additive permitted for direct addition to food for human consumption (21CFR 172.320 – amino acids). Although a Recommended Daily Allowance (RDA) has not been set, a Maximum Recommended Therapeutic Dose (MRTD) has been provided and set at 500 mg/kg body weight/day for L-arginine supplementation by the US FDA. The expected exposure to arginine from the use of dentifrice (maximum exposure, 2 yr old = 14 mg) is well below both the MRTD and the normal dietary intake.

Arginine has a good safety profile and is currently marketed in the United States (US) as an ingredient in dentifrice. Proven clinical benefits include the reduction of dentin hypersensitivity. There has been no observed pattern of adverse events (AEs) associated with its regular use.

2.3. Compliance Statement

The study will be conducted according to the protocol and in compliance with, International Council for Harmonization Good Clinical Practice (GCP) guidelines and other applicable local regulatory requirements and laws^{2,3}.

3. OBJECTIVES

The objective of this one-year study is to assess the safety and to evaluate the anti-carries efficacy of non-fluoride dentifrices containing 1.5%, 4% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10 to 14 year old children.

Superseded

4. OVERALL DESIGN AND PLAN OF THE STUDY

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in [Section 5](#) of this protocol. At each study site, each enrolled subject will be randomized into one of four parallel study groups (1.5% arginine dentifrice, 4.0% arginine dentifrice, 8.0% arginine dentifrice or 0.24% sodium fluoride dentifrice with no arginine). Voluntary participants will brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice. Measurements for efficacy, safety and assessment of product use compliance will be conducted at baseline, 6 months (± 1 month) and 1 year (± 1 month). Additional safety evaluations including evaluation of oral soft and hard tissues, as well as and product use compliance assessment will be performed at 3 months and 9 months (± 1 month). All subjects will be monitored for adverse events (AE) during the course of the study.

Subjects who are discontinued cannot reenter treatment and will not be replaced. Adverse events will be monitored for up to 30 days following study conclusion, until the AE is resolved or it is determined by the Study Investigator and Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) to be stable.

4.1. Overview

4.1.1. Screening and Selection of Subjects

Candidates will be screened by a trained and calibrated study examiner to identify those subjects who meet the inclusion/exclusion criteria ([Section 5](#)) and the findings will be recorded on an Inclusion/Exclusion case report form (CRF). Parents or legal guardians of participating children will be informed about all aspects of the study and informed consent/assent forms will be completed by each participating subject and by their parent or legal guardian.

At each site, subjects who, in addition to meeting the inclusion criteria, assent to voluntarily participate and whose parents or legal guardian have signed the informed consent form will be enrolled.

4.1.2. Baseline Clinical Examinations of Soft and Hard Tissue

The following evaluations will be performed at Baseline:

Soft and Hard Tissues will be examined and abnormalities will be noted in corresponding CRFs.

The soft tissue structures examined will include the soft palate, hard palate, gingival mucosa, buccal mucosa, mucogingival folds, tongue, sublingual and submandibular areas, salivary glands, tonsillar and pharyngeal areas. Observations will be listed as “Normal” and “Abnormal” and abnormalities will be described.

The hard tissue structures examined will include assessing for enamel irregularities, tooth fracture, pathologic tooth wear, cavitated caries lesions, residual roots, faulty restorations

and implants. Observations will be listed as “Normal” or “Abnormal” and conditions noted as abnormal will be described.

The International Caries Detection and Assessment System (ICDAS) will be used to determine caries severity and the caries lesion activity and to establish subject eligibility^{4,5,6}. As the subjects are recruited, baseline caries examinations will be performed by trained and calibrated study examiners who will carry out the examinations according to ICDAS Criteria. All examinations will be conducted after subjects have brushed their teeth with water and, if necessary, brushed again and possibly flossed by the study examiner or study personnel.

The severity criteria used in the ICDAS diagnostic system are as follows:

Code 0 Sound tooth surface

There should be no evidence of caries (either no or questionable change in enamel translucency after prolonged air drying (suggested drying time 5 s). Surfaces with developmental defects such as enamel hypoplasias; fluorosis; tooth wear (attrition, abrasion and erosion), and extrinsic or intrinsic stains will be recorded as sound. The examiner should also score as sound a surface with multiple stained fissures if such a condition is seen in other pits and fissures, a condition which is consistent with non-carious habits (*e.g.* frequent tea drinking).

Code 1 First visual change in enamel

Code 1: Pits and fissures

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air drying (approximately 5 s is suggested to adequately dehydrate a carious lesion in enamel) a carious opacity or discoloration (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel.

OR

When there is a change of color because of caries which is not consistent with the clinical appearance of sound enamel and is limited to the confines of the pit and fissure area (whether seen wet or dry). The appearance of these carious areas is not consistent with that of stained pits and fissures as defined in code 0.

Code 1: Smooth tooth surfaces

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air-drying a carious opacity (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel. This will be seen from the buccal or lingual surface.

Code 2 Distinct visual change in enamel

The tooth must be viewed wet. When wet there is a (i) carious opacity (white spot lesion) and/or (ii) brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel (Note: the lesion must still be visible when dry)

Code 3 Localized enamel breakdown because of caries with no visible dentin or underlying shadow

The tooth viewed wet may have a clear carious opacity (white spot lesion) and/or brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel. Once dried for approximately 5 s there is carious loss of tooth structure at the entrance to, or within, the pit or fissure/fossa. This will be seen visually as evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the fissure or pit, and although the pit or fissure may appear substantially and unnaturally wider than normal, the dentin is NOT visible in the walls or base of the cavity/discontinuity.

If in doubt, or to confirm the visual assessment, the WHO/CPI/PSR probe can be used gently across a tooth surface to confirm the presence of a cavity apparently confined to the enamel. This is achieved by sliding the ball end along the suspect pit or fissure and a limited discontinuity is detected if the ball drops into the surface of the enamel cavity/discontinuity.

Code 4 Underlying dark shadow from dentine from dentin with or without localized enamel breakdown

This lesion appears as a shadow of discolored dentin visible through an apparently intact enamel surface which may or may not show signs of localized breakdown (loss of continuity of the surface that is not showing the dentin). The shadow appearance is often seen more easily when the tooth is wet. The darkened area is an intrinsic shadow which may appear as grey, blue or brown in color. The shadow must clearly represent caries that started on the tooth surface being evaluated. If in the opinion of the examiner, the carious lesion started on an adjacent surface and there no evidence of any caries on the surface being scored then the surface should be coded '0'.

Code 5 Distinct cavity with visible dentine

Cavitation in opaque or discolored enamel exposing the dentin beneath.

The tooth viewed wet may have darkening of the dentin visible through the enamel. Once dried for 5 s there is visual evidence of loss of tooth structure at the entrance to or within the pit or fissure – frank cavitation. There is visual evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the pit or fissure and in the examiner judgment dentin is exposed.

The WHO/CPI/PSR probe can be used to confirm the presence of a cavity apparently in dentin. This is achieved by sliding the ball end along the suspect pit or fissure and a dentin cavity is detected if the ball enters the opening of the cavity and in the opinion of the examiner the base is in dentin. (In pits or fissures the thickness of the enamel is between 0.5 and 1.0 mm. Note the deep pulpal dentin should not be probed).

Code 6 Extensive distinct cavity with visible dentine

Obvious loss of tooth structure, the cavity is both deep and wide and dentin is clearly visible on the walls and at the base. An extensive cavity involves at least half of a tooth surface or possibly reaching the pulp.

Classification of the Tooth Profile, Surface Condition and Lesion Activity status in the ICDAS

Tooth Profile	
1	When a permanent or temporary filling is present, missing or defective
7	Not counted, unerupted teeth, congenitally missing or supernumerary teeth, teeth removed for reasons other than dental caries, and primary teeth retained in the permanent dentition
8	Trauma; poor prognosis (Not Counted)
9	When a tooth has been extracted due to caries

Surface Condition	
0	No filling, No sealant
1	Sealant (partial or complete)
2	Filling: when a permanent or temporary filling is present, missing or defective (e.g. composite, amalgam, crown, etc.)
3	Restoration: restored due to other reasons (e.g. cervical lesions, residual composite due to ortho or aligners, diastema closure, etc.)

Caries Lesion Activity Assessment (ICCMS Guide)⁶:

Code 0 Signs of Inactive Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located near the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing. Surrounding enamel has polished edges and may be shiny and hard and smooth when the ball-ended probe is moved gently across the surface.

Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning. The adjacent gingival tissue may show signs of inflammation or bleed upon probing.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.

A study examiner (dentist) will evaluate the condition of every surface of every tooth and will verbalize the findings to a trained recorder who will enter the data on to a CRF.

4.1.3 Subsequent Soft and Hard Tissue Examinations

Subsequent 6-month and 12-month clinical examinations will be conducted following the same examination criteria and procedures employed at baseline. Additional soft and hard tissue examinations will be conducted at 3 and 9 months for safety reasons. Examinations 3, 6 and 9 months will coincide with resupply of assigned toothpaste and toothbrush.

4.1.4 Calibration of Examiners

For each cohort, a didactic training session will be held to the participating examiners prior to the actual ICDAS clinical calibration session by a gold standard examiner (the Principal Investigator). This didactic session will include: 1) Review of ICDAS depicting the dental status examination criteria; 2) Evaluation of participating examiners' knowledge of the criteria; 3) Clinical Training with demonstration examinations; and 4) Practice Examinations of extracted teeth.

On training session day one, examiners from one cohort will see the first few qualifying screening subjects together and discuss their scores with the gold standard examiner and among each other. The calibration may start on day one or day two at the senior examiner's discretion. On calibration session (days 2 and 3) the participating examiners will conduct the examinations independently. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each permanent tooth surfaces will be scored. On day 3, approximately 3-5 willing subjects from calibration session (day 2) will be asked to return to the clinic for a repeat session. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each surface of permanent teeth will be scored.

Each tooth will be categorized into one of seven categories (0-6) based on its ICDAS score. Analyses will be performed at the tooth level and the subject level. Intra and inter-examiner reliability will be assessed using weighted kappa scores. A kappa score of 0.61

or higher will be considered substantial agreement for inter-examiner reliability. A kappa score of 0.81 or higher will be considered substantial agreement for intra-examiner reliability. If an examiner fails to achieve the said mark, the exercise may be repeated on some of the same subjects if they're willing to come back for future dates.

4.1.5 At-Home Product Use

After the baseline examinations are completed, dental study personnel (non-examiners) will give subjects tubes of their assigned dentifrice and adolescent size soft bristled toothbrushes. Subjects will be instructed to brush their teeth by applying a full ribbon of their assigned dentifrice to their assigned toothbrush head, and brush their teeth for 2 minutes twice daily. Subjects will also be requested to use no other dental products, such as other toothbrushes, mouth rinses or other dentifrices during the course of the study, however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with the dentist. Subjects that routinely use dental floss may continue to do so during the study period.

The assigned toothpaste and a new toothbrush will be re-supplied every three months.

4.1.6 Dental Treatment During the Study

Subjects will be instructed to continue regular visits to the dentist and routine dental treatment during the course of the study. In addition, at every scheduled study examination, subjects will receive a referral for dental care, if needed.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects meeting all criteria below will be included in the study:

1. Subject assent and parental/guardian informed consent for voluntary participation.
2. Willingness and ability to use the assigned products according to instructions, availability for all appointments and likelihood of completing the clinical trial.
3. Children ages 10-14 years at baseline.
4. Presence of permanent second molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through the mucosa.
5. Good general health as evidenced by a review of the medical history.
6. Subjects who, at study entry, have present two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth and previous caries experience (DMFT >1).

5.2. Exclusion Criteria

Subjects presenting any of the criteria below will be excluded from the study:

1. Presence of fixed or removable prosthetic appliance or orthodontic treatment involving more than four permanent teeth.
2. Use of medication that could increase the risk of developing dental caries, i.e. medications that reduces saliva flow and those with high sugar content.
3. Long-term antibiotic therapy.
4. Children with a confirmed diagnosis of cognitive and/or motor impairment.
5. Severe malocclusion.
6. Subjects who, at study entry, have present severe caries (ICDAS 5 or 6) on five or more teeth.
7. Evidence of moderate to severe periodontal disease.
8. Participation in any other clinical study within the 30 days preceding the start of the clinical study.
9. Known history of allergies or other adverse reactions to arginine, or oral care products, or their ingredients.

5.3. Withdrawal and Replacement of Subjects

A genuine effort will be made to determine the reason(s) why a subject fails to report to the scheduled examinations or has been dropped from the study. A subject will be dropped from the study if any of the following occurs:

1. Subject fails to report for the examinations.
2. Subject elects to terminate participation in the study.

3. Sponsor elects to terminate the study.
4. Subject experiences a serious adverse reaction to the test products. Withdrawal of the subject is at the discretion of the Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendation of the Medical Monitor). (See [Section 7.5.7](#) for SAE reporting procedures).
5. Subject is determined to be non-compliant by the Site PI in consultation with the Sponsor.

Subjects discontinued from the study for any reason will not be allowed to re-enter the study and will not be replaced. Subjects withdrawn due to AEs will receive follow-up as outlined in [Section 7.5.8](#)

5.4. Statistical Basis for Sample Size

The sample size requirement was determined based on the precision of the efficacy estimate for each treatment group. Details regarding this determination are provided in [Section 10.2](#) of this protocol.

5.5. Subject Identification, Randomization, and Blinding

Enrolled subjects at each study site will be assigned subject numbers specific to that site. An un-blinded biostatistician will generate a separate randomization listing for each study site, ensuring that the study biostatistician will remain blinded to the treatment assignments until the study has been completed. The randomization listings will be transferred to a designated un-blinded individual at each study site, who will manage randomized assignment, product dispensing and resupply. In addition to utilizing this information for the dispensing to treatment to enrolled subjects, this individual will also be on call to provide emergency un-blinding information for an individual subject if such a need should arise during the study. Each study site will maintain a list of all individuals who are privy to the randomization listing. At the conclusion of the study, after all data cleaning and statistical analyses have been programmed and completed (based on the blinded study data), the investigator at each study site will indicate that un-blinding can proceed. Un-blinding of the study data will not take place until this indication has been received from all study sites.

5.6. Un-blinding

If the Study Investigator determines that some event, such as a serious adverse event (SAE) has occurred and the treatment should be un-blinded for that subject, the Study Investigator should contact the Colgate Study Monitor. The Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendations of the Medical Monitor) will then make a decision about breaking the blind for the subject. The Colgate Study Monitor will then contact the study code un-blinder, and the subject will be un-blinded and documented accordingly.

6. STUDY PRODUCT

6.1. Identity

Study Product 1 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 1.5% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 2 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 4.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 3 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 8.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 4 (Control Product) Name: Dosage form: Manufacturer: Description:	Dentifrice 0.24% sodium fluoride (1100 ppm F) Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube

6.2 Packaging, Labeling, and Storage

The packaging and labeling will be performed by the sponsor according to all local legal requirements.

All supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to subjects, the study dentifrices will be stored in a securely locked area, only accessible to authorized personnel.

The study products will be coded and the identity of the products will be concealed.
The sponsor will provide the study dentifrices to the site.

Representative product labeling that will be placed on the outside box of each tube of toothpaste and on the tube of toothpaste itself can be found in Appendix IV.

6.3 Product Use Instructions

Subjects will be verbally instructed to brush their teeth twice daily (morning and evening before bed) for two minutes each time, using their assigned dentifrice and toothbrush. A timer will be provided to each participant as an aid to comply with 2-minute brushing. Subjects will also be instructed to dispense a full ribbon of toothpaste covering the full length of the toothbrush head for each tooth brushing. Study personnel will demonstrate this at the initial study visit. No oral hygiene products, other than the toothbrush and the dentifrice provided, should be used during the treatment period. Subjects that routinely use dental floss may continue to do so during the study period.

In addition to verbal product use instructions and essential information provided in product labels, subjects will be given written product use instructions to take home (Appendix V).

6.4 Study Product Dispensing

Kits containing dentifrices and toothbrushes shall be provided to the subjects every three months. All product dispensing and resupply will be handled by a study site individual unblinded to product assignment.

The initial distribution of the study products will occur at the examination facility after completion of the baseline examinations. Subsequent product dispensing will then take place every three months at the 3-month, 6-month and 9-month examination visits. Subjects will receive at each of these product resupply visits a new adolescent-sized, soft-bristled toothbrush and sufficient dentifrice will be dispensed to last until the next scheduled visit (one tube (4.7 oz tube) for every month) of product use.

Should additional dentifrice be required between routine deliveries, the subject will contact the study coordinator. The coordinator shall immediately ensure resupply via appropriate study personnel, preserving the double-blind design.

6.5 Study Product Accountability

The Sponsor will provide each study site with sufficient amounts of the study products.

The study site will confirm in writing receipt of all batches of study product.

The study site will administer/dispense study product only to subjects included in this study according to the procedures established in this study protocol. Each subject will be given only the dentifrice assigned to him/her. Each dispensed tube of dentifrice will be documented in the dispensing log.

All supplies must be accounted for at the end of the study. The study site must maintain accurate and adequate records, including dates dispensed, quantities received, subject dispensed to, date returned by the subject, amount returned by the subject, date returned to the sponsor and/or destroyed at the study site.

At the end of the study, no remaining supplies are to be in the study site's possession. The study monitor will procure and document that all remaining study supplies are properly discarded by the site.

6.6 Product Use Compliance

Subjects will be expected to return previously dispensed study dentifrice (empty, partially used or unused tubes of dentifrice included) to the site at each of the pre-established product resupply events and exchanged for new supply to last until the next scheduled visit (Appendix XV). Unused study dentifrice will also be collected at the site at the end of study participation. The study site will weigh all tubes of toothpaste at the time of dispensing and weigh the tubes when returned, maintaining a log of the gathered information on a subject per subject basis. For each individual, the amount of toothpaste used will be estimated by weight at each of the tube return/collection time points and compared to the expected use based on projection of using "two ribbons" per day. A timer will be provided to each participant as an aid to comply with 2-minute brushing.

6.7 Concomitant Medications

Any medication used during the study period, other than the study dentifrices specified in the protocol, is considered a concomitant medication. All concomitant medications must be recorded at the beginning of every study visit through completion of a health questionnaire.

7 SAFETY

7.1. Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. The DSMB will include clinical research scientists and statistician not otherwise connected with the study that, collectively, have extensive experience in the management of clinical trials and in the conduct and monitoring of randomized clinical trials and will be competent in applying this experience to the study of children with dental caries. The DSMB will elect a chair under rules they define in their organizational meeting and review and approve a DSMB Charter provided by the Sponsor. The DSMB will have access to un-blinded safety and effectiveness outcome data during the trial that will be provided by an un-blinded data manager. Specific for this trial, the incidence of caries progression in each of the study product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DSMB can recommend removal of individual subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor. The DSMB will meet at least every three months throughout the trial and distribute a report summarizing any safety concerns or serious adverse events that have occurred since the last three-month exam. This report will be submitted to the IRBs of each study site (or Central IRB), the Study Investigators and the Sponsor. Each report should contain an open section containing materials for blinded staff, and a closed section of treatment comparisons. Every precaution will be taken to maintain the blind from Study Investigators, study examiners, statisticians and the Sponsor. Interim conference calls may also be scheduled at the discretion of the board, Study Investigators or the Sponsor.

7.2. Stopping Rules

If an investigational product-related serious or unexpected AE occurs and it is determined to be an unacceptable risk to the health and safety of other investigational product recipients by the Study Investigator, Colgate Study Monitor, Medical Monitor, and DSMB, administration of investigational product will be discontinued until a thorough review of the events is undertaken by the Study Investigators, institutional review board (IRB) of record, and Colgate Monitor (who represents the recommendation of the Medical Monitor). The study may be resumed with the concurrence of the Medical Monitor (via Colgate Study Monitor), Study Investigators, and the US Food and Drug Administration (FDA).

7.3. Subject Safety Measures

Study subjects that have cavitated lesions (ICDAS 5/6) at their screening examinations will be referred to their dentist of record for necessary treatment. If the subject does not have a dentist, the study site will provide the names of three local dentists to the subject's parent/guardian.

7.4. Rescue Therapy

Any randomized subject that experiences pain, swelling, abscess or caries progression resulting in frank cavitation (ICDAS 5/6) during any follow up visit will be referred to their dentist of record for appropriate dental treatment. If the subject does not have a dentist, the study site will refer the subject to a local dentist or a dental school clinic.

7.5. Adverse Events (AEs)

Illnesses present at entry to the study are considered pre-existing conditions and will be documented on the Health Questionnaire (sample included as Appendix VII). AEs will be followed for up to 30 Days, until it resolves or is determined by the Study Investigator and the Medical Monitor (through the Colgate Study Monitor) to be stable.

All AEs must be reported and documented as described below.

7.5.1 Definitions

Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined by the ICH Guideline for Good Clinical Practice (ICH GCP) as follows:

Adverse Event: Any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include any clinically significant deterioration of a subject's medical status, after being enrolled in the study and signing an Informed Consent form. The AE may involve any organs or systems and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change from baseline, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring after the first administration of study medication is an adverse event. All such occurrences must be recorded and reported accordingly, whether they appear causally related to the study medication, or not.

Serious Adverse Event: Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening adverse event
- Inpatient hospitalization, or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience 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 important 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.

7.5.2 Assessment of Adverse Events

Volunteered, observed, and elicited AEs will be recorded. This includes those the subject reports spontaneously, those the study examiner observes, and those the study examiner elicits in response to open-ended questions at the times indicated on the Schedule of Study Activities, [Section 8.1](#).

All clinical complaints, symptoms, or signs that meet the adverse event definition will be recorded on the Adverse Events case report form (Appendix XIII) using a recognized medical term or diagnosis that accurately reflects the event. Source documentation should be maintained that allows for clear identification of each adverse event and the following parameters required for the CRF:

- AE description
- Date of onset
- Date of resolution
- Outcome
- Severity
- Seriousness
- Relationship to study drug (causality)
- Actions taken

Adverse events will be assessed by the investigator or designee for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification of the sponsor.

For CRF data collection purposes, the outcome of all adverse events recorded on the Adverse Event form should be reported within two (2) weeks of the study completion. The Investigator will include this information in the Site Report providing a line listing using the Periodic/End of Study Report Form (Appendix XIV) and attaching the individual adverse event form for each case reported. However, the Investigator is responsible for following all

adverse events until resolution or until no longer of clinical concern, and providing these data to the Sponsor.

When protocol duration, is six (6) months or longer, a Periodic/End of Study Report Form must be completed and included as part of your Site Report every six (6) months for the duration of the protocol.

7.5.3 Serious Adverse Events (SAEs)

Federal law defines an SAE as any event, occurring at any dose, which suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, an SAE can be described as one or more of the following:

- **Fatal:**

This includes deaths that appear to be completely unrelated to study product (e.g., car accident). If a subject dies during the study and an autopsy is performed, autopsy results will become part of this subject's CRF. Possible evidence of organ toxicity and the potential relationship of the toxicity to the study product will be of particular interest. The autopsy report should distinguish the relationship between the underlying diseases, the study product's side effects, and the cause of death.

- **Life-threatening:**

A life-threatening AE is any adverse event during which the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered a life-threatening event though drug-induced hepatitis can be fatal.

- Permanently or significantly disabling
- Requiring/prolonging inpatient hospitalization
- A congenital anomaly/birth defect

AEs that fall outside of these categories are not considered serious.

7.5.4 Severity

Regardless of the classification of an AE as serious or not, its severity must be assessed according to the following categories:

Mild:	does not interfere with routine activities
Moderate:	interferes with routine activities
Severe:	impossible to perform routine activities

Note that a severe AE need not be serious and that an SAE need not, by definition, be severe.

7.5.5 Relationship to Study Product

The study examiner will assess the relationship between the study product and the AE.

The following definitions are used to determine the relationship between the study product and the AE.

Definite: (must have four of the following)

This category applies to those AEs that the study examiner feels are incontrovertibly related to study product. This relationship may be considered definite if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose and recurs with re-exposure to study product (Note: this is not to be construed as a requirement to re-expose the subject; however, a category of definitely related can only be used when recurrence is observed);
- follows a known pattern of response to study product;
- is associated with toxic levels of the study product in the blood or positive results on drug sensitivity tests (e.g., skin test).

Probable: (must have 3 of the following)

This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to study product. This relationship may be considered probable if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the study product, yet the event is clearly related to the study product (e.g., tardive dyskinesia);
- follows a known pattern of response to study product.

Possible: (must have two of the following)

This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the study product appears unlikely, but cannot be ruled out with certainty. This relationship may be considered possible if or when the adverse event:

- follows a reasonable temporal sequence after administration of the study product;
- could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- follows a known pattern of response to study product.

Unlikely: (must have two of the following)

In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study product. This may be considered unlikely if or when the adverse event:

- does not follow a reasonable temporal sequence after administration of the study product;
- could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- does not follow a known pattern of response to study product;
- does not reappear or worsen when the study product is re-administered.

Not related:

This category applies to those AEs that, after careful consideration, are clearly and incontrovertibly due to causes other than the study product (e.g., disease or environment).

7.5.6 Recording Adverse Events (AEs)

All AEs, regardless of relationship to study product, must be recorded on the Adverse Events CRF. All AE reports should contain the date the AE occurred, a brief description of the event, time of onset, duration of event, intensity, treatment required, relationship to study product, study product action taken, outcome, and whether the event is classified as serious.

7.5.7 Reporting Non Serious Adverse Events (NSAEs) and Serious Adverse Events (SAEs)

The Study Investigator must complete the Report of Adverse Event when an AE is identified. The Study Investigator must report any NSAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 72 hours of the event. The Study Investigator will provide the NSAE Report to Central IRB within 1 month of the event. The Colgate Study Monitor will then report the NSAEs to the DSMB within 1 month of discovering the event.

The Study Investigator must report any SAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 24 hours of the event. The Study Investigator will provide SAE Report to Central IRB no later than 2 weeks (10 business days) of the event. The Colgate Study Monitor will then report the SAEs to the DSMB within 5 days of discovering the event.

The Study Investigator must also follow local IRB guidelines for Adverse Event reporting. The Study Investigator may be asked to submit substantiating data, such as diagnostic test reports, to the Colgate Study Monitor.

The Study Investigator and the Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) will review each Serious Adverse Event Report and evaluate the relationship of the event to study product.

Based on the Investigator and Sponsor's assessments of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new AE related to arginine raises concern over the safety of continued administration of the study product to subjects, the Sponsor will take immediate steps to notify the Federal Food and Drug Administration (FDA) and all investigators participating in clinical trials with arginine.

Further action that may be required includes the following:

- Modification of the protocol
- Discontinuation or suspension of the study
- Modification of the existing consent/assent form and informing current study participants of new findings
- Addition of any newly identified arginine-related AEs to the list of expected AEs.

7.5.8 Follow-Up of Adverse Events (AEs)

The Investigator must continue to follow all SAEs and those non-serious events possibly related to study product until they resolve or until the Study Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

Any SAE occurring within 30 days after the end of the study and considered to be at least possibly caused by the study product, and therefore a possible adverse product reaction, must be reported as above.

7.5.9 Reporting Safety Information

The Study Investigator must promptly report to the Colgate Study Monitor, Central IRB, his or her Institutional Review Board (IRB), according to the specific guidelines of that IRB, all unanticipated problems involving risks to subjects. The Clinical Study Monitor will provide all unanticipated problems involving risks to subjects to the DSMB. This includes death from any cause and all SAEs associated, or possibly associated, with the use of the study product.

7.5.10 Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis, only in the event of an emergency. The Study Investigator or other physician in attendance in such an emergency must contact the Colgate Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Study Investigator will decide, in consultation with the Colgate Monitor (who consults with and represents the recommendations of the Medical Monitor), whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be recorded.

8. STUDY CONDUCT

8.1. Schedule of Study Activities

Assessment	Baseline	3 Month (±1 Month)	6 Month (±1 Month)	9 Month (±1 Month)	12 Month (±1 Month)
Informed Consent/Assent	X				
Baseline Medical History/ Concomitant Medications	X				
Hard and Soft Tissue Examinations	X	X	X	X	X
Conformance with Entry Criteria	X				
Caries Examination	ICDAS	Visual Monitoring for Safety	ICDAS	Visual Monitoring for Safety	ICDAS
Medical History Update/Concomitant Medications		X	X	X	X
Visit Form (Continuance)		X	X	X	X
Dentist Notice/Referral (when Necessary)	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X
Randomization, Study Group Assignment and Initial Toothpaste and Toothbrush Supply	X				
Study toothpaste and toothbrush re-supply		X	X	X	
Collection of previously dispensed study toothpaste and toothbrush		X	X	X	X
Assessment of Product Use Compliance		X	X	X	X
Periodic/End of Study Report Form for Non-interventional Studies on Humans			X		X

8.2. Observations by Visit

8.2.1 Baseline Examination

- Obtain parental written informed consent and participant assent
- Verify conformance with entry criteria (inclusion/exclusion criteria).
- Medical history/concomitant medications
- Hard and soft tissue evaluation
- ICDAS Caries Examinations

- Randomization
- Adverse Events
- Dentifrice and toothbrush distribution and written and oral instructions for use
- Dentist Notice/Referral (if necessary)

8.2.2 3 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- Adverse Events
- Dentifrice and brush collection and resupply
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)

8.2.3 6 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- ICDAS Caries Examinations
- [REDACTED]
- Adverse Events
- Dentifrice and brush collection and resupply
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)
- Periodic/End of Study Report Form for Non-interventional Studies on Humans

8.2.4 9 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- Adverse Events
- Dentifrice and brush collection and resupply
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)

8.2.5 12 Month Examinations (± 1 Month)

- Medical history update/concomitant medications
- Visit Form (Continuance)
- Hard and soft tissue evaluation (including caries safety monitoring)
- ICDAS Caries Examinations
- [REDACTED]
- Adverse Events

- Dentifrice and brush collection
- Compliance assessment (assessment of returned product use)
- Dentist Notice/Referral (if necessary)
- Periodic/End of Study Report Form for Non-interventional Studies on Humans

8.2.6 Follow-Up Procedures

Subjects will be followed for AE resolution, as defined in [Section 7.5.8](#)

8.3. Site / Study Termination

If the Sponsor, or the Investigator discovers conditions arising during the study that indicate that the study should be halted, it must be terminated after appropriate consultation between the study Sponsor, project manager, and Investigator. Conditions that may warrant termination include, but are not limited to:

- * The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- * Failure of the Study Investigator to enter subjects at an acceptable rate.
- * Insufficient adherence to protocol requirements.
- * A decision on the part of the sponsor to suspend or discontinue development of the study product.

9. DATA HANDLING AND RECORD KEEPING

9.1. Data Quality Assurance

Colgate Study Monitors will conduct a site visit to verify the qualifications of the Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

An Investigator's meeting will be held to introduce the Investigators and their key personnel to the study protocol, CRFs, procedures, and regulatory requirements.

The Study Investigator is required to prepare and maintain adequate and accurate case histories, designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRFs for this study must be consistent with the subject's source documentation (i.e., medical records).

9.2. Case Report Forms (CRFs) and Source Documentation

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

In this clinical trial visit forms, confirmation of enrollment, randomization, study group assignment, log of product dispensing, data from soft tissue and hard tissue examinations, data from caries examinations, and administration of [REDACTED] will be captured on electronic case report forms (eCRFs). Direct data entry into eCRFs will be captured and stored in Veeva Vault Clinical Suite. Paper case report forms (paper CRFs) will be used to capture all other data that will not be directly entered into the Veeva system, such as report of adverse events and documentation of product use compliance. Paper CRFs will be retained as original source documents and will be scanned and uploaded to the Veeva Vault Clinical Suite.

Veeva Vault is a cloud-based Content Management System (CMS) developed by Veeva Systems. The Vault Clinical Suite includes Vault eTMF and Vault CTMS. Vault Clinical enables increased compliance of clinical processes, inspection readiness, and permits a unified and connected view of clinical operations business functions. In addition, Veeva Vault produces secure and compliant audit trails in accordance with the FDA 21 CFR Part 11 Electronic Records, Electronic Signatures, and Eudralex Annex11: Computerized Systems regulations. All data collected from the web based EDC hosted on a private Google Cloud Platform (GCP) cloud will be verified before being sent through encoded HTTP POST requests to the Veeva Vault cloud hosted on Amazon's Web Services cloud (AWS).

A study coordinator, designated by the study center Investigator will be responsible for overseeing management principles including validated data entry at the point of data generation, data storage in one comprehensive relational database and data security.

9.3. CRF Fields as Database Entry Sources

CRFs should be considered the only source for database entry. Data should not be entered on any other form. Should an AE occur that requires clinical laboratory or electrocardiogram (ECG) data, the original printout should be attached to the Adverse Event CRF.

9.4. Direct Access to Source Data

During the course of the study, the Colgate Study Monitors will make site visits to review protocol compliance, compare CRFs and individual subject's medical records/study records, assess product accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records/study records will be performed in a manner to ensure that subject confidentiality is maintained.

Reviewing the CRFs for completeness and clarity, and cross-checking with source documents will be required to monitor the progress of the study. Moreover, regulatory authorities and/or the Sponsor's clinical quality assurance group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

9.5. Documentation of Consent, Privacy Notice and Storage of Study Documents

All informed consent/assent forms and privacy notices will be administered in either English or Spanish, whichever is most appropriate, and will be kept as source documentation. Informed Consent/Assent forms will be stored in a secure locked room designated for research charts storage in the clinical site. The Study Investigator will provide each subject's parent with a clear and understandable Privacy Notice (Appendix I-A presents the Sponsor's standard privacy notice) regarding the processing in connection with the study of personal data (i.e., any information relating to an identified or identifiable individual) by the Study Investigator, Sponsor and other persons involved in the study. The Study Investigator will obtain parental signature to this privacy notice. The original signed copy of the privacy notice for each subject participating in the study will be retained in the Investigator's study records. Each subject's parent will be given a copy of the privacy notice and the privacy notice will be referenced in and form a part of the overall study informed consent/notice process.

A baseline privacy notice is included in this protocol for that purpose. Any deviation to the privacy notice as regards processing by the Sponsor (including its vendors, monitors and other representatives) must be agreed with the Sponsor. In addition, The Study Investigator is responsible for ensuring that all study subjects' parents receive a copy of the privacy notice, and that the privacy notice includes any local requirements regarding data security and privacy laws and regulations applicable to the study and the subjects. Should the privacy notice provided by the Sponsor fail to meet any applicable local requirements, the Study Investigator is responsible for amending the privacy notice to bring it into compliance with local applicable regulations and the Study Investigator agrees to indemnify and be liable to the Sponsor for any damages resulting from such non-compliance. Subjects' study charts will be stored in a secure locked room designated for research charts storage in the clinical site.

The chart room is a limited- access area and only delegated study personnel will have access to the study charts and subjects' data.

9.6. Archiving Study Records

Essential documents should be retained for a minimum of 5 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or for at least 5 years since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local regulations.

Superseded

10. STATISTICAL METHODS

10.1 Study Objectives and Hypotheses

10.1.1 Primary Study Objective

The primary objective of the study is the estimation of the effectiveness of the three test products (1.5%, 4.0%, and 8.0% Arginine) each relative to the positive control (0% arginine/sodium fluoride 0.24%).

Toward this end, the following null hypothesis will be considered for each of the three test products (1.5%, 4.0%, and 8.0% Arginine) in the analysis of the data:

- H_0 : There is no difference between the anti-caries efficacy of the test product and that of a dentifrice containing 0% arginine/ sodium fluoride 0.24% (1100 ppm F).

These hypotheses will each be tested through a comparison of the mean caries DMFS increments for the respective dentifrices. The secondary efficacy endpoints, counts of clinically significant changes in ICDAS severity (progression and regression) and caries lesion activity scores between the baseline and the 6-month and one-year examinations and between the 6-month and one-year examinations will also be compared among the four dentifrices. The analysis methods are described in [section 10.6](#).

10.2 Sample Size Considerations

The sample size determination was based on the expected half width of the 95% confidence interval for the one-year DMFS increment for each treatment group. Based on past data we expect a standard deviation of approximately 3.0. Using the normal approximation and 450 subjects per group at one year, the confidence interval half-width would be ± 0.28 . These estimates will provide data to be used in planning the next (pivotal) study.

10.3 Randomization

Separate randomization listings for each study site will be provided. Within each randomization, subjects will be assigned to each of the 8.0% arginine/0 ppm F dentifrice, 4.0% arginine/0 ppm F dentifrice, the 1.5% arginine/0ppm F dentifrice and the 0% arginine/ sodium fluoride 0.24% (1100 ppm F), in a 1:1:1:1 ratio.

10.4 Analysis Populations

Analysis populations for this study are as follows:

- Intent to Treat (ITT): The ITT population will consist of all subjects randomized and dispensed treatment.
- Safety: The Safety population will consist of all randomized subjects who received at least one administration of the study treatment

- **Per-Protocol (PP):** The PP population will consist of those subjects in the ITT population who completed all study examinations, and who experienced no serious protocol violations.

For the purpose of this determination, serious protocol violations:

1. Subject fails to report for examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.
4. Subject is treated with medications that may affect the parameters under investigation during the study.

All analyses performed on the ITT population will be based on treatments as randomized. Analyses performed on both the Safety and PP populations will be based on treatments actually received. Analyses performed to investigate safety will be performed on the Safety population. Analyses to investigate efficacy will be performed on both the ITT and PP populations; however, the primary efficacy analyses will be those based on the PP population.

10.5 Planned Interim Analyses

No interim analysis is planned for this study.

10.6 Final Analysis Plan

10.6.1 Procedures for Handling Missing, Unused, and Spurious Data

All analyses performed on the Safety and PP populations will be based on data as observed. For the ITT population, multiple imputation methodology will be employed to impute missing values for subjects who have missed visits, or who have dropped out of the study. Multiple imputation will be implemented using baseline subject characteristics to randomly impute each data point five times. The five complete data sets will be analyzed and then combined to incorporate both the estimated within and between data set error terms.

10.6.2 General Statistical Considerations

Data summaries for continuous variables will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

Baseline values for all parameters will be the most recent value prior to the first administration of study treatment.

10.6.3 Analyses for Efficacy

Based on the caries assessments performed on each tooth surface at each examination, subject-wise DMFS and DMFT scores will be calculated.

The primary efficacy endpoint will be the incremental subject-wise DMFS score after one year of product use.

Secondary efficacy endpoints will include:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use;
- Incremental subject-wise DMFT scores after 6-months and after one year of product use.
- Clinically significant change in ICDAS severity scores between the baseline and the six-months and one-year examinations and between the six-months and one-year. Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6. Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.

A score summary of all efficacy endpoints will be provided at each assessment time point.

The analysis of the primary endpoint (DMFS increment) will consist of the estimation of the mean and 95% confidence interval for each treatment group. This will allow the sponsor to make an informed decision on the choice of the treatment to pursue in a pivotal study.

The analyses of the secondary efficacy endpoints will consist of the preparation of descriptive summaries, which will include 95% confidence intervals.

Although the study is not powered to detect differences among the treatment groups, statistical models will still be implemented for the primary and secondary efficacy endpoints. Generalized linear models (GLIM) will be used for all analyses. For analyses of DMFS and DMFT increments, we anticipate that a normal error term will be appropriate. For counts of clinically significant changes, Poisson regression will be the most appropriate GLIM with the number of teeth at risk as the offset. This model is appropriate for analysis of progression or regression although the number of teeth at risk will differ. For changes in activity scores the GLIM will be in the form of a multinomial logistic regression with four categories (0 at both times, 0 to 1, 1 to 0 and 1 at both times) that compares the distributions among the treatment groups. All statistical tests will be performed using a two-tailed 5% significance level. 95% confidence intervals for the differences between treatments will also be calculated based on the models. In addition, the models will yield estimates of the pooled within group variance which can be used for planning further studies.

Analyses as described above will be performed on both the PP population, and the ITT population.

Listings of data will be provided for DMFS scores and for all efficacy endpoints.

10.6.5 Analyses for Safety

A summary of the hard- and soft-tissue findings will be provided, showing the incidence of findings in each treatment group.

Adverse events will be summarized by treatment group.

Data listings will be provided for all adverse event data, and for all soft- and hard-tissue findings.

10.6.6 Modifications to Statistical Methodology

Any modifications made to the analysis methodology described here will be clearly presented and explained in an amendment.

11. ETHICS, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1. Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Study Investigators abide by the principles of the GCP guidelines of the ICH. Also, the study will be carried out in accordance with local legal requirements.

The Study Investigator confirms the above by signing this study protocol.

11.2. Informed Consent/Assent

Before being enrolled in the study, informed consent will be obtained from the parent or legal guardian of each subject and assent will be obtained from the subjects according to the regulatory and legal requirements of the state. The consent and assent forms must be signed and dated and retained by the Study Investigator as part of the study records.

Should a protocol addendum be made, the consent/assent forms may be revised to reflect changes in the protocol.

The Study Investigator will not undertake any investigation specifically required by the protocol until valid consent/assent has been obtained.

11.3. Approval of Study Protocol

Before the start of the study, the study protocol and/or other appropriate documents will be submitted to the IRB and/or the authorities, in accordance with local legal requirements.

The Sponsor and the Study Investigator must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study.

11.4. Amending the Protocol

This protocol is to be followed exactly. Alterations and amendments must be written, receive approval from all persons who approved the original protocol, and receive FDA and IRB approval prior to implementation. Administrative changes (not affecting the patient benefit/risk ratio) may be made by the clinical monitor without any further approvals. All amendments will be distributed to all protocol recipients with instructions to append them to the protocol.

11.5. Confidentiality

All records of subject participation in this study are confidential and these records are available only to the investigator, specifically trained site personnel, supervising dentist/examiner, potentially the Sponsoring Company, Ethics/Institutional Review Board (IRB), the Food and Drug Administration of the United States (FDA) or other local regulatory agency. The results of this study may be published in a scientific journal or a government public clinical database. If any publication occurs, only the subject's study number/ID, gender and/or age may be used. They will agree to verify, by letter, that they participated in this study, if called upon to do so.

In addition, the identity of participating subjects must be protected. Only investigators (and specifically trained clinical site staff) will collect and have access to a subject's private information (e.g., name, medical records, etc.). Investigators will assign a study number to

subjects which will be used to conceal their identity on all case report forms and other documents prior to their sharing with the broader study team, including the sponsor. Documents that identify the subject by name (e.g., the signed informed consent form or health questionnaire) will not be transferred or submitted to the sponsor, and will be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate national or local authorities or to sponsor personnel to verify subject, product safety and study compliance.

Parents or legal guardians of participating subjects will be asked to review a participant privacy notice ([Appendix I-A](#)) and will be given a copy of the accepted and signed notice.

11.6. Advertising

No newspaper, radio, or television advertising will be used for recruitment purposes. If needed, a flyer may be created to recruit participants. If used, the flyer will be approved by an Institutional Review Board prior to posting or dissemination.

11.7. New Findings

Subjects will be informed of any significant new findings related to study products or procedures when they become known during the course of this clinical research study. Such information may affect the subject's decision to continue participation in the study.

11.8. Publication Policy

Colgate discourages any individual investigator from publishing his/her own results independently. An investigator shall not publish any data (poster, abstract, paper, etc.) without having received permission in advance from Colgate-Palmolive. The above procedure also applies to information on prematurely discontinued and other non-completed studies. Results from the investigator shall not be made available to any third party by the investigating team outside the publication procedure as set out above. Colgate-Palmolive will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

12. REFERENCES

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6. ICCMS™ Guide for Practitioners and Educators, 2014 <https://www.iccms-web.com/uploads/asset/59284654c0a6f822230100.pdf>
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APPENDIX I

**PARENTAL/LEGAL GUARDIAN CONSENT TO PARTICIPATE
IN A CLINICAL RESEARCH STUDY
AND
AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH
INFORMATION
AND
ASSENT FORM FOR CHILD PARTICIPANTS AGES 10 TO 14**

Sponsor / Study Title: Colgate-Palmolive / “A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine in each comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.”

Protocol Number: CRO-2020-CAR-ARG-ED

**Principal Investigator:
(Study Doctor)** «PiFullName»

Telephone: «IcfPhoneNumber»

Address: «PiLocations»

Taking Part in this Study is Voluntary

Your son or daughter is invited to voluntarily participate in a one-year clinical research study.

Before agreeing to your child’s participation in this research study, it is important that you read this form. This form, called a consent form, describes the purpose, procedures, benefits, risks and discomforts expected from participation in this research study. It also describes your right to withdraw consent for your child to participate in this research study at any time. No promises or guarantees can be made as to the results of this research study. Please ask as many questions as you want in order to decide whether you want your child be in this research study. This consent form may contain words that you do not understand. Please ask the research study doctor or the research study staff to explain any words or information that you do not clearly understand.

Please review the rest of this document for more details about this study and the things you should know before making a decision about whether to allow your child to participate in this study.

Why is this Study Being Done?

The purpose of the study is to compare the effectiveness in reducing tooth cavities of a commercially available fluoride toothpaste to non-fluoride dental toothpastes containing arginine (a safe and essential amino acid that is naturally found in saliva and produced by the human body). The use of the study product in this study is investigational which means it has not been approved by the United States Food and Drug Administration (FDA).

How Many People Will Take Part?

If you decide to allow your son/daughter to participate, know that he/she will be one of about 2,000 (two thousand) participants in the study. The study will be conducted simultaneously in many sites across the United States and Puerto Rico.

What Will Happen During the Study?

In order to be in this study your child must meet the following criteria.

1. Your son/daughter must be in the age range of 10 to 14 years and in good general health and absent of allergies.
2. The study examiner must find that conditions of your child's teeth and gums are satisfactory for the study and meet other teeth criteria that will be considered. This includes a prior experience with cavities, the current presence of tooth changes consistent with early cavities.

During your child's initial examination, the study doctor will evaluate your child's teeth and gums. If your child qualifies for the study, he/she will be assigned, using a procedure similar to flipping a coin, to one of four study groups. You, your child or the study doctor will not know to which toothpaste your child will be assigned to use for the one (1) year duration of the study. Every three (3) months, your child will be provided with toothpaste and a new toothbrush and he/she will be expected to return the previously dispensed tubes of toothpaste (no matter if full or empty). During the course of the study your child will be asked to not use any other oral hygiene products; however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with your child's dentist.

Your child will be examined every three (3) months for one (1) year.

Examination 1 (Screening)

You will be asked to read, sign and date this consent form and also fill out some other documents about the study. Your child will be provided with an assent form providing him/her with the opportunity to choose if he/she wants to participate in the study.

The study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study doctor will also check his/her teeth to see if there are any cavities.

After this examination, it will be decided if your child can be in this study.

Examination 2 (Baseline)

This examination may take place the same day of the screening examination. A study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study doctor will also check his/her teeth to see if there are any cavities. Your child will be asked to brush his/her teeth with water before he/she sees the study doctor.

Your child will also be given a short questionnaire for him or her to share how he or she feels about his/her oral health and his/her self-perception about oral function, social and emotional well-being. Similar questions will be asked after six (6) months and after twelve (12) months of assigned study product use.

Your child will be given the first supply of toothpaste and a toothbrush to take home. Your child will be instructed to brush his or her teeth twice per day (morning and evening) for two minutes each time, once in the morning and once before going to bed and not to use any other toothpastes, mouth rinses or other toothbrushes.

Your child will be asked to return the tubes of toothpaste provided (empty or not) at the next scheduled examination.

If the study doctor finds a cavity you will be notified and you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one. During this study, the investigator will not treat any abnormal issues in the mouth and will not fill cavities.

Examinations after three (3, 6, 9 and 12) months of study product use

A study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The same procedures as in the Examination 2 (Baseline) described above will be followed. After six (6) months and after twelve (12) months of assigned study product use, your child will be asked to complete the short questionnaire.

What are the Risks of Taking Part in the Study?

The risk of your child includes the possibility that the study product assigned may not prevent cavities as well as the fluoride. Your child will not be permitted during the study to receive fluoride treatments or sealants. There may be irritation caused by the dental examinations. Risks from the study product are expected to be the same as those for any currently marketed toothpaste. These include minor oral irritation and peeling skin in some sensitive individuals.

The risks associated with minor and rare irritations from dental examinations will be minimized by having trained and licensed oral care professionals conduct the oral examination, following standard clinical procedures.

There is a risk of possible loss of confidentiality while maintaining all research observations and data. There may be risks which are currently unknown.

Any significant findings will be communicated to you and, when necessary, will include a referral to a dentist or a note to his/her dentist. We encourage you inform your child's regular dentist of his/her participation in this study. If your child experiences any problems, you should contact the study doctor at the telephone number listed on page one of this form.

Discomfort with questionnaires

Some people feel uncomfortable when answering questions about the [REDACTED]. Though it is always better to have fully completed questionnaires, your child does not need to answer any questions that make him/her feel uncomfortable.

What are the Potential Benefits of Taking Part in the Study?

It is expected that your child will receive a direct dental benefit from participation in this study. Although it cannot be guaranteed for every child, a cavity reduction benefit is expected from all toothpastes in the study. Your child's teeth and gums will be monitored by examinations every three (3) months. Any significant findings will be communicated to you and, if necessary, will include a referral to a dentist or a note to his/her dentist. Participation in this clinical study does not replace the need for your son or daughter to visit his or her dentist on a regular basis. The results of this study may help the sponsor improve the study product and help dental professionals provide proper advice to their patients.

How will your Child's Information be Protected?

Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information may be disclosed if required by law. No information which could identify your child will be shared in publications about this study.

Organizations that may inspect and/or copy your child's research records for quality assurance and data analysis include groups such as the study doctor and his/her study staff, Advarra IRB, Colgate Palmolive, the U.S. Food and Drug Administration (FDA), and any state or federal agencies who may need to access your medical and/or research records (as allowed by law).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Will my Child's Information be used for Research in the Future?

Information collected from your child for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify your child will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

Alternatives to Participation

This research study is for research purposes only. The only alternative is to not participate in this study.

Will there be a Cost or Payment to Participate?

There is no cost to you or your child for the oral examinations and the use of toothpaste, toothbrush or any other study related product.

«Compensation»

Your child may receive an incentive for participation in the clinical study consisting of _____ (SITE TO DETERMINE IF APPLICABLE, ETC).

Who will Pay for my Child's Treatment if he/she gets Injured?

In the event of physical injury resulting from your child's participation in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your child's health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

Whom To Contact About This Study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
Study Subject Adviser
Advarra IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046

- or call **toll free:** 877-992-4724
- or by **email:** adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00040997.

Can my Child Withdraw from the Study?

Your child's participation is voluntary, and you may refuse to participate and/or withdraw your child at any time without penalty or loss of benefits to which your child would otherwise be entitled up to the point of withdrawal. Your child's study dentist has the right to withdraw your child from the study at any time if he or she feels that it is in your child's best interest or if your child fails to comply with the terms of the study.

Your child's participation may be terminated by the study doctor without regard to your consent in circumstances when the study doctor feels it may not be beneficial to your child.

You will be told about new information that may affect your child's health, welfare, or willingness to stay in the study.

Study Sponsor

This clinical research study is sponsored by the Colgate-Palmolive Company. The Study Site will receive financial support and material for this study. The study staff and study doctor have no financial interest in the Colgate-Palmolive Company.

Informed Consent Statement

I have read the contents of the consent form and have listened to the verbal explanation given by the study doctor. My questions concerning this study have been answered to my satisfaction. I hereby give voluntary consent for my child to participate in this study. Signing and dating this consent document does not waive my or my child's rights nor does it release the study doctor, study staff, institution, or sponsors from their responsibilities. I will receive a copy of this signed and dated consent document.

I voluntarily agree for my child to participate in this study. I understand that I will be been given a copy of this consent form after signing and dating it.

CHILD'S NAME _____

Signature of Parent or Legal Guardian

Print Name of Parent or Legal Guardian

Date

I attest that the requirements for informed consent from the research study described in this form have been satisfied, that I have discussed the research study with the participant's parent or legal guardian and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Signature of Person Obtaining Consent

Printed Name of Person Obtaining Consent

Date: _____

SPONSOR'S PRIVACY NOTICE

In addition to the informed consent that explains the clinical study in which your child may participate in, this authorization gives you additional detailed information about how your child's health information will be protected. By signing and dating this document you are allowing Colgate Palmolive Co. to disclose personal health information to outside organizations or people involved with the processing of this study.

What personal health information is collected and used in this study and might be shared?

1. Name, address and telephone number
2. Medical history
3. Current medications
4. Procedures performed in this study such as: Oral health exams and stress related proteins

Why is your personal information being used?

So the study staff may contact you during the study. Your child's health information is used to ensure your child's safety while selecting participants for the study. Results and data are collected for the advancement of medicine, dentistry and clinical care.

Which of our personnel may use or disclose your child's personal health information?

The following individuals and organizations may use or disclose your child's personal health information for this research study:

1. The study doctor and associated study staff
2. The Institutional Review Board
3. Safety and Regulatory departments at Colgate Palmolive Co.
4. Authorized members of the clinical site who may need your information in the performance of their duties associated with this research (for example, to provide treatment, ensure integrity of the research, accounting, scheduling etc.)

Who outside Colgate Palmolive Co. or the study doctor might receive your child's personal health information?

1. Institutional Review Board

2. Food and Drug Administration (your child will be identified only by his/her first name and last initial)

How long will Colgate or the Clinical Site be able to use or disclose your child's personal health information?

Your authorization for this specific study does not expire however the information may not be re-used or re-disclosed for another purpose other than the research described in this document unless you give written permission to do so. In California and any other state that requires an expiration date, the Authorization will expire in 50 years after you sign and date this authorization document. The Institutional Review Board may grant permission to the study doctor or others to use your child's information for another purpose after ensuring that appropriate privacy safeguards are in place. The Institutional Review Board is a committee whose job it is to protect the safety and privacy of research participants. Results of tests and procedures are done solely for this research study and will not be included in your child's dental record.

Will you be able to access your child's records?

You will be able to access your child's dental record when the study is completed. During the study you will not have access to prevent knowledge of study results from affecting the reliability of the study. Should an emergency or need for care arise that would require your child's treating physician or dentist to know this information the records would be provided.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your child's personal information for research but you must do so in writing to the study doctor at the address provided on the first page in your parental informed consent. Even if you withdraw your permission, the study doctor may still use your child's personal information that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission to use your child's personal health information that means your child will also be withdrawn from the research study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. By signing and dating this document I am permitting Colgate Palmolive Co or the Study Site to use and disclose personal health information collected about my child for research purposes as described above. I will receive a signed and dated copy of this form. I am not giving up any of my legal rights by signing and dating this form.

CHILD'S NAME _____

Signature of Parent or Legal Guardian
Guardian

Print Name of Parent or Legal

Date

Signature of Person Obtaining
Authorization

Printed Name of Person Obtaining
Authorization

Date: _____

ASSENT FORM
FOR CHILD PARTICIPANTS AGES 10 TO 14 YEARS

Sponsor / Study Title: Colgate-Palmolive / “A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine in each comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.”

Protocol Number: CRO-2020-CAR-ARG-ED

Principal Investigator: «PiFullName»
(Study Doctor)

Telephone: «IcfPhoneNumber»

Address: «PiLocations»

You are invited to join in a research study that is described below:

WHAT IS THIS STUDY ABOUT?

We would like to find out if new toothpastes can prevent cavities as well as a fluoride toothpaste. If you qualify for the study and you agree to participate in the study, you will be assigned to one of four (4) study groups. The toothpaste to be assigned to you will be determined using a procedure similar to flipping a coin. You will not know what toothpaste you will be assigned to use. During the study, which will last one (1) year, you will be asked to brush your teeth with the toothpaste assigned to you and not use any other toothpastes or mouth rinses; however, you should continue with treatment and checkups with your regular dentist.

If you decide to participate, you will be one of about 2,000 (two thousand) other children participating in the study.

WHAT WILL HAPPEN TO ME IN THIS STUDY?

If you decide that you want to be in this study, you will be examined by the study doctor six (6) times in the one (1) year-long study. Here is what will happen at each of these examinations:

First Examination (Screening)

You will be asked to read, sign and date this form and also fill out some other documents about the study. Your parents will also need to sign and date a permission form.

A study doctor will look at your lips, cheeks, tongue and all other areas inside of your mouth. The study doctor will also check your teeth to see if you have any cavities.

After this examination, the study doctor will decide if you can be in this study.

Second Examination (Baseline)

This second examination may happen the same day as the first examination. You may be asked to brush your teeth with water before you have this more detailed second examination. If the study doctor wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

If the study doctor decides that you will be in the study, you will be given a toothbrush and the toothpaste assigned to you. You will be asked to brush your teeth for two (2) minutes, two (2) times a day, once in the morning and once before going to bed. You will be asked not to use any other toothpastes or mouth rinses.

You will be asked to return the tubes of toothpaste provided (empty or not) at your next scheduled examination.

If the study doctor finds a cavity, you will be asked to see your regular dentist or if you don't have one, the study dentist will recommend one.

Examinations three (3), four (4), five (5) and six (6)

You will be examined again every three (3) months after you start brushing with the toothpaste and the toothbrush that you will be given. During these examinations, the study doctor will look at your lips, cheeks, tongue and all other areas inside of your mouth. The study doctor will check your teeth to see if you have any cavities. Sometimes you may be asked to brush your teeth with water before you see the study doctor. If the study doctor wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

You will be asked to return the tubes of toothpaste provided (empty or not) at your next scheduled examination.

If the study doctor finds a cavity, you will be asked to see your regular dentist or if you don't have one, the study dentist will recommend one.

CAN ANYTHING BAD HAPPEN TO ME IN THIS STUDY?

We will try to be as careful as we can during the examinations but there is a chance that something could happen such as getting a sore spot in your mouth. There is also the possibility that the study product assigned to you may not prevent cavities as well as the fluoride getting a cavity and irritation caused by the dental examinations. Risks from the study product are expected to be the same as those for any currently marketed toothpaste. These include minor oral irritation and peeling skin in some sensitive individuals. We encourage you inform your parent/legal guardian or regular dentist of your participation in this study.

Discomfort with questionnaires

Some people feel uncomfortable when answering questions about the [REDACTED]. Though it is always better to have fully completed questionnaires, you do not need to answer any questions that make you feel uncomfortable.

WHAT IS GOOD ABOUT BEING IN THIS STUDY?

You may have a cavity reduction from the toothpaste you use in the study. Your mouth and teeth will be checked every three (3) months. You will be told if you have any problems in your mouth and you may be asked to see your dentist. The results of this study may help the company paying for the study to improve their toothpaste products and help dentists provide proper advice to their patients.

WHAT DO I HAVE TO TELL THE STUDY EXAMINER ABOUT?

If you choose to join this study, the study examiner may ask you questions about your health and medicines that you may be taking. We ask that you tell the study doctor about your health and answer any questions the best you can.

You also need to tell your parents or legal guardian and the study doctor if you do not feel well after your examinations.

DO I HAVE TO BE IN THIS STUDY?

You do not have to be in this research study if you do not want to. You can say “yes” or you can say “no”. You can stop later if you change your mind. No one will be angry with you if you say “no”. Your regular doctor and dentist will still take care of you.

WHO CAN I TALK TO ABOUT THE STUDY?

You can ask questions about the study at any time. If you feel sick, you or your mom or dad can call the study doctor.

STATEMENT OF ASSENT

DO YOU WANT TO PARTICIPATE?

☐
☐

Yes, I will be in this study.

No, I do not want to do this.

If you have any questions about the study, you may ask the study staff at any time. Your parent/legal guardian will be given a copy of the consent letter that has telephone numbers of people to call when you have questions. If you want to be in this study, read the next paragraph and sign and date in the space below.

I agree to participate in this research study. I may decide to stop at any time without hurting my chances of being in future dental studies.

Child's Name (Please Print)

Child's Signature

Date

Signature of Study Personnel Obtaining Assent

Date

Printed Name of Study Personnel Obtaining Ass

Superseded

APPENDIX II

FORMULATIONS

CONTROL DENTIFRICE

This product is a commercially-available dentifrice of the Colgate-Palmolive Company under the commercial name Colgate Ultra Brite Anti-cavity Fluoride Toothpaste which is in compliance with the OTC Anti-caries Drug Monograph. It contains 0.24% sodium fluoride (1100 ppm F) in a silica base.

TEST DENTIFRICE 1

[1.5% Arginine in a calcium base]

This is a dentifrice containing 1.5% arginine in a calcium base.

TEST DENTIFRICE 2

[4.0% Arginine in a calcium base]

This is a dentifrice containing 4.0% arginine in a calcium base.

TEST DENTIFRICE 3

[8.0% Arginine in a calcium base]

This is a dentifrice containing 8.0% arginine in a calcium base.

APPENDIX III

PRODUCT LABEL INFORMATION

Caution: New Drug - Limited by Federal (or United States) law to investigational use. Not for sale.

Protocol Number: CRO-2020-CAR-ARG-ED

Product Code _____ Subject # _____

Brush your teeth twice daily (morning and evening) for two minutes each time. Apply a full ribbon of toothpaste on the toothbrush head. Use only the toothpaste and toothbrush provided.

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study

For study-related questions call:

Dr. _____ at phone number (____) ____ - ____.

In case of emergency call:

Dr. _____ at phone number (____) ____ - ____.

APPENDIX IV

PRODUCT USE INSTRUCTIONS

Important Product Information

Colgate Palmolive Sponsored Clinical Study (Protocol Number: *CRO-2020-CAR-ARG-ED*)

Caution:

For Investigational Use Only. Not for sale.

- Brush your teeth twice daily in the morning and in the evening before bed
- Brush for two minutes each time. Use the timer as aid.
- Apply a full ribbon of toothpaste on the toothbrush head just like it was demonstrated at the beginning of the study.
- Use only the toothpaste and toothbrush provided.
- The study products are only for your use.

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study

For study-related questions call:

Dr. _____ at phone number (____) ____-____.

In case of emergency call:

Dr. _____ at phone number (____) ____-____.

APPENDIX V

INITIAL SCREENING FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

The following questions will be answered based upon Investigator/Examiner/Study Personnel discretion:

1. Has the parental/ legal guardian provided informed consent for voluntary participation of the child and has the child provided written assent?	Yes	No
2. Is the subject in good general health?	Yes	No
3. Is the child willing and able to use the assigned products according to instructions, available for all appointments and likely to complete the study?	Yes	No

If any answer to any questions 1-3 is 'NO', the subject is ineligible for study. Dismiss subject and complete question 13 below. If the subject is eligible, continue to questions 4-13.

4. Is the subject undergoing orthodontic treatment, wears intraoral appliance?	Yes	No
5. Does the subject use medications that could increase the risk of developing soft tissue irritations?	Yes	No
6. Is the subject taking long-term antibiotic therapy or have a condition which would require an antibiotic prior to a dental procedure?	Yes	No
7. Does the child have cognitive and/or motor impairment?	Yes	No
8. Does the subject have severe malocclusion?	Yes	No
9. Does the subject appear to have evidence of moderate to severe periodontal disease?	Yes	No
10. Is the subject participating in any other clinical study within 30 days preceding the start of the clinical study?	Yes	No
11. History of allergies or other adverse reactions to arginine or oral care products, or their ingredients?	Yes	No
12. Are you pregnant and/or currently breastfeeding?	Yes	No N/A
13. IS THE SUBJECT ELIGIBLE FOR ENTRY INTO STUDY?	Yes	No

Please note any additional observations (if applicable)

Text

APPENDIX VI

CONTINUATION FORM (REVIEW ELIGIBILITY CRITERIA)

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

The following questions will be answered based upon Investigator/Examiner/Study Personnel discretion:

1. Does the parental/ legal guardian <u>still</u> consent for voluntary participation of the child and does the child <u>still</u> assent to participate?	Yes	No
2. Is the subject in good general health?	Yes	No
3. Is the child still willing and able to use the assigned products according to instructions, available for all appointments and likely to complete the study?	Yes	No

If any answer to any questions 1-3 is 'NO', the subject is ineligible for study. Dismiss subject and complete question 13 below. If the subject is eligible, continue to questions 4-13.

4. Has the subject undergone orthodontic treatment, or currently wears an intraoral appliance?	Yes	No
5. Does the subject use any new medications that could increase the risk of developing soft tissue irritations?	Yes	No
6. Is the subject currently taking long-term antibiotic therapy or have a condition which would require an antibiotic prior to a dental procedure?	Yes	No
7. Does the child have cognitive and/or motor impairment?	Yes	No
8. Does the subject have severe malocclusion?	Yes	No
9. Does the subject appear to have evidence of moderate to severe periodontal disease?	Yes	No
10. Has the subject participated in any other clinical study since enrollment?	Yes	No
11. History of allergies or other adverse reactions to arginine or oral care products, or their ingredients?	Yes	No
12. Are you pregnant and/or currently breastfeeding?	Yes	No N/A
13. IS THE SUBJECT ELIGIBLE TO CONTINUE WITH THE STUDY?	Yes	No

Please note any additional observations (if applicable)

Text

APPENDIX VII

HEALTH QUESTIONNAIRE

Name: _____ today's date: (mm/dd/yyyy) _____

Date of Birth: (mm/dd/yyyy) _____

Name of Physician: _____ Phone#: _____

Date of last visit: (mm/dd/yyyy) _____

Phone #: _____ Home ☐ Cell ☐

Email: _____

Home Address: _____

Are we allowed to contact you? Phone ☐ Cell ☐ email ☐

☐ By checking this box YOU are providing consent to be contacted by the clinical site

Emergency contact Name: _____ Phone#: _____

Your current physical health is: ___ Good ___ Fair ___ Poor

Have you ever had any serious operations? ☐ Yes ☐ No

If yes, please explain: _____

Are you currently under the care of a physician? ☐ Yes ☐ No

If yes, please explain: _____

Please check if you have been treated for or told that you have:

☐ Abnormal bleeding	☐ Anemia
☐ Hemophilia	☐ AIDS
☐ Blood transfusion	☐ Arthritis
☐ Ulcers/Colitis	☐ Glaucoma
☐ Heart problems	☐ Drug addiction
☐ Epilepsy/Seizures	☐ Skin problems
☐ Asthma or Hay fever	☐ Blood Disorders
☐ Chemo/Radiation therapy	☐ Cancer/Tumor
☐ Diabetes/abnormal blood sugar	☐ Kidney/Liver disease
☐ Difficulty breathing	☐ Hepatitis /Jaundice
☐ Lung problems	☐ Emphysema
☐ High/Low blood pressure	☐ Rheumatic fever

Please describe any of the above conditions:

Do you have a history of allergies to whitening oral care products, personal care consumer products, or their ingredients?

If yes, please fill explain: _____

Do you take any medications? If yes, please fill out following:

List any prescription or over the counter medications which you are taking:

Name of Medication	Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy)	Amount taken	How often	Reason

DENTAL HISTORY

Name of your dentist: _____ Phone#: _____

How often do you visit your Dentist? _____

Date of last visit: (mm/dd/yyyy) _____

WOMEN ONLY

Please answer the following:

Are you pregnant? ☐ Yes ☐ No

If yes, list due date (mm/dd/yyyy) _____;

Are you currently nursing or breastfeeding? ☐ Yes ☐ No

I understand that the information that I have given today is correct to the best of my knowledge. I also understand that this information will be held in the strictest of confidence, and it is my responsibility to inform this office of any changes in my medical status. I understand that my participation in this study is voluntary and that I can drop from the study at any time.

Signature _____

Date (mm/dd/yyyy) _____

APPENDIX VIII
ORAL SOFT TISSUE ASSESSMENT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

<u>AREA</u>	<u>NORMAL</u>	
1. Lips	YES _____	NO _____
2. Soft Palate	YES _____	NO _____
3. Hard Palate	YES _____	NO _____
4. Gingival Mucosa	YES _____	NO _____
5. Buccal Mucosa	YES _____	NO _____
6. Mucogingival Folds	YES _____	NO _____
7. Tongue	YES _____	NO _____
8. Sublingual and Submandibular areas	YES _____	NO _____
9. Salivary glands	YES _____	NO _____
10. Tonsillar and Pharyngeal areas	YES _____	NO _____

If answer to any of questions 1-10 is "NO", please explain or add a comment:

Signature, Examiner

Date

APPENDIX IX

ORAL HARD TISSUE ASSESSMENT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

	Absent	Present	If Present, please specify findings
Enamel Irregularities	☐	☐	
Tooth Fracture	☐	☐	
Pathologic Tooth Wear	☐	☐	
Cavitated Lesion	☐	☐	
Active Non-Cavitated Lesion	☐	☐	
Residual Root	☐	☐	
Faulty Restoration	☐	☐	
Implant	☐	☐	

Signature, Examiner

Date

APPENDIX X

UPDATED HEALTH QUESTIONNAIRE VISIT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

1. Were there any unexpected or serious reactions since the previous examination? YES NO

If yes, describe _____

2. Was any treatment prescribed for the above? YES NO

If yes, describe _____

3. Was any dental treatment received since the previous examination? YES NO

If yes, describe _____

4. Was any new medication (including OTC products) prescribed for subject since previous examination? YES NO

If yes, describe dose, duration and reason _____

Name of Medication	Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy)	Amount taken	How often	Reason

5. Do any of the responses to Questions 1-4 warrant exclusion of this subject's data from the statistical analysis? YES NO

If yes, explain _____

Signature, Examiner

Date

APPENDIX XI

SAMPLE CARIES EXAMINATION FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Caries

Study Name:

Subject #:
Initials:

Visit Date:
Gender:

Visit
DOB:

UPPER TEETH																					
Tooth	2			3			4			5			6			7			8		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																					
M																					
D																					
V																					
P																					

Tooth	9			10			11			12			13			14			15		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																					
M																					
D																					
V																					
P																					

LOWER TEETH																											
Tooth	16			17			18			19			20			21			22			23			24		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																											
M																											
D																											
V																											
L																											

Tooth	25			26			27			28			29			30			31		
	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
D																					
M																					
D																					
V																					
L																					

Calculations

ICDAS Mean:					
DT	MT	FT	DMF-T	Total T	
DS	MS	FS	DMF-S	Total S	

Examiner:
Version:
Reason Comment:

Approval Date:
Reason:

Classification of the Tooth Profile, Surface Condition and Lesion Activity status in the ICDAS

Tooth Profile	
1	When a permanent or temporary filling is present, missing or defective
7	Not counted, unerupted teeth, congenitally missing or supernumerary teeth, teeth removed for reasons other than dental caries, and primary teeth retained in the permanent dentition
8	Trauma; poor prognosis (Not Counted)
9	When a tooth has been extracted due to caries

Surface Condition	
0	No filling, No sealant
1	Sealant (partial or complete)
2	Filling: when a permanent or temporary filling is present, missing or defective (e.g. composite, amalgam, crown, etc.)
3	Restoration: restored due to other reasons (e.g. cervical lesions, residual composite due to ortho or aligners, diastema closure, etc.)

Caries Lesion Activity Assessment (ICCMS Guide):

Code 0 Signs of Inactive Lesions

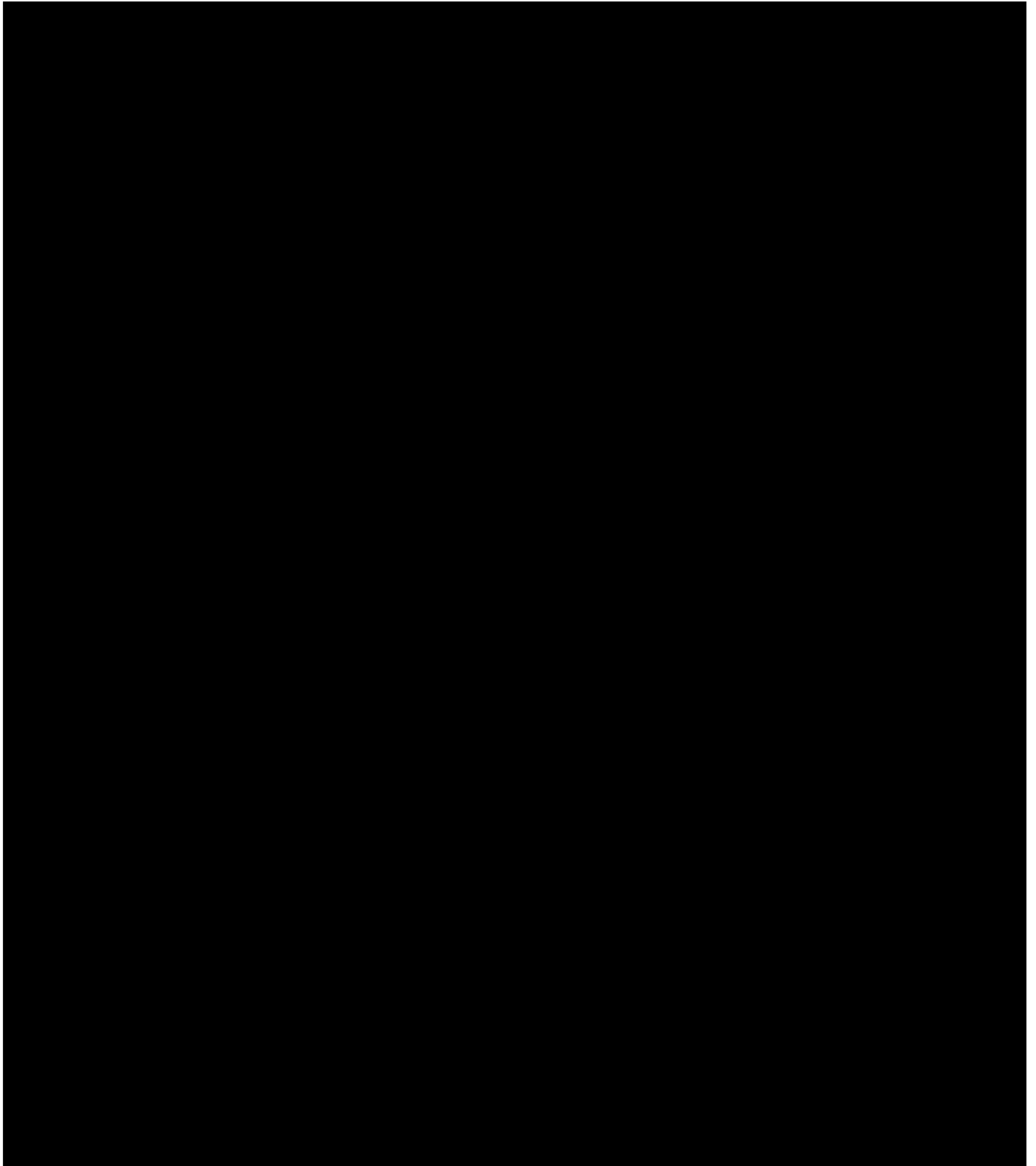
For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located at some distance from the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing.

Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.



APPENDIX XIV

REPORT OF ADVERSE EVENT

Instructions: Refer to the General Instructions & Supplemental Guidance pages for specific details on completing sections of the form. Additional pages may be added, if necessary, to report all information.

Awareness date – Colgate-Palmolive:		Awareness Date- Investigator:	
1) Study Information			
Protocol #:		Centre Name:	
Study Title:		Investigator:	
Indication /Objective of Protocol:		Address:	
Study Type: ☐ Clinical Trial (Interventional) ☐ Consumer ☐ Panel ☐ Phase II Clinical Trial ☐ Other Clinical ☐ Other Specify		Tel.: Fax:	
Study Originator/Monitor:		Email:	
Contact #		Health Care Professional : ☐ Yes ☐ No Specify occupation:	

2) Subject Information			
Subject's ID #: Initials:	Gender ☐ Male ☐ Female	Age/(Age Group): Or Date of Birth: - -	Weight ☐ LB ☐ KG
If subject is pregnant, how many months?			

3) Reporter Information (Complete only if different from Investigator named above)	
Sender/Reporter Name:	
Address	Country:
Email:	Telephone: Fax:
☐ Healthcare Professional Specify occupation:	☐ Non-Healthcare Professional

4) Phase of study the earliest event (s) occurred during:

☐ After consent ☐ Pre-randomization ☐ Randomization: no product ☐ Randomization: product exposure
☐ Baseline ☐ 3-Month ☐ 6-Month ☐ 9-Month ☐ 12-Month ☐ Other:

5) Study products (Please indicate if Test product, Blinded Product, Comparator (control product) was used by subject)

Product Name	Lot No/ Batch No/ Serial No (If MOCD)	Route of administration	Dosage & Frequency	Start Date (DD-MMM- YYYY)	Stop Date (DD-MMM- YYYY)	Action taken with Product
				- -	- -	
				- -	- -	
				- -	- -	
				- -	- -	

6) Adverse Event/Reaction Information

Adverse Events (AEs)	Start Date of AEs (DD-MMM- YYYY)	Stop Date of AEs (DD-MMM- YYYY)	Seriousness Criteria	Causality	Outcome
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	

Death (dd/mmm/yyyy):

Autopsy: ☐ YES ☐ NO ☐ Unknown

Cause of death if known:

Outcome:

Describe event (s)/reactions(s) in detail:

Protocol status of subject:		
☐ Subject continued in protocol ☐ Unrelated ☐ Unable to assess Subject continued in protocol	☐ Subject discontinued from protocol ☐ Unrelated ☐ Unable to assess Subject discontinued from protocol	
Was the subject treated for the event(s)/reaction(s) (Medical Intervention)? ☐ YES ☐ No If yes, please specify or describe:		
Event/Reaction abated after study product(s) stopped or dose reduced?		
☐ YES	☐ NO	☐ N.A.
Event/Reaction reappeared after study product(s) reintroduced?		
☐ YES	☐ NO	☐ N.A.

7) Subject Medical History: ☐ None ☐ Unknown <i>(Provide the medical history including pre-existing medical conditions)</i>

8) Other Medications/ Products used simultaneously: ☐ None ☐ Unknown					
Other Medications/ Products	Start Date (DD-MMM- YYYY)	Stop Date (DD-MMM- YYYY)	Indication	Dosage & Frequency	Route of administration
	-	-			
	-	-			
	-	-			
	-	-			

9) Laboratory data & other test procedure(s) relevant to the AE/AER(s)		
Test	Date (dd/mmm/yyyy)	Result (Specific value, normal, abnormal, clinically significant)

Investigator/Designee Signature: _____	Date (dd/mmm/yyyy): _____

Superseded

APPENDIX XIV

Periodic/End of Study Report Form for Non-interventional Studies on Humans (Colgate-Palmolive 105362)

Section A: Study Information	
Study Title:	Study Type: Clinical ☐ Phase II ☐ Consumer ☐ Panel ☐ Other ☐ Specify if selecting Other:
Protocol #:	Ref #:
Indication/Objective of Protocol:	
Primary Study Product/PDM#:	
Study Start Date (dd/MMM/yyyy):	State where study was conducted:
Investigator Name:	Study Originator Name:

Investigator/ Designee Signature: _____ Date dd/mmm/yyyy: _____

Section B: Report Type

Check applicable report type

☐ Periodic Report

☐ End of Study report

Were any adverse events/reactions reported during the study? If 'Yes' is checked, please complete section C

☐ Yes ☐ No

Section C: Adverse Event/Reaction Information

Protocol #:

Investigator Name:

Complete the table below *only* if an adverse event/reaction was reported during the study.

Case ID No.	Study Site Aware Date	Subject Information			Study Product Information			Adverse Events/Reactions			Other Products Used	Outcome with Date	Comments
		ID No.	Age/Date of Birth	Gender	Product Name	Dose & Frequency	Duration of Use	Description	Causality	Serious (Yes/No)			

Note: If needed attach additional pages of Section C to document all events/reactions reported during the study.

APPENDIX XV

CLINICAL PRODUCTS RETURN LOG SHEET

Organization _____

Principal Investigator _____

Date	Subject #	Product Code	1)Tube Before Use (Weight_g)	2)Tube After Use (Weight_g)	Weight Difference 1) – 2)

Print Name of Person Weighing Products

[Signature][Date]

APPENDIX XVI
REFERRAL/NOTICE FORM

Patient Name: _____ Patient DOB: _____

Patient Referred By: _____

- ☐ We did not find any condition that needs immediate treatment, but we recommend that you visit your dentist every 6 months
- ☐ During your next visit to the dentist you should let him/her know that you may have a dental problem
- ☐ You should visit the dentist as soon as possible
- ☐ You should visit the dentist for an emergency visit

Comments:

Doctor Signature: _____

Date: _____

Signature Page for VV-TMF-00176 v1.1
Protocol Number: CRO-2020-CAR-ARG-ED

Reason for signing: Approved	[Redacted]
Reason for signing: Approved	Name: Domenick Zero Role: Principal Investigator Date of signature: 24-Jul-2020 18:20:24 GMT+0000
Reason for signing: Approved	Name: Maria Ryan Role: Executive Approver Date of signature: 24-Jul-2020 19:03:33 GMT+0000
Reason for signing: Approved	[Redacted]
Reason for signing: Approved	[Redacted]

Signature Page for VV-TMF-00176 v1.1
Colgate-Palmolive Co.

CLINICAL TRIAL PROTOCOL

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Superseded

Investigator's Agreement

I understand that all documentation supplied to me by the sponsor concerning this study, which has not been previously published, will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

The study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the sponsor, and the IRB, except where necessary to eliminate an immediate hazard to the subjects.

I agree to monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority (ies) as required.

I understand that there is nothing in this document which is intended to limit my authority as a dentist to provide emergency care under applicable regulations.

I have read and approved this protocol. My signature confirms my agreement that the clinical study will be conducted in full compliance with the protocol and all applicable laws, regulations and regulatory requirements including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki and all applicable country-specific and local regulations. All required study information will be archived as required by regulatory authorities.

I have read, understood, and do agree to abide by all the conditions and instructions contained in this protocol, "A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children."

Protocol # CRO-2020-CAR-ARG-ED

Investigator Signature

Date

Investigator Name Printed

Colgate-Palmolive
Protocol Number: *CRO-2020-CAR-ARG-ED*

Sponsor Agreement

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

STUDY NO.: *CRO-2020-CAR-ARG-ED*

SPONSOR: Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

The signatures of the Sponsor's representatives below constitute the Sponsor's agreement:

- a) to all provisions of the protocol;
- b) to comply with ICH GCP Guidelines and all applicable country-specific and local laws, regulations and guidelines.



Maria E Ryan, DDS, PhD, Vice President, Chief Dental Officer
Oral Care Research & Development
Colgate-Palmolive Technology Center

07/23/2020
Date

COLGATE-PALMOLIVE

Clinical Study Protocol

Title: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Protocol No. CRO-2020-CAR-ARG-ED

IND #

140794

Investigational Medicinal Product (IMP) COL101 (arginine)

Indication

Reduction in dental caries

Sponsor:

Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

Medical Director:

Maria E Ryan, DDS, PhD
VP and Chief Dental Officer
Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

Study Investigators:

Details of participating Study Investigators, clinical study sites and other study personnel is contained in the Clinical Trials Master File and may be obtained from the Sponsor

PROTOCOL SYNOPSIS

Protocol Title:	A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children
Protocol Number:	CRO-2020-CAR-ARG-ED
Study Phase:	Phase II
Rationale for the Study:	Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia <i>et al.</i>, 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and also creates an environment that disfavors cariogenic bacteria and their deleterious activities. The present study is intended to evaluate anti-carries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year. The outcome of this study may lead to an alternative method of caries prevention.

Study Design:

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in Section 5 of this protocol. At each study site, each enrolled subject will be randomized in a 1:1:1:1 ratio into one of four parallel study groups.

Group 1 dentifrice	1.5% arginine
Group 2 dentifrice	4.0% arginine
Group 3 dentifrice	8.0% arginine
Group 4 dentifrice	0.24% sodium fluoride with no arginine

Subjects will be required to brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice for one year. Measurements for safety and product use compliance will be conducted after 3 months, 6 months, 9 months and 12 months of assigned product use. In addition, caries examinations using the International Caries Detection and Assessment System (ICDAS) will be conducted at Baseline and at the 6 months and 12 months' time points. All subjects will be monitored for adverse events (AEs) during the course of the study.

Objectives:

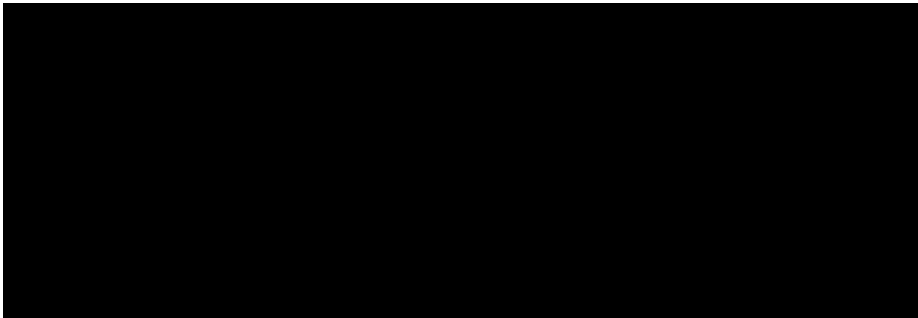
The objective of this study is to assess the safety and to evaluate the anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices containing 1.5%, 4.0% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10-14 year-old children over a one year period.

Main Endpoints:

Primary Endpoint: The primary efficacy endpoint will be the incremental subject-wise DMFS score after one-year of product use

Secondary Endpoints:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use.

- Clinically significant change in ICDAS severity scores between the baseline and the six-month and one-year examinations and between the six-month and one-year examinations.
 - Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6.
 - Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.
- 

Study Population:

Healthy school children 10 to 14 years of age with the presence of second permanent molars or evidence of erupting permanent second molars and evidence of previous caries experience.

Number of Subjects Planned:

2000 children (10-14 years of age) will be enrolled with the expectation that at least 1,800 subjects will complete the clinical trial at the end of a one-year period (10% annual attrition).

Number of Centers:

This study will be conducted by Study Investigators that are faculty from U.S. dental schools with standing approval from the Commission on Dental Accreditation and a Clinical Research Organization. Nine sites are planned.

Main Criteria for Inclusion:	• Healthy children 10-14 years of age of either sex. Subjects must be in good general health as evidenced by a review of their medical history • Subjects must have presence of second permanent molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through. • Subjects must have evidence of previous caries experience (DMFT >1). D= Decayed is defined as ICDAS scores of 3 or greater. • Subjects must have two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth.
Test Products:	COL101 (arginine) dentifrices: 1.5%, 4.0%, and 8.0% arginine.
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Reference Therapy:	Positive control dentifrice: 0.24% sodium fluoride (1100 ppm F)
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Duration of Treatment:	For all dentifrices, subjects will be instructed to brush their teeth for two minutes twice daily using their assigned dentifrice for one year.
Efficacy Parameters:	Increments in Decayed Missing or Filled Surfaces (DMFS) over the one-year duration of the study. Caries threshold at the “moderate” cavitation caries level of ≥ 3 in the International Caries Detection and Assessment System (ICDAS).
Safety Parameters:	Safety will be assessed by an evaluation of all reported/observed adverse events during the course of the study and by hard and soft-oral tissue examinations conducted at Baseline, 3 months (± 1 month), 6 months (± 1 month), 9 months (± 1 month) and at 1 year (± 1 month).

Primary Objective:	The objective of the study is the estimation of the effectiveness on the reduction of caries of each of the three test products (1.5%, 4.0%, and 8.0% Arginine) relative to the positive control (0% arginine/sodium fluoride 0.24%).
Study Monitoring (Data Safety Monitoring Board):	The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. Specific for this trial, the incidence of caries progression in each of the Study Product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DSMB can recommend removal of individual subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor.
Statistical Methods:	Efficacy of each of the four treatment groups will be estimated by the mean 1-year DMFS increment. Associated 95% confidence intervals will also be calculated. Generalized linear models will also be used to compare the DMFS increments statistically. Hard- and soft-tissue findings will be summarized by treatment group. Adverse events will be summarized by treatment group.

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LIST OF ABBREVIATIONS

ADA	American Dental Association
AE	Adverse Event
ANCOVA	Analysis of covariance
CRF	Case Report Form
CFR	Code of Federal Regulations
CPI	Community Periodontal Index
DMFS	Decayed Missing Filled Surfaces
DMFT	Decayed Missing Filled Teeth
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
ICCMS	International Caries Classification and Management System
ICDAS	International Caries Detection and Assessment System
ICH	International Conference on Harmonisation
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MRTD	Maximum Recommended Therapeutic Dose
NaF	Sodium Fluoride
NSAE	Non Serious Adverse Event
PSR	Periodontal Screening and Recording
SAE	Serious Adverse Event
US	United States
WHO	World Health Organization

1 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

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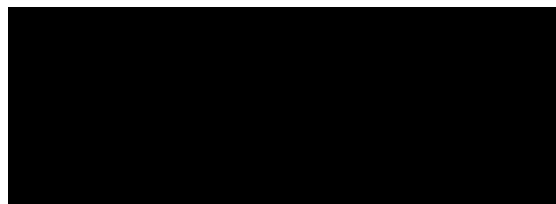
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2 INTRODUCTION AND BACKGROUND

Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia *et al.*, 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and creates an environment that disfavors cariogenic bacteria and their deleterious activities.

2.1 Rationale for the Study

The present study is intended to evaluate anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year. The outcome of this study may lead to an alternative method of caries prevention.

2.2 Risk-Benefit Assessment

L-arginine is a semi-essential amino acid that can be obtained through dietary sources such as dairy products, beef, pork, soybeans, poultry, and granola among other sources. The normal intake of L-arginine from dietary sources is orders of magnitude higher than incidental ingestion from dentifrice. This amino acid is considered semi-essential because it can be synthesized *de novo* from glutamine, glutamate, and proline. Endogenous synthesis of arginine can, however, be insufficient e.g. during periods of growth, in inflammatory disease states or during infections.

L-arginine is generally recognized as safe (GRAS) by the US FDA when used in accordance with good manufacturing practice (21CFR 582.5145) and has been approved for use as a food additive permitted for direct addition to food for human consumption (21CFR 172.320 – amino acids). Although a Recommended Daily Allowance (RDA) has not been set, a Maximum Recommended Therapeutic Dose (MRTD) has been provided and set at 500 mg/kg body weight/day for L-arginine supplementation by the US FDA. The expected exposure to arginine from the use of dentifrice (maximum exposure, 2 yr old = 14 mg) is well below both the MRTD and the normal dietary intake.

Arginine has a good safety profile and is currently marketed in the United States (US) as an ingredient in dentifrice. Proven clinical benefits include the reduction of dentin hypersensitivity. There has been no observed pattern of adverse events (AEs) associated with its regular use.

2.3 Compliance Statement

The study will be conducted according to the protocol and in compliance with, International Council for Harmonization Good Clinical Practice (GCP) guidelines and other applicable local regulatory requirements and laws^{2, 3}.

3 OBJECTIVES

The objective of this one-year study is to assess the safety and to evaluate the anti-caries efficacy of non-fluoride dentifrices containing 1.5%, 4.0% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10 to 14 year old children.

4 OVERALL DESIGN AND PLAN OF THE STUDY

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in Section 5 of this protocol. At each study site, each enrolled subject will be randomized into one of four parallel study groups (1.5% arginine dentifrice, 4.0% arginine dentifrice, 8.0% arginine dentifrice or 0.24% sodium fluoride dentifrice with no arginine). Voluntary participants will brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice. Measurements for efficacy, safety and assessment of product use compliance will be conducted at baseline, 6 months (± 1 month) and 1 year (± 1 month). Additional safety evaluations including evaluation of oral soft and hard tissues, as well as product use compliance assessment will be performed at 3 months and 9 months (± 1 month). All subjects will be monitored for adverse events (AE) during the course of the study.

Subjects who are discontinued cannot reenter treatment and will not be replaced. Adverse events will be monitored for up to 30 days following study conclusion, until the AE is resolved or it is determined by the Study Investigator and Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) to be stable.

4.1 Overview

4.1.1 Screening and Selection of Subjects

Candidates will be screened by a trained and calibrated study examiner to identify those subjects who meet the inclusion/exclusion criteria (Section 5) and the findings will be recorded on an Inclusion/Exclusion case report form (CRF). Parent or legal guardians of participating children will be informed about all aspects of the study and informed consent/assent forms will be completed by each participating subject and by their parent or legal guardian.

At each site, subjects who, in addition to meeting the inclusion criteria, assent to voluntarily participate and whose parents or legal guardian have signed the informed consent form will be enrolled.

4.1.2 Baseline Clinical Examinations of Soft and Hard Tissue

The following evaluations will be performed at Baseline:

Soft and Hard Tissues will be examined and abnormalities will be noted in corresponding CRFs.

The soft tissue structures examined will include the lips, soft palate, hard palate, gingival mucosa, buccal mucosa, mucogingival folds, tongue, sublingual and submandibular areas, salivary glands, tonsillar and pharyngeal areas. Observations will be listed as “Normal” and “Abnormal” and abnormalities will be described.

The hard tissue structures examined will include assessing for enamel irregularities, tooth fracture, pathologic tooth wear, cavitated lesion, active non-cavitated lesion, residual root, faulty restoration and implant. Observations will be listed as “Absent” or “Present” and conditions noted as present will be described.

The International Caries Detection and Assessment System (ICDAS) will be used to determine caries severity and the caries lesion activity and to establish subject eligibility^{4,5,6}. As the subjects are recruited, baseline caries examinations will be performed by trained and calibrated study examiners who will carry out the examinations according to ICDAS Criteria. All examinations will be conducted after subjects have brushed their teeth with water and, if necessary, brushed again and possibly flossed by the study examiner or study personnel.

The severity criteria used in the ICDAS diagnostic system are as follows:

Code 0 Sound tooth surface

There should be no evidence of caries (either no or questionable change in enamel translucency after prolonged air drying (suggested drying time 5 s). Surfaces with developmental defects such as enamel hypoplasias; fluorosis; tooth wear (attrition, abrasion and erosion), and extrinsic or intrinsic stains will be recorded as sound. The examiner should also score as sound a surface with multiple stained fissures if such a condition is seen in other pits and fissures, a condition which is consistent with non-carious habits (*e.g.* frequent tea drinking).

Code 1 First visual change in enamel

Code 1: Pits and fissures

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air drying (approximately 5 s is suggested to adequately dehydrate a carious lesion in enamel) a carious opacity or discoloration (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel.

OR

When there is a change of color because of caries which is not consistent with the clinical appearance of sound enamel and is limited to the confines of the pit and fissure

area (whether seen wet or dry). The appearance of these carious areas is not consistent with that of stained pits and fissures as defined in code 0.

Code 1: Smooth tooth surfaces

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air-drying a carious opacity (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel. This will be seen from the buccal or lingual surface.

Code 2 *Distinct visual change in enamel*

The tooth must be viewed wet. When wet there is a (i) carious opacity (white spot lesion) and/or (ii) brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel (Note: the lesion must still be visible when dry)

Code 3 *Localized enamel breakdown because of caries with no visible dentin or underlying shadow*

The tooth viewed wet may have a clear carious opacity (white spot lesion) and/or brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel. Once dried for approximately 5 s there is carious loss of tooth structure at the entrance to, or within, the pit or fissure/fossa. This will be seen visually as evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the fissure or pit, and although the pit or fissure may appear substantially and unnaturally wider than normal, the dentin is NOT visible in the walls or base of the cavity/discontinuity.

If in doubt, or to confirm the visual assessment, the WHO/CPI/PSR probe can be used gently across a tooth surface to confirm the presence of a cavity apparently confined to the enamel. This is achieved by sliding the ball end along the suspect pit or fissure and a limited discontinuity is detected if the ball drops into the surface of the enamel cavity/discontinuity.

Code 4 *Underlying dark shadow from dentin with or without localized enamel breakdown*

This lesion appears as a shadow of discolored dentin visible through an apparently intact enamel surface which may or may not show signs of localized breakdown (loss of continuity of the surface that is not showing the dentin). The shadow appearance is often seen more easily when the tooth is wet. The darkened area is an intrinsic shadow which may appear as grey, blue or brown in color. The shadow must clearly represent caries that started on the tooth surface being evaluated. If in the opinion of the examiner, the

carious lesion started on an adjacent surface and there no evidence of any caries on the surface being scored then the surface should be coded '0'.

Code 5 *Distinct cavity with visible dentine*

Cavitation in opaque or discolored enamel exposing the dentin beneath.

The tooth viewed wet may have darkening of the dentin visible through the enamel. Once dried for 5 s there is visual evidence of loss of tooth structure at the entrance to or within the pit or fissure – frank cavitation. There is visual evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the pit or fissure and in the examiner judgment dentin is exposed.

The WHO/CPI/PSR probe can be used to confirm the presence of a cavity apparently in dentin. This is achieved by sliding the ball end along the suspect pit or fissure and a dentin cavity is detected if the ball enters the opening of the cavity and in the opinion of the examiner the base is in dentin. (In pits or fissures the thickness of the enamel is between 0.5 and 1.0 mm. Note the deep pulpal dentin should not be probed).

Code 6 *Extensive distinct cavity with visible dentine*

Obvious loss of tooth structure, the cavity is both deep and wide and dentin is clearly visible on the walls and at the base. An extensive cavity involves at least half of a tooth surface or possibly reaching the pulp.

Classification of the Tooth Profile, Surface Condition and Lesion Activity status in the ICDAS

Tooth Profile	
1	When a permanent or temporary filling is present, missing or defective
7	Not counted, unerupted teeth, congenitally missing or supernumerary teeth, teeth removed for reasons other than dental caries, and primary teeth retained in the permanent dentition
8	Trauma; poor prognosis (Not Counted)
9	When a tooth has been extracted due to caries

Surface Condition	
0	No filling, No sealant
1	Sealant (partial or complete)
2	Filling: when a permanent or temporary filling is present, missing or defective (e.g. composite, amalgam, crown, etc.)
3	Restoration: restored due to other reasons (e.g. cervical lesions, residual composite due to ortho or aligners, diastema closure, etc.)

Caries Lesion Activity Assessment (ICCMS Guide)⁶:**Code 0 Signs of Inactive Lesions**

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located near the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing. Surrounding enamel has polished edges and may be shiny and hard and smooth when the ball-ended probe is moved gently across the surface.

Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning. The adjacent gingival tissue may show signs of inflammation or bleed upon probing.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.

A study examiner (dentist) will evaluate the condition of every surface of every tooth and will verbalize the findings to a trained recorder who will enter the data on to a CRF.

4.1.3 Subsequent Soft and Hard Tissue Examinations

Subsequent 6-month and 12-month clinical examinations will be conducted following the same examination criteria and procedures employed at baseline. Additional soft and hard tissue examinations will be conducted at 3 and 9 months for safety reasons. Examinations at 3, 6 and 9 months will coincide with resupply of assigned toothpaste and toothbrush.

4.1.4 Calibration of Examiners

For each cohort, a didactic training session will be held to the participating examiners prior to the actual ICDAS clinical calibration session by a gold standard examiner (the Principal Investigator). This didactic session will include: 1) Review of ICDAS depicting the dental status examination criteria; 2) Evaluation of participating examiners' knowledge of the criteria; 3) Clinical Training with demonstration examinations; and 4) Practice Examinations of extracted teeth.

On training session day one, examiners from one cohort will see the first few qualifying screening subjects together and discuss their scores with the gold standard examiner and among each other. The calibration may start on day one or day two at the senior examiner's discretion. On calibration session (days 2 and 3) the participating examiners will conduct the examinations independently. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each permanent tooth surfaces will be scored. On day 3, approximately 3-5 willing subjects from calibration session (day 2) will be asked to return to the clinic for a repeat session. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each surface of permanent teeth will be scored.

Each tooth will be categorized into one of seven categories (0-6) based on its ICDAS score. Analyses will be performed at the tooth level and the subject level. Intra and inter-examiner reliability will be assessed using weighted kappa scores. A kappa score of 0.61 or higher will be considered substantial agreement for inter-examiner reliability. A kappa score of 0.81 or higher will be considered substantial agreement for intra-examiner reliability. If an examiner fails to achieve the said mark, the exercise may be repeated on some of the same subjects if they're willing to come back for future dates.

The recommended loupes for the study will be Orascropic™ (Madison, WI) with the following specifications – magnification: 2.5; weight: 1.12 oz (31.8g); light intensity: 32 lumens; color temperature: 6500° K; focus: 2.75" (6.98 cm); spotlight at 12" (30.5 cm) focused beam.

4.1.5 At-Home Product Use

After the baseline examinations are completed, dental study personnel (non-examiners) will give each subject tubes of their assigned dentifrice and an adolescent size soft bristled toothbrush. Subjects will be instructed to brush their teeth by applying a full

ribbon of their assigned dentifrice to their assigned toothbrush head, and brush their teeth for 2 minutes twice daily. Subjects will also be requested to use no other dental products, such as other toothbrushes, mouth rinses or other dentifrices during the course of the study, however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with the dentist. Subjects that routinely use dental floss may continue to do so during the study period.

The assigned toothpaste and a new toothbrush will be re-supplied every three months.

4.1.6 Dental Treatment During the Study

Subjects will be instructed to continue regular visits to the dentist and routine dental treatment during the course of the study. In addition, at every scheduled study examination, subjects will receive a referral for dental care, if needed.

Superseded

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects meeting all criteria below will be included in the study:

1. Subject assent and parental/guardian informed consent for voluntary participation.
2. Willingness and ability to use the assigned products according to instructions, availability for all appointments and likelihood of completing the clinical trial.
3. Children ages 10-14 years at baseline.
4. Presence of permanent second molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through the mucosa.
5. Good general health as evidenced by a review of the medical history.
6. Subjects who, at study entry, have present two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth and previous caries experience (DMFT >1), D= Decayed is defined as ICDAS scores of 3 or greater.

5.2 Exclusion Criteria

Subjects presenting any of the criteria below will be excluded from the study:

1. Presence of fixed or removable prosthetic appliance or orthodontic treatment involving more than four permanent teeth.
2. Use of medication that could increase the risk of developing dental caries, i.e. medications that reduces saliva flow and those with high sugar content.
3. Long-term antibiotic therapy.
4. Children with a confirmed diagnosis of cognitive and/or motor impairment.
5. Severe malocclusion.
6. Subjects who, at study entry, have present severe caries (ICDAS 5 or 6) on five or more permanent teeth.
7. Evidence of moderate to severe periodontal disease.
8. Participation in any other clinical study within the 30 days preceding the start of the clinical study.
9. Known history of allergies or other adverse reactions to arginine, or oral care products, or their ingredients.
10. Self-reported history of being currently pregnant, intending to become pregnant during the trial period or breast-feeding.

5.3 Withdrawal and Replacement of Subjects

A genuine effort will be made to determine the reason(s) why a subject fails to report to the scheduled examinations or has been dropped from the study. A subject will be dropped from the study if any of the following occurs:

1. Subject fails to report for the examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.
4. Subject experiences a serious adverse reaction to the test products. Withdrawal of the subject is at the discretion of the Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendation of the Medical Monitor). (See Section 7.5.7 for SAE reporting procedures).
5. Subject is determined to be non-compliant by the Site PI in consultation with the Sponsor.

Subjects discontinued from the study for any reason will not be allowed to re-enter the study and will not be replaced. Subjects withdrawn due to AEs will receive follow-up as outlined in Section 7.5.8

5.4 Statistical Basis for Sample Size

The sample size requirement was determined based on the precision of the efficacy estimate for each treatment group. Details regarding this determination are provided in Section 10.2 of this protocol.

5.5 Subject Identification, Randomization, and Blinding

Enrolled subjects at each study site will be assigned subject numbers specific to that site. Subjects living in the same household will be assigned the same product code. An un-blinded biostatistician will generate a separate randomization listing for each study site, ensuring that the study biostatistician will remain blinded to the treatment assignments until the study has been completed. The randomization listings will be transferred to a designated un-blinded individual at each study site, who will manage randomized assignment, product dispensing and resupply. In addition to utilizing this information for the dispensing the treatment product to enrolled subjects, this individual will also be on call to provide emergency un-blinding information for an individual subject if such a need should arise during the study. Each study site will maintain a list of all individuals who are privy to the randomization listing. At the conclusion of the study, after all data cleaning and statistical analyses have been programmed and completed (based on the blinded study data), the investigator at each study site will indicate that un-blinding can proceed. Un-blinding of the study data will not take place until this indication has been received from all study sites.

5.6 Un-blinding

If the Study Investigator determines that some event, such as a serious adverse event (SAE) has occurred and the treatment should be un-blinded for that subject, the Study Investigator should contact the Colgate Study Monitor. The Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendations of the Medical Monitor) will then make a decision about breaking the blind for the subject. The Colgate Study Monitor will then contact the study code un-blinder, and the subject will be un-blinded and documented accordingly.

Superseded

6 STUDY PRODUCT

6.1 Identity

Study Product 1 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 1.5% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 2 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 4.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 3 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 8.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 4 (Control Product) Name: Dosage form: Manufacturer: Description:	Dentifrice 0.24% sodium fluoride (1100 ppm F) Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube

6.2 Packaging, Labeling, and Storage

The packaging and labeling will be performed by the sponsor according to all local legal requirements.

All supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to subjects, the study dentifrices will be stored in a securely locked area, only accessible to authorized personnel.

The study products will be coded and the identity of the products will be concealed.

The sponsor will provide the study dentifrices to the site.

Representative product labeling that will be placed on the outside box of each tube of toothpaste and on the tube of toothpaste itself can be found in Appendix III.

6.3 Product Use Instructions

Subjects will be verbally instructed to brush their teeth twice daily (morning and evening before bed) for two minutes each time, using their assigned dentifrice and toothbrush. A timer will be provided to each participant as an aid to comply with 2-minute brushing. Subjects will also be instructed to dispense a full ribbon of toothpaste covering the full length of the toothbrush head for each tooth brushing. Study personnel will demonstrate this at the initial study visit. No oral hygiene products, other than the toothbrush and the dentifrice provided, should be used during the treatment period. Subjects that routinely use dental floss may continue to do so during the study period.

In addition to verbal product use instructions and essential information provided in product labels, subjects will be given written product use instructions to take home (Appendix IV).

6.4 Study Product Dispensing

Kits containing dentifrices and toothbrushes shall be provided to the subjects every three months. All product dispensing and resupply will be handled by a study site individual un-blinded to product assignment.

The initial distribution of the study products will occur at the examination facility after completion of the baseline examinations. Subsequent product dispensing will then take place every three months at the 3-month, 6-month and 9-month examination visits. Subjects will receive at each of these product resupply visits a new adolescent-sized, soft-bristled toothbrush and sufficient dentifrice will be dispensed to last until the next scheduled visit (one tube (4.7 oz tube) for every month) of product use.

Should additional dentifrice be required between routine deliveries, the subject will contact the study coordinator. The coordinator shall immediately ensure resupply via appropriate study personnel, preserving the double-blind design.

6.5 Study Product Accountability

The Sponsor will provide each study site with sufficient amounts of the study products. The study site will confirm in writing receipt of all batches of study product.

The study site will administer/dispense study product only to subjects included in this study according to the procedures established in this study protocol. Each subject will be given only the dentifrice assigned to him/her. Each dispensed tube of dentifrice will be documented in the dispensing log.

All supplies must be accounted for at the end of the study. The study site must maintain accurate and adequate records, including dates dispensed, quantities dispensed, subject dispensed to, date returned by the subject, amount returned by the subject, date returned to the sponsor and/or destroyed at the study site.

At the end of the study, no remaining supplies are to be in the study site's possession. The study monitor will procure and document that all remaining study supplies are properly discarded by the site.

6.6 Product Use Compliance

Subjects will be expected to return previously dispensed study dentifrice (empty, partially used or unused tubes of dentifrice included) to the site at each of the pre-established product resupply events and exchanged for new supply to last until the next scheduled visit (Appendix XVI). Unused study dentifrice will also be collected at the site at the end of study participation. The study site will weigh all tubes of toothpaste at the time of dispensing and weigh the tubes when returned, maintaining a log of the gathered information on a subject per subject basis. For each individual, the amount of toothpaste used will be estimated by weight at each of the tube return/collection time points and compared to the expected use based on projection of using "two ribbons" per day. A timer will be provided to each participant as an aid to comply with 2-minute brushing.

6.7 Concomitant Medications

Any medication used during the study period, other than the study dentifrices specified in the protocol, is considered a concomitant medication. All concomitant medications must be recorded at the beginning of every study visit through completion of a health questionnaire.

7 SAFETY

7.1 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. The DSMB will include general dentists with expertise in cariology,

pediatric dentist, pediatrician, and statistician not otherwise connected with the study that, collectively, have extensive experience in the management of clinical trials and in the conduct and monitoring of randomized clinical trials and will be competent in applying this experience to the study of children with dental caries. The DSMB will elect a chair under rules they define in their organizational meeting and review and approve a DSMB Charter provided by the Sponsor. The DSMB will have access to un-blinded safety and effectiveness outcome data during the trial that will be provided by an un-blinded data manager. Specific for this trial, the incidence of caries progression in each of the study product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DSMB can recommend removal of individual subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor. The DSMB will meet at least every three months throughout the trial and distribute a report summarizing any safety concerns or serious adverse events that have occurred since the last three-month exam. This report will be submitted to the IRBs of each study site (or Central IRB), the Study Investigators and the Sponsor. Each report should contain an open section containing materials for blinded staff, and a closed section of treatment comparisons. Every precaution will be taken to maintain the blind from Study Investigators, study examiners, statisticians and the Sponsor. Interim conference calls may also be scheduled at the discretion of the board, Study Investigators or the Sponsor.

7.2 Stopping Rules

If an investigational product-related serious or unexpected AE occurs and it is determined to be an unacceptable risk to the health and safety of other investigational product recipients by the Study Investigator, Colgate Study Monitor, Medical Monitor, and DSMB, administration of investigational product will be discontinued until a thorough review of the events is undertaken by the Study Investigators, institutional review board (IRB) of record, and Colgate Monitor (who represents the recommendation of the Medical Monitor). The study may be resumed with the concurrence of the Medical Monitor (via Colgate Study Monitor), Study Investigators, and the US Food and Drug Administration (FDA). Additional information for stopping rules, including examples of serious, unexpected adverse events and expected adverse reactions, can be found in Appendix XVIII.

7.3 Subject Safety Measures

Study subjects that have cavitated lesions (ICDAS 5/6) at their screening examinations will be referred to their dentist of record for necessary treatment. If the subject does not have a dentist, the study site will provide the names of three local dentists to the subject's parent/guardian.

7.4 Rescue Therapy

Any randomized subject that experiences pain, swelling, abscess or caries progression resulting in frank cavitation (ICDAS 5/6) during any follow up visit will be referred to their dentist of record for appropriate dental treatment. If the subject does not have a dentist, the study site will refer the subject to a local dentist or a dental school clinic.

7.5 Adverse Events (AEs)

Illnesses present at entry to the study are considered pre-existing conditions and will be documented on the Health Questionnaire (sample included as Appendix VII). AEs will be followed for up to 30 Days, until it resolves or is determined by the Study Investigator and the Medical Monitor (through the Colgate Study Monitor) to be stable.

All AEs must be reported and documented as described below.

7.5.1 Definitions

Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined by the ICH Guideline for Good Clinical Practice (ICH GCP) as follows:

Adverse Event: Any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include any clinically significant deterioration of a subject's medical status, after being enrolled in the study and signing an Informed Consent form. The AE may involve any organs or systems and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change from baseline, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring after the first administration of study medication is an adverse event. All such occurrences must be recorded and reported accordingly, whether they appear causally related to the study medication, or not.

Serious Adverse Event: Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening adverse event
- Inpatient hospitalization, or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience 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 important 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.

7.5.2 Assessment of Adverse Events

Volunteered, observed, and elicited AEs will be recorded. This includes those the subject reports spontaneously, those the study examiner observes, and those the study examiner elicits in response to open-ended questions at the times indicated on the Schedule of Study Activities, Section 8.1.

All clinical complaints, symptoms, or signs that meet the adverse event definition will be recorded on the Adverse Events case report form (Appendix XIV) using a recognized medical term or diagnosis that accurately reflects the event. Source documentation should be maintained that allows for clear identification of each adverse event and the following parameters required for the CRF:

- AE description
- Date of onset
- Date of resolution
- Outcome
- Severity
- Seriousness
- Relationship to study drug (causality)
- Actions taken

Adverse events will be assessed by the investigator or designee for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification of the sponsor.

For CRF data collection purposes, the outcome of all adverse events recorded on the Adverse Event form should be reported within two (2) weeks of the study completion. The Investigator will include this information in the Site Report providing a line listing

using the Periodic/End of Study Report Form (Appendix XV) and attaching the individual adverse event form for each case reported. However, the Investigator is responsible for following all adverse events until resolution or until no longer of clinical concern, and providing these data to the Sponsor.

When protocol duration, is six (6) months or longer, a Periodic/End of Study Report Form must be completed and included as part of your Site Report every six (6) months for the duration of the protocol.

7.5.3 Serious Adverse Events (SAEs)

Federal law defines an SAE as any event, occurring at any dose, which suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, an SAE can be described as one or more of the following:

- **Fatal:**
This includes deaths that appear to be completely unrelated to study product (e.g., car accident). If a subject dies during the study and an autopsy is performed, autopsy results will become part of this subject's CRF. Possible evidence of organ toxicity and the potential relationship of the toxicity to the study product will be of particular interest. The autopsy report should distinguish the relationship between the underlying diseases, the study product's side effects, and the cause of death.
- **Life-threatening:**
A life-threatening AE is any adverse event during which the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered a life-threatening event though drug-induced hepatitis can be fatal.
 - Permanently or significantly disabling
 - Requiring/prolonging inpatient hospitalization
 - A congenital anomaly/birth defect

AEs that fall outside of these categories are not considered serious.

7.5.4 Severity

Regardless of the classification of an AE as serious or not, its severity must be assessed according to the following categories:

Mild:	does not interfere with routine activities
Moderate:	interferes with routine activities
Severe:	impossible to perform routine activities

Note that a severe AE need not be serious and that an SAE need not, by definition, be severe.

7.5.5 Relationship to Study Product

The study examiner will assess the relationship between the study product and the AE.

The following definitions are used to determine the relationship between the study product and the AE.

Definite: (must have four of the following)

This category applies to those AEs that the study examiner feels are incontrovertibly related to study product. This relationship may be considered definite if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose and recurs with re-exposure to study product (Note: this is not to be construed as a requirement to re-expose the subject; however, a category of definitely related can only be used when recurrence is observed);
- follows a known pattern of response to study product;
- is associated with toxic levels of the study product in the blood or positive results on drug sensitivity tests (e.g., skin test).

Probable: (must have 3 of the following)

This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to study product. This relationship may be considered probable if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the study product, yet the event is clearly related to the study product (e.g., tardive dyskinesia);
- follows a known pattern of response to study product.

Possible: (must have two of the following)

This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the study product appears unlikely, but cannot be ruled out with certainty. This relationship may be considered possible if or when the adverse event:

- follows a reasonable temporal sequence after administration of the study product;
- could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- follows a known pattern of response to study product.

Unlikely: (must have two of the following)

In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study product. This may be considered unlikely if or when the adverse event:

- does not follow a reasonable temporal sequence after administration of the study product;
- could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- does not follow a known pattern of response to study product;
- does not reappear or worsen when the study product is re-administered.

Not related:

This category applies to those AEs that, after careful consideration, are clearly and incontrovertibly due to causes other than the study product (e.g., disease or environment).

7.5.6 Recording Adverse Events (AEs)

All AEs, regardless of relationship to study product, must be recorded on the Adverse Events CRF. All AE reports should contain the date the AE occurred, a brief description of the event, time of onset, duration of event, intensity, treatment required, relationship to study product, study product action taken, outcome, and whether the event is classified as serious.

7.5.7 Reporting Non Serious Adverse Events (NSAEs) and Serious Adverse Events (SAEs)

The Study Investigator must complete the Report of Adverse Event when an AE is identified. The Study Investigator must report any NSAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 72 hours of the event. The Study Investigator will provide the NSAE Report to Central IRB within 1 month of the event. The Colgate Study Monitor will then report the NSAEs to the DSMB within 1 month of discovering the event.

The Study Investigator must report any SAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 24 hours of the event. The Study Investigator will provide SAE Report to Central IRB no later than 2 weeks (10 business days) of the event. The Colgate Study Monitor will then report the SAEs to the DSMB within 5 days of discovering the event.

The Study Investigator must also follow local IRB guidelines for Adverse Event reporting. The Study Investigator may be asked to submit substantiating data, such as diagnostic test reports, to the Colgate Study Monitor.

The Study Investigator and the Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) will review each Serious Adverse Event Report and evaluate the relationship of the event to study product.

Based on the Investigator and Sponsor's assessments of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new AE related to arginine raises concern over the safety of continued administration of the study product to subjects, the Sponsor will take immediate steps to notify the Federal Food and Drug Administration (FDA) and all investigators participating in clinical trials with arginine.

Further action that may be required includes the following:

- Modification of the protocol
- Discontinuation or suspension of the study
- Modification of the existing consent/assent form and informing current study participants of new findings
- Addition of any newly identified arginine-related AEs to the list of expected AEs.

7.5.8 Follow-Up of Adverse Events (AEs)

The Investigator must continue to follow all SAEs and those non-serious events possibly related to study product until they resolve or until the Study Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

Any SAE occurring within 30 days after the end of the study and considered to be at least possibly caused by the study product, and therefore a possible adverse product reaction, must be reported as above.

7.5.9 Reporting Safety Information

The Study Investigator must promptly report to the Colgate Study Monitor, Central IRB, his or her Institutional Review Board (IRB), according to the specific guidelines of that IRB, all unanticipated problems involving risks to subjects. The Clinical Study Monitor will provide all unanticipated problems involving risks to subjects to the DSMB. This includes death from any cause and all SAEs associated, or possibly associated, with the use of the study product.

7.5.10 Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis, only in the event of an emergency. The Study Investigator or other physician in

attendance in such an emergency must contact the Colgate Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Study Investigator will decide, in consultation with the Colgate Monitor (who consults with and represents the recommendations of the Medical Monitor), whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be recorded.

8 STUDY CONDUCT

8.1 Schedule of Study Activities

Assessment	Baseline	3 Month (±1 Month)	6 Month (±1 Month)	9 Month (±1 Month)	12 Month (±1 Month)
Informed Consent/Assent	X				
Baseline Medical History/ Concomitant Medications	X				
Hard and Soft Tissue Examinations	X	X	X	X	X
Conformance with Entry Criteria	X				
Caries Examination	ICDAS	Visual Monitoring for Safety	ICDAS	Visual Monitoring for Safety	ICDAS
Medical History Update/Concomitant Medications		X	X	X	X
Visit Form (Continuance)		X	X	X	X
Dentist Notice/Referral (when Necessary)	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X
Randomization, Study Group Assignment and Initial Toothpaste and Toothbrush Supply	X				
Study toothpaste and toothbrush re-supply		X	X	X	
Collection of previously dispensed study toothpaste and toothbrush		X	X	X	X
Assessment of Product Use Compliance		X	X	X	X
Periodic/End of Study Report Form			X		X

8.2 Observations by Visit

8.2.1 Baseline Examination

- * Obtain parental written informed consent and participant assent
- * Verify conformance with entry criteria (inclusion/exclusion criteria). Medical history/concomitant medications
- * Hard and soft tissue evaluation
- * ICDAS Caries Examination
- * [REDACTED]
- * [REDACTED]
- * Randomization
- * Adverse Events
- * Dentifrice and toothbrush distribution and written and oral instructions for use
- * Dentist Notice/Referral (if necessary)

8.2.2 3 Month Examinations (± 1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * Adverse Events
- * Dentifrice and brush collection and resupply
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)

8.2.3 6 Month Examinations (± 1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * ICDAS Caries Examination
- * [REDACTED]
- * Adverse Events
- * Dentifrice and brush collection and resupply
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)
- * Periodic/End of Study Report Form

8.2.4 9 Month Examinations (± 1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * Adverse Events
- * Dentifrice and brush collection and resupply
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)

8.2.5 12 Month Examinations (±1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * ICDAS Caries Examination
- * [REDACTED]
- * Adverse Events
- * Dentifrice and brush collection
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)
- * Periodic/End of Study Report Form

8.2.6 Follow-Up Procedures

Subjects will be followed for AE resolution, as defined in Section 7.5.8

8.3 Site / Study Termination

If the Sponsor, or the Investigator discovers conditions arising during the study that indicate that the study should be halted, it must be terminated after appropriate consultation between the study Sponsor, project manager, and Investigator. Conditions that may warrant termination include, but are not limited to:

- * The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- * Failure of the Study Investigator to enter subjects at an acceptable rate.
- * Insufficient adherence to protocol requirements.
- * A decision on the part of the sponsor to suspend or discontinue development of the study product.

9 DATA HANDLING AND RECORD KEEPING**9.1 Data Quality Assurance**

Colgate Study Monitors will conduct a site visit to verify the qualifications of the Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

An Investigator's meeting will be held to introduce the Investigators and their key personnel to the study protocol, CRFs, procedures, and regulatory requirements.

The Study Investigator is required to prepare and maintain adequate and accurate case histories, designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRFs for this study must be consistent with the subject's source documentation (i.e., medical records).

9.2 Case Report Forms (CRFs) and Source Documentation

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

In this clinical trial, visit forms, confirmation of enrollment, randomization, study group assignment, log of product dispensing, data from soft tissue and hard tissue examinations, data from caries examinations, and administration of [REDACTED] will be captured on electronic case report forms (eCRFs). Direct data entry into eCRFs will be captured and stored in Veeva Vault Clinical Suite. Paper case report forms (paper CRFs) will be used to capture all other data that will not be directly entered into the Veeva system, such as report of adverse events and documentation of product use compliance. Paper CRFs will be retained as original source documents and will be scanned and uploaded to the Veeva Vault Clinical Suite.

Veeva Vault is a cloud-based Content Management System (CMS) developed by Veeva Systems. The Vault Clinical Suite includes Vault eTMF and Vault CTMS. Vault Clinical enables increased compliance of clinical processes, inspection readiness, and permits a unified and connected view of clinical operations business functions. In addition, Veeva Vault produces secure and compliant audit trails in accordance with the FDA 21 CFR Part 11 Electronic Records, Electronic Signatures, and Eudralex Annex11: Computerized Systems regulations. All data collected from the web based EDC hosted on a private Google Cloud Platform (GCP) cloud will be verified before being sent through encoded HTTP POST requests to the Veeva Vault cloud hosted on Amazon's Web Services cloud (AWS).

A study coordinator, designated by the study center Investigator will be responsible for overseeing management principles including validated data entry at the point of data generation, data storage in one comprehensive relational database and data security.

9.3 CRF Fields as Database Entry Sources

CRFs should be considered the only source for database entry. Data should not be entered on any other form. Should an AE occur that requires clinical laboratory or electrocardiogram (ECG) data, the original printout should be attached to the Adverse Event CRF.

9.4 Direct Access to Source Data

During the course of the study, the Colgate Study Monitors will make site visits to review protocol compliance, compare CRFs and individual subject's medical records/study records, assess product accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records/study records will be performed in a manner to ensure that subject confidentiality is maintained.

Reviewing the CRFs for completeness and clarity, and cross-checking with source documents will be required to monitor the progress of the study. Moreover, regulatory authorities and/or the Sponsor's clinical quality assurance group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

9.5 Documentation of Consent, Privacy Notice and Storage of Study Documents

All informed consent/assent forms and privacy notices will be administered in either English or Spanish, whichever is most appropriate, and will be kept as source documentation. Informed Consent/Assent forms will be stored in a secure locked room designated for research charts storage in the clinical site. The Study Investigator will provide each subject's parent or legal guardian with a clear and understandable Privacy Notice (Appendix I the Sponsor's standard privacy notice) regarding the processing in connection with the study of personal data (i.e., any information relating to an identified or identifiable individual) by the Study Investigator, Sponsor and other persons involved in the study. The Study Investigator will obtain parental signature to this privacy notice. The original signed copy of the privacy notice for each subject participating in the study will be retained in the Investigator's study records. Each subject's parent or legal guardian will be given a copy of the privacy notice and the privacy notice will be referenced in and form a part of the overall study informed consent/notice process.

A baseline privacy notice is included in this protocol for that purpose. Any deviation to the privacy notice as regards processing by the Sponsor (including its vendors, monitors and other representatives) must be agreed with the Sponsor. In addition, the Study Investigator is responsible for ensuring that all study subjects' parents receive a copy of the privacy notice, and that the privacy notice includes any local requirements regarding data security and privacy laws and regulations applicable to the study and the subjects. Should the privacy notice provided by the Sponsor fail to meet any applicable local requirements, the Study Investigator is responsible for amending the privacy notice to bring it into compliance with local applicable regulations and the Study Investigator agrees to indemnify and be liable to the Sponsor for any damages resulting from such non-compliance. Subjects' study charts will be stored in a secure locked room designated for research charts storage in the clinical site. The chart room is a limited-access area and only delegated study personnel will have access to the study charts and subjects' data.

9.6 Archiving Study Records

Essential documents should be retained for a minimum of 5 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or for at least 5 years since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local regulations.

10. STATISTICAL METHODS

10.1 Study Objectives and Hypotheses

10.1.1 Primary Study Objective

The primary objective of the study is the estimation of the effectiveness of the three test products (1.5%, 4.0%, and 8.0% Arginine) each relative to the positive control (0% arginine/sodium fluoride 0.24%).

Toward this end, the following null hypothesis will be considered for each of the three test products (1.5%, 4.0%, and 8.0% Arginine) in the analysis of the data:

- H_0 : There is no difference between the anti-caries efficacy of the test product and that of a dentifrice containing 0% arginine/ sodium fluoride 0.24% (1100 ppm F).

These hypotheses will each be tested through a comparison of the mean caries DMFS increments for the respective dentifrices. The secondary efficacy endpoints, counts of clinically significant changes in ICDAS severity (progression and regression) and caries lesion activity scores between the baseline and the 6-month and one-year examinations and between the 6-month and one-year examinations will also be compared among the four dentifrices. The analysis methods are described in section 10.6.

10.2 Sample Size Considerations

The sample size determination was based on the expected half width of the 95% confidence interval for the one-year DMFS increment for each treatment group. Based on past data we expect a standard deviation of approximately 3.0. Using the normal approximation and 450 subjects per group at one year, the confidence interval half-width would be ± 0.28 . These estimates will provide data to be used in planning the next (pivotal) study.

10.3 Randomization

Separate randomization listings for each study site will be provided. Within each randomization, subjects will be assigned to each of the 8.0% arginine/0 ppm F dentifrice, 4.0% arginine/0 ppm F dentifrice, the 1.5% arginine/0ppm F dentifrice and the 0% arginine/ sodium fluoride 0.24% (1100 ppm F), in a 1:1:1:1 ratio.

10.4 Analysis Populations

Analysis populations for this study are as follows:

- Intent to Treat (ITT): The ITT population will consist of all subjects randomized and dispensed treatment.

- **Safety:** The Safety population will consist of all randomized subjects who received at least one administration of the study treatment
- **Per-Protocol (PP):** The PP population will consist of those subjects in the ITT population who completed all study examinations, and who experienced no serious protocol violations.

For the purpose of this determination, serious protocol violations:

1. Subject fails to report for examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.
4. Subject is treated with medications that may affect the parameters under investigation during the study.

All analyses performed on the ITT population will be based on treatments as randomized. Analyses performed on both the Safety and PP populations will be based on treatments actually received. Analyses performed to investigate safety will be performed on the Safety population. Analyses to investigate efficacy will be performed on both the ITT and PP populations; however, the primary efficacy analyses will be those based on the PP population.

10.5 Planned Interim Analyses

No interim analysis is planned for this study.

10.6 Final Analysis Plan

10.6.1 Procedures for Handling Missing, Unused, and Spurious Data

All analyses performed on the Safety and PP populations will be based on data as observed. For the ITT population, multiple imputation methodology will be employed to impute missing values for subjects who have missed visits, or who have dropped out of the study. Multiple imputation will be implemented using baseline subject characteristics to randomly impute each data point five times. The five complete data sets will be analyzed and then combined to incorporate both the estimated within and between data set error terms.

10.6.2 General Statistical Considerations

Data summaries for continuous variables will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

Baseline values for all parameters will be the most recent value prior to the first administration of study treatment.

10.6.3 Analyses for Efficacy

Based on the caries assessments performed on each tooth surface at each examination, subject-wise DMFS and DMFT scores will be calculated.

The primary efficacy endpoint will be the incremental subject-wise DMFS score after one year of product use.

Secondary efficacy endpoints will include:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use;
- Incremental subject-wise DMFT scores after 6-months and after one year of product use.
- Clinically significant change in ICDAS severity scores between the baseline and the six-months and one-year examinations and between the six-months and one-year. Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6. Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.

A score summary of all efficacy endpoints will be provided at each assessment time point.

The analysis of the primary endpoint (DMFS increment) will consist of the estimation of the mean and 95% confidence interval for each treatment group. This will allow the sponsor to make an informed decision on the choice of the treatment to pursue in a pivotal study.

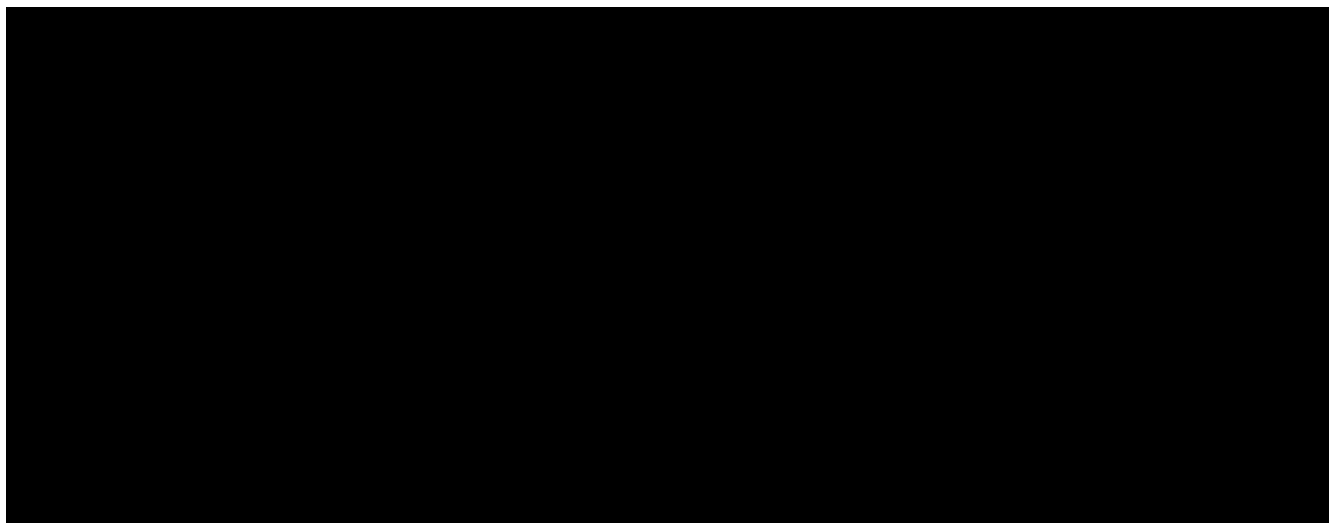
The analyses of the secondary efficacy endpoints will consist of the preparation of descriptive summaries, which will include 95% confidence intervals.

Although the study is not powered to detect differences among the treatment groups, statistical models will still be implemented for the primary and secondary efficacy endpoints. Generalized linear models (GLIM) will be used for all analyses. For analyses of DMFS and DMFT increments, we anticipate that a normal error term will be appropriate. For counts of clinically significant changes, Poisson regression will be the most appropriate GLIM with the number of teeth at risk as the offset. This model is appropriate for analysis of progression or regression although the number of teeth at risk will differ. For changes in activity scores the GLIM will be in the form of a multinomial logistic regression with four categories (0 at both times, 0 to 1, 1 to 0 and 1 at both times) that compares the distributions among the treatment groups. All statistical tests will be performed using a two-tailed 5% significance level. 95% confidence intervals for the differences between treatments will also be calculated based on the models. In addition,

the models will yield estimates of the pooled within group variance which can be used for planning further studies.

Analyses as described above will be performed on both the PP population, and the ITT population.

Listings of data will be provided for DMFS scores and for all efficacy endpoints.



10.6.5 Analyses for Safety

A summary of the hard- and soft-tissue findings will be provided, showing the incidence of findings in each treatment group.

Adverse events will be summarized by treatment group.

Data listings will be provided for all adverse event data, and for all soft- and hard-tissue findings.

10.6.6 Modifications to Statistical Methodology

Any modifications made to the analysis methodology described here will be clearly presented and explained in an amendment.

11. ETHICS, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1. Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Study Investigators abide by the principles of the GCP guidelines of the ICH. Also, the study will be carried out in accordance with local legal requirements.

The Study Investigator confirms the above by signing this study protocol.

11.2. Informed Consent/Assent

Before being enrolled in the study, informed consent will be obtained from the parent or legal guardian of each subject and assent will be obtained from the subjects according to the regulatory and legal requirements of the state to the study investigation site. The consent and assent forms must be signed and dated and retained by the Study Investigator as part of the study records.

Should a protocol addendum be made, the consent/assent forms may be revised to reflect changes in the protocol.

The Study Investigator will not undertake any investigation specifically required by the protocol until valid consent/assent has been obtained.

11.3. Approval of Study Protocol

Before the start of the study, the study protocol and/or other appropriate documents will be submitted to the IRB and/or the authorities, in accordance with local legal requirements.

The Sponsor and the Study Investigator must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study.

11.4. Amending the Protocol

This protocol is to be followed exactly. Alterations and amendments must be written, receive approval from all persons who approved the original protocol, and receive FDA and IRB approval prior to implementation. Administrative changes (not affecting the patient benefit/risk ratio) may be made by the clinical monitor without any further approvals. All amendments will be distributed to all protocol recipients with instructions to append them to the protocol.

11.5. Confidentiality

All records of subject participation in this study are confidential and these records are available only to the investigator, specifically trained site personnel, supervising dentist/examiner, potentially the Sponsoring Company, Ethics/Institutional Review Board (IRB), the Food and Drug Administration of the United States (FDA) or other local regulatory agency. The results of this study may be published in a scientific journal or a government public clinical database. If any publication occurs, only the subject's study number/ID, gender and/or age may be used. They will agree to verify, by letter, that they participated in this study, if called upon to do so.

In addition, the identity of participating subjects must be protected. Only investigators (and specifically trained clinical site staff) will collect and have access to a subject's private information (e.g., name, medical records, etc.). Investigators will assign a study number to subjects which will be used to conceal their identity on all case report forms and other documents prior to their sharing with the broader study team, including the sponsor. Documents that identify the subject by name (e.g., the signed informed consent form or health questionnaire) will not be transferred or submitted to the sponsor, and will be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate national or local authorities or to sponsor personnel to verify subject, product safety and study compliance.

Parents or legal guardians of participating subjects will be asked to review a participant privacy notice (Appendix I) and will be given a copy of the accepted and signed notice.

11.6. Advertising

No newspaper, radio, or television advertising will be used for recruitment purposes. If needed, a flyer may be created to recruit participants. If used, the flyer will be approved by an Institutional Review Board prior to posting or dissemination.

11.7. New Findings

Subjects will be informed of any significant new findings related to study products or procedures when they become known during the course of this clinical research study. Such information may affect the subject's decision to continue participation in the study.

11.8. Publication Policy

Colgate discourages any individual investigator from publishing his/her own results independently. An investigator shall not publish any data (poster, abstract, paper, etc.) without having received permission in advance from Colgate-Palmolive. The above procedure also applies to information on prematurely discontinued and other non-completed studies. Results from the investigator shall not be made available to any third party by the investigating team outside the publication procedure as set out above. Colgate-Palmolive will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

12. REFERENCES

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6. ICCMSTTM Guide for Practitioners and Educators, 2014 <https://www.iccms-web.com/uploads/asset/59284654c0a6f822230100.pdf>
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APPENDIX I

**PARENTAL/LEGAL GUARDIAN CONSENT TO PARTICIPATE
IN A CLINICAL RESEARCH STUDY
AND
AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH
INFORMATION
AND
ASSENT FORM FOR CHILD PARTICIPANTS AGES 10 TO 14**

Sponsor / Study Title: Colgate-Palmolive / “A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine in each comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.”

Protocol Number: CRO-2020-CAR-ARG-ED

**Principal Investigator:
(Study Doctor)** «PiFullName»

Telephone: «IcfPhoneNumber»

Address: «PiLocations»

Taking Part in this Study is Voluntary

Your son or daughter is invited to voluntarily participate in a one-year clinical research study.

Before agreeing to your child’s participation in this research study, it is important that you read this form. This form, called a consent form, describes the purpose, procedures, benefits, risks and discomforts expected from participation in this research study. It also describes your right to withdraw consent for your child to participate in this research study at any time. No promises or guarantees can be made as to the results of this research study. Please ask as many questions as you want in order to decide whether you want your child be in this research study. This consent form may contain words that you do not understand. Please ask the research study doctor or the research study staff to explain any words or information that you do not clearly understand.

Please review the rest of this document for more details about this study and the things you should know before making a decision about whether to allow your child to participate in this study.

Why is this Study Being Done?

The purpose of the study is to compare the effectiveness in reducing tooth cavities of a marketed (can be bought in stores) fluoride toothpaste to non-fluoride toothpastes containing arginine (a safe and essential amino acid that is naturally found in saliva and produced by the human body). The use of the study product in this study is investigational which means it has not been approved by the United States Food and Drug Administration (FDA).

How Many People Will Take Part?

If you decide to allow your son/daughter to participate, know that he/she will be one of about 2,000 (two thousand) participants in the study. The study will be conducted in many sites across the United States and Puerto Rico at the same time.

What Will Happen During the Study?

In order to be in this study your child must meet the following criteria.

1. Your son/daughter must be in the age range of 10 to 14 years and in good general health and not have any allergies.
2. The study examiner must find that the conditions of your child's teeth and gums are satisfactory for the study and meet other teeth criteria that will be considered. This includes having cavities in the past and having tooth changes that show signs of early cavities now.
3. If your child becomes pregnant, they will be withdrawn from the study and must be followed throughout the pregnancy due date.

During your child's first examination, the study doctor will look at your child's teeth and gums. If your child qualifies for the study, he/she will be assigned, using a procedure similar to pulling from a hat, to one of four study groups. You, your child or the study doctor will not know to which toothpaste your child will be assigned to use for the one (1) year duration of the study. Every three (3) months, your child will be provided with toothpaste and a new toothbrush and he/she will be expected to return the used tubes of toothpaste (no matter if full or empty). During the course of the study your child will be asked to not use any other oral hygiene products (like toothpastes or mouth rinses); however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with your child's dentist.

Your child will be examined every three (3) months for one (1) year.

Examination 1 (Screening)

You will be asked to read, sign and date this consent form and fill out some other documents about the study. Your child will be provided with an assent form providing him/her with the opportunity to choose if he/she wants to participate in the study.

The study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study doctor will also check his/her teeth to see if there are any cavities.

After this examination, it will be decided if your child can be in this study.

Examination 2 (Baseline)

This examination may take place the same day of the screening examination. A study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study doctor will also check his/her teeth to see if there are any cavities. Your child will be asked to brush his/her teeth with water before he/she sees the study doctor.

Your child will also be given a short questionnaire to share how he or she feels about his/her oral health and how they see themselves and how they feel about their mouth and face. Similar questions will be asked after six (6) months and after twelve (12) months of assigned study product use.

Your child will be given the first supply of toothpaste and a toothbrush to take home. Your child will be instructed to brush his or her teeth twice per day (morning and evening) for two minutes each time, once in the morning and once before going to bed and not to use any other toothpastes, mouth rinses or other toothbrushes.

Your child will be asked to return the tubes of toothpaste provided (empty or not) at the next scheduled examination.

If the study doctor finds a cavity you will be notified and, you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one. During this study, the investigator will not treat any abnormal issues in the mouth and will not fill cavities.

Examinations after three (3, 6, 9 and 12) months of study product use

A study doctor will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The same procedures as in the Examination 2 (Baseline) described above will be followed. After six (6) months and after twelve (12) months of assigned study product use, your child will be asked to complete the short questionnaire.

What are the Risks of Taking Part in the Study?

The risk of your child includes the possibility that the study product assigned may not prevent cavities as well as the fluoride toothpaste. Your child will not be asked to refrain from routine dental care/treatment or any emergency dental treatment throughout the course of the study. However, if your child has any dental treatment after joining this research study, you will be requested to notify the clinical site about any treatments received, frequency and any medications prescribed. There may be irritation caused by the dental examinations. Risks from the study product are expected to be the same as those for any currently marketed toothpaste. These include minor oral irritation and peeling skin in some

sensitive individuals. Some of the related/unrelated adverse events experienced by consumers worldwide using toothpastes, that contain some flavors used in this trial, in general descending order are: Mouth Irritation, Nausea / Gagging / Vomiting, Canker Sores / Mouth Ulcers / Boils, Allergic Reaction, Gastrointestinal disorder, Throat Irritation, Tooth Sensitivity, Coughing, Mouth Swelling, Oral Numbing, Skin Irritation, Oral Exfoliation, Diarrhea, Accidental Injury, Cracked / Lost Tooth / Filling, Effect on Sleep, Headache, Human Ingestion, Toothache, Vertigo / Dizziness, Dermal Cut / Scratch, Dermal Staining, Dermatological disorder, Difficult / Irregular Breathing, Dry Mouth, Effect on Taste, Mouth Bleeding, Oral Staining, Respiratory disorder, Oral disorder / Undefined, Oral Discoloration, Eye Irritation, Oral Cut / Scratch / Pinch, Dermal Numbing, Nasal Passage Irritation, Accidental Exposure, and Dermatological Misc / Undefined.

The risks associated with minor and rare irritations from dental examinations will be reduced by having trained and licensed oral care professionals conduct the oral examination, following standard clinical procedures.

There is a risk of possible loss of confidentiality while maintaining all research observations and data.

There may be risks which are currently unknown.

Any significant findings will be communicated to you and, when necessary, will include a referral to a dentist or a note to his/her dentist. We encourage you inform your child's regular dentist of his/her participation in this study. If your child experiences any problems, you should contact the study doctor at the telephone number listed on page one of this form.

Discomfort with questionnaires

Some people feel uncomfortable when answering questions about the [REDACTED]. Though it is always better to have fully completed questionnaires, your child does not need to answer any questions that make him/her feel uncomfortable.

What are the Potential Benefits of Taking Part in the Study?

It is expected that your child will receive a direct dental benefit from participation in this study. Although it cannot be guaranteed for every child, a cavity reduction benefit is expected from all toothpastes in the study. Your child's teeth and gums will be monitored by examinations every three (3) months. Any significant findings will be communicated to you and, if necessary, will include a referral to a dentist or a note to his/her dentist. Participation in this clinical study does not replace the need for your son or daughter to visit his or her dentist on a regular basis. The results of this study may help the sponsor improve the study product and help dental professionals provide proper advice to their patients.

How will your Child's Information be Protected?

Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information may be disclosed if required by law. No information which could identify your child will be shared in

publications about this study.

Organizations that may inspect and/or copy your child's research records for quality assurance and data analysis include groups such as the study doctor and his/her study staff, Advarra IRB, Colgate Palmolive, the U.S. Food and Drug Administration (FDA), and any state or federal agencies who may need to access your medical and/or research records (as allowed by law).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Will my Child's Information be used for Research in the Future?

Information collected from your child for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify your child will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

Alternatives to Participation

This research study is for research purposes only. The only alternative is to not participate in this study.

Will there be a Cost or Payment to Participate?

There is no cost to you or your child for the oral examinations and the use of toothpaste, toothbrush or any other study related product.

«Compensation»

Your child may receive an incentive for participation in the clinical study consisting of (SITE TO DETERMINE IF APPLICABLE, ETC).

Who will Pay for my Child's Treatment if he/she gets Injured?

In the event of physical injury resulting from your child's participation in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your child's health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

Whom To Contact About This Study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency

care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
Study Subject Adviser
Advarra IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046
- or call **toll free:** 877-992-4724
- or by **email:** adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00040997.

Can my Child Withdraw from the Study?

Your child's participation is voluntary, and you may refuse to participate and/or withdraw your child at any time without penalty or loss of benefits to which your child would otherwise be entitled up to the point of withdrawal. Your child's study doctor has the right to withdraw your child from the study at any time if he or she feels that it is in your child's best interest or if your child fails to comply with the terms of the study.

Your child's participation may be terminated by the study doctor without regard to your consent in circumstances when the study doctor feels it may not be beneficial to your child.

You will be told about new information that may affect your child's health, welfare, or willingness to stay in the study.

Study Sponsor

This clinical research study is sponsored by the Colgate-Palmolive Company. The Study Site will receive financial support and material for this study. The study staff and study doctor have no financial interest in the Colgate-Palmolive Company.

Informed Consent Statement

I have read the contents of the consent form and have listened to the verbal explanation given by the study staff. My questions concerning this study have been answered to my satisfaction. I hereby give voluntary consent for my child to participate in this study. Signing and dating this consent document does not waive my or my child's rights nor does it release the study doctor, study staff, institution, or sponsors from their responsibilities. I will receive a copy of this signed and dated consent document.

I voluntarily agree for my child to participate in this study. I understand that I will be given a copy of this consent form after signing and dating it.

CHILD'S NAME _____

Signature of Parent or Legal Guardian

Print Name of Parent or Legal Guardian

Date

I attest that the requirements for informed consent from the research study described in this form have been satisfied, that I have discussed the research study with the participant's parent or legal guardian and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Signature of Person Obtaining Consent

Printed Name of Person Obtaining Consent

Date: _____

SPONSOR'S PRIVACY NOTICE

In addition to the informed consent that explains the clinical study in which your child may participate in, this authorization gives you additional detailed information about how your child's health information will be protected. By signing and dating this document you are allowing Colgate Palmolive Co. to disclose personal health information to outside organizations or people involved with the processing of this study.

What personal health information is collected and used in this study and might be shared?

1. Name, address and telephone number
2. Medical history
3. Current medications
4. Procedures performed in this study such as: Oral health exams and stress related proteins

Why is your personal information being used?

So the study staff may contact you during the study. Your child's health information is used to ensure your child's safety while selecting participants for the study. Results and data are collected for the advancement of medicine, dentistry and clinical care.

Which of our personnel may use or disclose your child's personal health information?

The following individuals and organizations may use or disclose your child's personal health information for this research study:

1. The study doctor and associated study staff
2. The Institutional Review Board
3. Safety and Regulatory departments at Colgate Palmolive Co.
4. Authorized members of the clinical site who may need your information in the performance of their duties associated with this research (for example, to provide treatment, ensure integrity of the research, accounting, scheduling etc.)

Who outside Colgate Palmolive Co. or the study doctor might receive your child's personal health information?

1. Institutional Review Board

-
2. Food and Drug Administration (your child will be identified only by his/her first name and last initial)

How long will Colgate or the Clinical Site be able to use or disclose your child's personal health information?

Your authorization for this specific study does not expire however the information may not be re-used or re-disclosed for another purpose other than the research described in this document unless you give written permission to do so. In California and any other state that requires an expiration date, the Authorization will expire in 50 years after you sign and date this authorization document. The Institutional Review Board may grant permission to the study doctor or others to use your child's information for another purpose after ensuring that appropriate privacy safeguards are in place. The Institutional Review Board is a committee whose job it is to protect the safety and privacy of research participants. Results of tests and procedures are done solely for this research study and will not be included in your child's dental record.

Will you be able to access your child's records?

You will be able to access your child's dental record when the study is completed. During the study you will not have access to prevent knowledge of study results from affecting the reliability of the study. Should an emergency or need for care arise that would require your child's treating physician or dentist to know this information the records would be provided.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your child's personal information for research but you must do so in writing to the study doctor at the address provided on the first page in your parental informed consent. Even if you withdraw your permission, the study doctor may still use your child's personal information that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission to use your child's personal health information that means your child will also be withdrawn from the research study.

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STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. By signing and dating this document I am permitting Colgate Palmolive Co or the Study Site to use and disclose personal health information collected about my child for research purposes as described above. I will receive a signed and dated copy of this form. I am not giving up any of my legal rights by signing and dating this form.

CHILD'S NAME _____

Signature of Parent or Legal Guardian

Print Name of Parent or Legal

Date

Signature of Person Obtaining
Authorization

Printed Name of Person Obtaining
Authorization

Date: _____

ASSENT FORM

FOR CHILD PARTICIPANTS AGES 10 TO 14 YEARS

Sponsor / Study Title: Colgate-Palmolive / “A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine in each comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.”

Protocol Number: CRO-2020-CAR-ARG-ED

Principal Investigator: «PiFullName»
(Study Doctor)

Telephone: «IcfPhoneNumber»

Address: «PiLocations»

You are being asked to join in a research study that you will learn more about below:

WHAT IS THIS STUDY ABOUT?

We would like to find out if new toothpastes can stop cavities as well as regular toothpaste. If you qualify for the study and you agree to be in the study, you will be put into one of four (4) study groups. The toothpaste you will be given will be chosen like pulling from a hat. You will not know what toothpaste you are given to use. The study will last one (1) year, you will be asked to brush your teeth with the toothpaste given to you twice a day and not use any other toothpastes or mouth rinses. You should keep seeing your regular dentist.

WHAT WILL HAPPEN TO ME IN THIS STUDY?

If you choose to be in this study, your mouth will be checked by the study doctor six (6) times in the one (1) year-long study. Here is what will happen at each checkup:

First Checkup (Screening)

You will be asked to read, sign and date this form and also fill out some paperwork about the study. Your parents will also need to sign and date paperwork.

A study doctor will look at your lips, cheeks, tongue and all other places inside of your mouth. The study doctor will also check your teeth to see if you have any cavities.

After this checkup, the study doctor will decide if you can be in this study.

Second Checkup (Baseline)

This second checkup may happen the same day as the first one. You may be asked to brush your teeth with water before you have the second checkup. If the study doctor wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

If the study doctor decides that you will be in the study, you will be given a toothbrush and toothpaste. You will be asked to brush your teeth for two (2) minutes, two (2) times a day, once in the morning and once before going to bed. You will be asked not to use any other toothpastes or mouth rinses.

You will be asked to give the toothpaste back (empty or not) at your next scheduled checkup.

If the study doctor finds a cavity, they will let your parent know. You will also be asked to answer some questions about how you feel about your mouth and face.

Third(3rd), Fourth(4th), Fifth(5th), Sixth (6th) Checkups

You will have more checkups every three (3) months after you start brushing with the toothpaste and the toothbrush that you will be given. During these checkups, the study doctor will look at your lips, cheeks, tongue and all other areas inside of your mouth. The study doctor will check your teeth to see if you have any cavities. Sometimes you may be asked to brush your teeth with water before you see the study doctor. If the study doctor wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

You will be asked to return the tubes of toothpaste provided (empty or not) at your next scheduled checkup.

If the study doctor finds a cavity, they will let your parent know. You will also be asked to answer some questions about how you feel about your mouth and face.

CAN ANYTHING BAD HAPPEN TO ME IN THIS STUDY?

We will try to be as careful as we can during the checkups, but there is a chance that something could happen like getting a sore spot in your mouth. There is also a chance that the study toothpaste given to you may not stop cavities as well as regular toothpaste. Some of the bad things that may happen from the study toothpaste are the same as those for any toothpaste you can buy in the store, such as your mouth may get sore and your stomach may feel sick. These include minor oral irritation and peeling skin in some sensitive individuals. We encourage you inform your parent/legal guardian or regular dentist of your participation in this study. Some other things that have happened to events experienced by people worldwide using toothpastes, that contain some flavors used in this study are: Mouth Irritation, Nausea / Gagging / Vomiting, Mouth Sores, Allergic Reaction, Stomach Ache, Sore Throat, Sensitive Teeth, Coughing, Mouth Swelling and Numbing, Skin Irritation, Diarrhea, Toothache, Effect on Sleep, Headache, Swallowing of Toothpaste, Dizziness, Skin Cut / Scratch, Skin Staining, Trouble Breathing, Dry Mouth, Change in Taste, Mouth Bleeding and Staining, Eye Irritation, Oral Cut / Scratch / Pinch, Skin Numbing, and Nose Irritation. Your gums may be sore from using the toothpaste and there may be a small chance of you getting a cavity. Also there is a small chance that other people might see your study papers. There may be other things that can happen in this study that is in your parent's paperwork that they may want to talk to you about. Things may happen that we

don't know about yet. If they do, we will make sure that you get help with anything that might happen. You can tell your regular dentist that you are in this study.

Discomfort with questions you will be asked

You will be asked to answer a lot of questions. You may not like every question that is asked. It is always best to answer every question but you do not need to answer any questions if you don't want to.

WHAT IS GOOD ABOUT BEING IN THIS STUDY?

You may have less cavities from using the toothpaste given to you. Your mouth and teeth will be checked every three (3) months. You and your parent will be told if you have any problems in your mouth and you may be asked to see your dentist. The results of this study may help the company paying for the study to improve their toothpastes and help dentists give good advice to their patients.

WHAT DO I HAVE TO TELL THE STUDY DOCTOR ABOUT?

If you choose to join this study, you and your parent may be asked about your health and medicines that you may be taking. We ask that you answer any questions the best you can.

If you become pregnant, you will be asked to tell the study doctor. You will be taken out of the study and you will be followed until the end of the pregnancy. You will be asked to stop using the study toothpaste.

You also need to tell your parents or legal guardian and the study doctor if you do not feel well after your checkups.

DO I HAVE TO BE IN THIS STUDY?

You do not have to be in this research study if you do not want to. You can say "yes" or you can say "no". You can stop being in the study later if you change your mind. No one will be angry with you if you say "no". Your regular doctor and dentist will still take care of you.

WHO CAN I TALK TO ABOUT THE STUDY?

You can ask questions about the study at any time. If you feel sick, you or your mom or dad can call the study doctor.

STATEMENT OF ASSENT

DO YOU WANT TO PARTICIPATE?

☐

Yes, I will be in this study.

☐

No, I do not want to do this.

If you have any questions about the study, you may ask the study staff at any time. Your parent/legal guardian will be given a copy of the consent letter that has telephone numbers of

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people to call when you have questions. If you want to be in this study, read the next paragraph and sign and date in the space below.

I agree to participate in this research study. I may decide to stop at any time without hurting my chances of being in future dental studies.

Child's Name (Please Print)

Child's Signature

Date

Signature of Study Personnel Obtaining Assent

Date

Printed Name of Study Personnel Obtaining Assent

APPENDIX II

FORMULATIONS

CONTROL DENTIFRICE

This product is a commercially-available dentifrice of the Colgate-Palmolive Company under the commercial name Colgate Ultra Brite Anti-cavity Fluoride Toothpaste which is in compliance with the OTC Anti-caries Drug Monograph. It contains 0.24% sodium fluoride (1100 ppm F) in a silica base.

TEST DENTIFRICE 1

[1.5% Arginine in a calcium base]

This is a dentifrice containing 1.5% arginine in a calcium base.

TEST DENTIFRICE 2

[4.0% Arginine in a calcium base]

This is a dentifrice containing 4.0% arginine in a calcium base.

TEST DENTIFRICE 3

[8.0% Arginine in a calcium base]

This is a dentifrice containing 8.0% arginine in a calcium base.

APPENDIX III**PRODUCT LABEL INFORMATION**

Caution: New Drug - Limited by Federal (or United States) law to investigational use. Not for sale.

Protocol Number: CRO-2020-CAR-ARG-ED

Product Code _____ Subject # _____

Brush your teeth twice daily (morning and evening) for two minutes each time. Apply a full ribbon of toothpaste on the toothbrush head. Use only the toothpaste and toothbrush provided.

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study

For study-related questions call:

Dr. _____ at phone number (____) ____-____.

In case of emergency call:

Dr. _____ at phone number (____) ____-____.

APPENDIX IV**PRODUCT USE INSTRUCTIONS****Important Product Information**

Colgate Palmolive Sponsored Clinical Study (Protocol Number: *CRO-2020-CAR-ARG-ED*)

Caution:

For Investigational Use Only. Not for sale.

- **Brush your teeth twice daily in the morning and in the evening before bed.**
- **Brush for two minutes each time. Use the timer as aid.**
- **Apply a full ribbon of toothpaste on the toothbrush head just like it was demonstrated at the beginning of the study.**
- **Use only the toothpaste and toothbrush provided.**
- **The study products are only for your use.**

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study.

For study-related questions call:

Dr. _____ at phone number (____) ____-____.

In case of emergency call:

Dr. _____ at phone number (____) ____-____.

APPENDIX V**INITIAL SCREENING FORM****SUBJECT NUMBER** _____ **SUBJECT'S INITIALS** _____ **DATE** _____

The following questions will be answered based upon Investigator/Examiner/Study Personnel discretion:

1. Has the parental/ legal guardian provided informed consent for voluntary participation of the subject and has the subject provided written assent?	Yes	No
2. Is the subject in good general health?	Yes	No
3. Is the subject willing and able to use the assigned products according to instructions, available for all appointments and likely to complete the study?	Yes	No

If any answer to any questions 1-3 is 'NO', subject is ineligible for study. Dismiss subject and complete question 13 below. If subject is eligible continue to questions 4-13.

4. Is the subject undergoing orthodontic treatment, wears intraoral appliance?	Yes	No
5. Does the subject use medications that could increase the risk of developing soft tissue irritations?	Yes	No
6. Is the subject taking long-term antibiotic therapy or have a condition which would require an antibiotic prior to a dental procedure?	Yes	No
7. Does the subject have cognitive and/or motor impairment?	Yes	No
8. Does the subject have severe malocclusion?	Yes	No
9. Does the subject appear to have evidence of moderate to severe periodontal disease?	Yes	No
10. Is the subject participating in any other clinical study within 30 days preceding the start of the clinical study?	Yes	No
11. Does the subject have a history of allergies or other adverse reactions to arginine or oral care products, or their ingredients?	Yes	No
12. Is the subject pregnant and/or currently breastfeeding?	Yes	No N/A
13. IS THE SUBJECT ELIGIBLE FOR ENTRY INTO STUDY?	Yes	No

Please note any additional observations (if applicable)

Text

Signature, Examiner_____
Date

APPENDIX VI**CONTINUATION FORM (REVIEW ELIGIBILITY CRITERIA)****SUBJECT NUMBER** _____ **SUBJECT'S INITIALS** _____ **DATE** _____

The following questions will be answered based upon Investigator/Examiner/Study Personnel discretion:

1. Does the parental/ legal guardian <u>still</u> consent for voluntary participation of the subject and does the subject <u>still</u> assent to participate?	Yes	No
2. Is the subject in good general health?	Yes	No
3. Is the subject still willing and able to use the assigned products according to instructions, available for all appointments and likely to complete the study?	Yes	No

If any answer to any questions 1-3 is 'NO', subject is ineligible for study. Dismiss subject and complete question 13 below. If subject is eligible continue to questions 4-13.

4. Has the subject undergone orthodontic treatment, or currently wears an intraoral appliance?	Yes	No
5. Does the subject use any new medications that could increase the risk of developing soft tissue irritations?	Yes	No
6. Is the subject currently taking long-term antibiotic therapy or have a condition which would require an antibiotic prior to a dental procedure?	Yes	No
7. Does the subject have cognitive and/or motor impairment?	Yes	No
8. Does the subject have severe malocclusion?	Yes	No
9. Does the subject appear to have evidence of moderate to severe periodontal disease?	Yes	No
10. Has the subject participated in any other clinical study since enrollment?	Yes	No
11. Does the subject have a history of allergies or other adverse reactions to arginine or oral care products, or their ingredients?	Yes	No
12. Is the subject pregnant and/or currently breastfeeding?	Yes	No N/A
13. IS THE SUBJECT ELIGIBLE TO CONTINUE WITH THE STUDY?	Yes	No

Please note any additional observations (if applicable)

Text

Signature, Examiner_____
Date

Colgate-Palmolive
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APPENDIX VII

HEALTH QUESTIONNAIRE

Name: _____ today's date: (mm/dd/yyyy) _____

Date of Birth: (mm/dd/yyyy) _____

Name of Physician: _____ Phone#: _____

Date of last visit: (mm/dd/yyyy) _____

Phone #: _____ Home ☐ Cell ☐

Email: _____

Home Address: _____

Race: Check as many as applies

- ☐ White
 ☐ Native Hawaiian or Other Pacific Islander
 ☐ Black or African American
☐ American Indian or Alaska Native
 ☐ Asian
 ☐ Other, Specify _____
☐ Prefer not to answer

Ethnicity: Please select one

- ☐ Hispanic or Latino
 ☐ Not Hispanic or Latino
 ☐ Unknown
 ☐ Prefer not to answer

Are we allowed to contact you? Phone ☐ Cell ☐ email ☐

[] By checking this box YOU are providing consent to be contacted by the clinical site

Emergency contact Name: _____ Phone#: _____

Your current physical health is: ___ Good ___ Fair ___ Poor

Have you ever had any serious operations? [] Yes [] No

If yes, please explain: _____

Are you currently under the care of a physician? [] Yes [] No

If yes, please explain: _____

Please check if you have been treated for or told that you have:

☐ Abnormal bleeding	☐ Anemia
☐ Hemophilia	☐ AIDS
☐ Blood transfusion	☐ Arthritis
☐ Ulcers/Colitis	☐ Glaucoma
☐ Heart problems	☐ Drug addiction
☐ Epilepsy/Seizures	☐ Skin problems
☐ Asthma or Hay fever	☐ Blood Disorders
☐ Chemo/Radiation therapy	☐ Cancer/Tumor
☐ Diabetes/abnormal blood sugar	☐ Kidney/Liver disease
☐ Difficulty breathing	☐ Hepatitis /Jaundice

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☐ Lung problems

☐ Emphysema

☐ High/Low blood pressure

☐ Rheumatic fever

Please describe any of the above conditions:

Do you have a history of allergies to whitening oral care products, personal care consumer products, or their ingredients?

If yes, please fill explain: _____

Do you take any medications? If yes, please fill out following:

List any prescription or over the counter medications which you are taking:

Name of Medication	Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy)	Amount taken	How often	Reason

DENTAL HISTORY

Name of your dentist: _____ Phone#: _____

How often do you visit your Dentist? _____

Date of last visit: (mm/dd/yyyy) _____

WOMEN ONLY

Please answer the following:

Are you pregnant? ☐ Yes ☐ No

If yes, list due date (mm/dd/yyyy) _____;

Are you currently nursing or breastfeeding? ☐ Yes ☐ No

I understand that the information that I have given today is correct to the best of my knowledge. I also understand that this information will be held in the strictest of confidence, and it is my responsibility to inform this office of any changes in my medical status. I understand that my participation on this study is voluntary and that I can drop from the study at any time.

Signature

Date (mm/dd/yyyy)

Colgate-Palmolive
Protocol Number: CRO-2020-CAR-ARG-ED

APPENDIX VIII

ORAL SOFT TISSUE ASSESSMENT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

<u>AREA</u>	<u>NORMAL</u>
1. Lips	YES _____ NO _____
2. Soft Palate	YES _____ NO _____
3. Hard Palate	YES _____ NO _____
4. Gingival Mucosa	YES _____ NO _____
5. Buccal Mucosa	YES _____ NO _____
6. Mucogingival Folds	YES _____ NO _____
7. Tongue	YES _____ NO _____
8. Sublingual and Submandibular areas	YES _____ NO _____
9. Salivary glands	YES _____ NO _____
10. Tonsillar and Pharyngeal areas	YES _____ NO _____

If answer to any of questions 1-10 is "NO", please explain or add a comment:

Signature, Examiner

Date

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APPENDIX IX

ORAL HARD TISSUE ASSESSMENT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

	Absent	Present	If Present, please specify findings
Enamel Irregularities	☐	☐	
Tooth Fracture	☐	☐	
Pathologic Tooth Wear	☐	☐	
Cavitated Lesion	☐	☐	
Active Non-Cavitated Lesion	☐	☐	
Residual Root	☐	☐	
Faulty Restoration	☐	☐	
Implant	☐	☐	

Signature, Examiner

Date

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APPENDIX X

UPDATED HEALTH QUESTIONNAIRE VISIT FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

1. Were there any unexpected or serious reactions since the previous examination? YES NO

If yes, describe _____

2. Was any treatment prescribed for above? YES NO

If yes, describe _____

3. Was any dental treatment received since previous examination? YES NO

If yes, describe _____

4. Was any new medication (including OTC products) prescribed for subject since previous examination? YES NO

If yes, describe dose, duration and reason _____

Name of Medication	Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy)	Amount taken	How often	Reason

5. Do any of the responses to Questions 1-4 warrant exclusion of this subject's data from the statistical analysis? YES NO

If yes, explain _____

Signature, Examiner

Date

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Protocol Number: CRO-2020-CAR-ARG-ED

APPENDIX XI

CARIES EXAMINATION FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

UPPER TEETH																					
	2			3			4			5			6			7			8		
TOOTH	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
B																					
L																					

	9			10			11			12			13			14			15		
TOOTH	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
B																					
L																					

LOWER TEETH																					
	18			19			20			21			22			23			24		
TOOTH	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
B																					
L																					

	25			26			27			28			29			30			31		
TOOTH	PROFILE			PROFILE			PROFILE			PROFILE			PROFILE			PROFILE					
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
B																					
L																					

Calculations				
ICDAS Mean:				
DT	MT	FT	DMF-T	Total T
DS	MS	FS	DMF-S	Total S

Signature, Examiner _____

Date _____

Classification of the Tooth Profile, Surface Condition and Lesion Activity status in the ICDAS

Tooth Profile	
1	When a permanent or temporary filling is present, missing or defective
7	Not counted, unerupted teeth, congenitally missing or supernumerary teeth, teeth removed for reasons other than dental caries, and primary teeth retained in the permanent dentition
8	Trauma; poor prognosis (Not Counted)
9	When a tooth has been extracted due to caries

Surface Condition	
0	No filling, No sealant
1	Sealant (partial or complete)
2	Filling: when a permanent or temporary filling is present, missing or defective (e.g. composite, amalgam, crown, etc.)
3	Restoration: restored due to other reasons (e.g. cervical lesions, residual composite due to ortho or aligners, diastema closure, etc.)

Caries Lesion Activity Assessment (ICCMS Guide):**Code 0 Signs of Inactive Lesions**

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located at some distance from the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing.

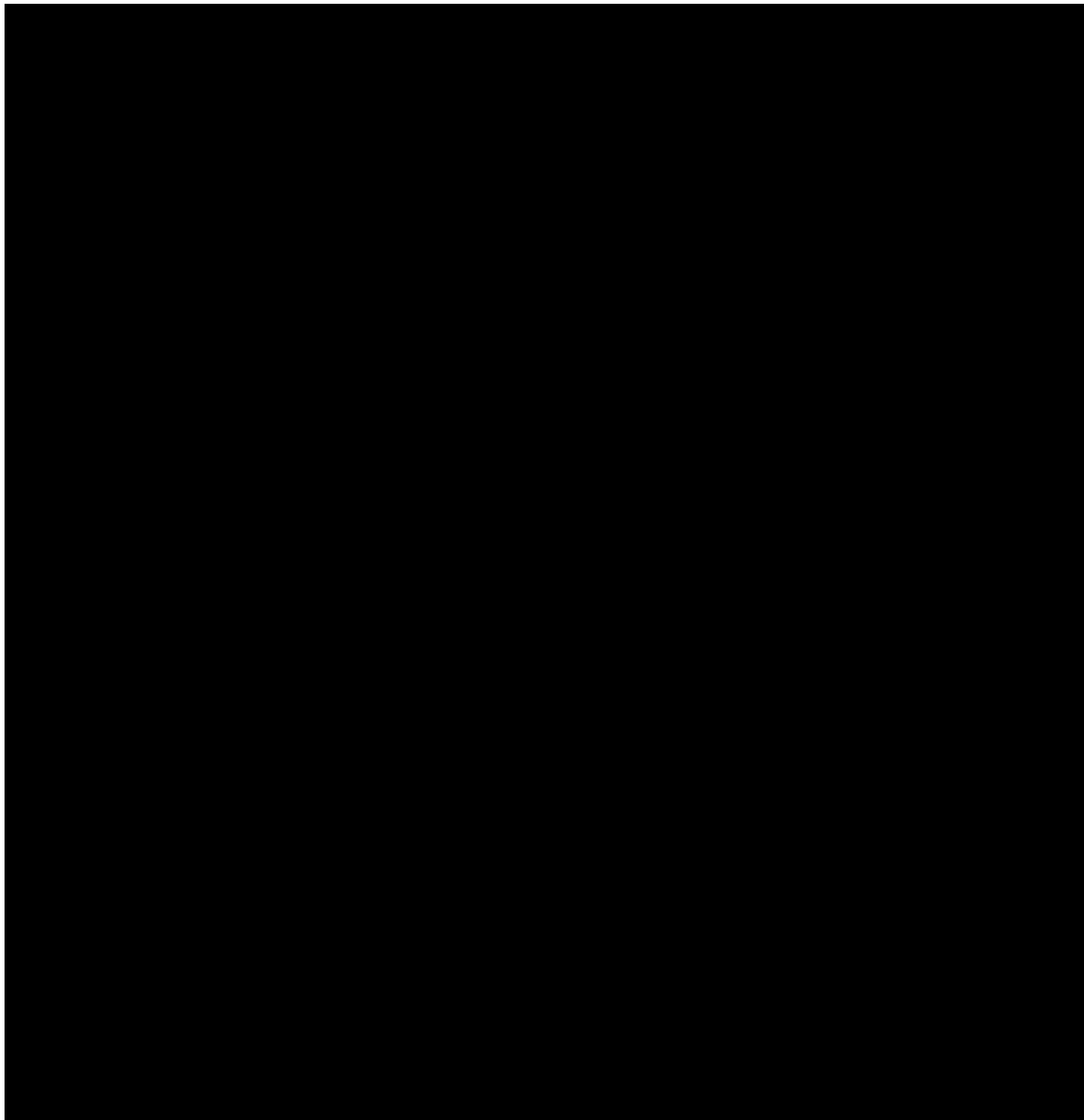
Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.

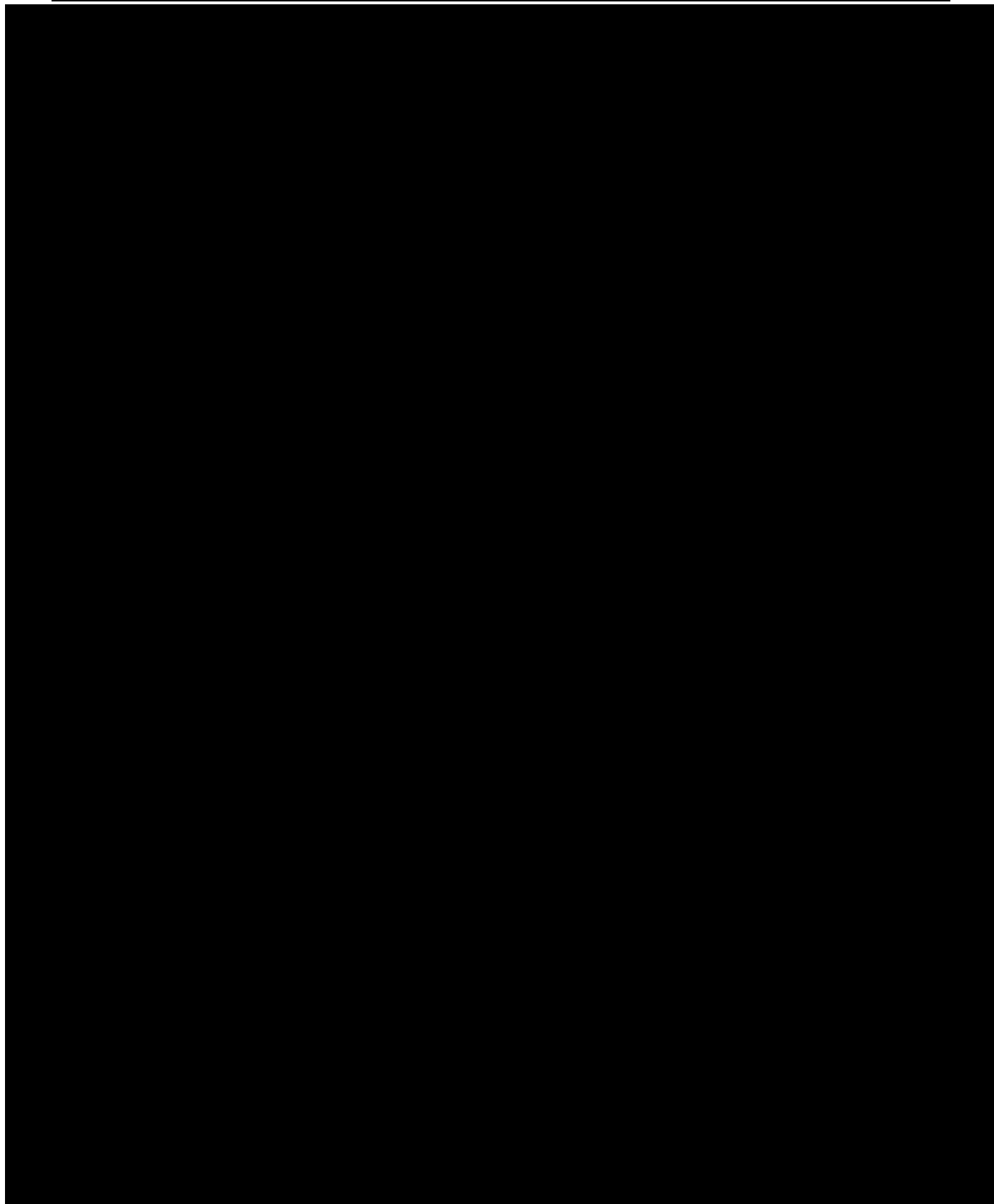
Colgate-Palmolive

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Colgate-Palmolive

Protocol Number: *CRO-2020-CAR-ARG-ED*



APPENDIX XIV**REPORT OF ADVERSE EVENT****General Instructions:**

- Do **NOT** leave any field blank. – If information is not known or is not available complete a field with Unknown or Not Available (N/A).
- The completed form should be sent within 1 Calendar day (no later than 1 business day) of awareness –
 - By the Investigator to the Study Originator
 - By the Study Originator to:

1) Global Pharmacovigilance (GPV) at globalpcv@colpal.com &

2) Safety Clearance Review Process (SCRCP) at SCRCP@colpal.com

Supplemental Guidance for filling the tables:

1. **Awareness Date-** Colgate-Palmolive –
Write the date / Select the date from dropdown list when Colgate-Palmolive has first received the report.
2. **Awareness Date- Investigator-**
Write the date / Select the date from dropdown list when investigator or their delegate has first received the report

Note: For reporting follow up information, give the dates on which Colgate-Palmolive and Investigator or their delegate became aware of follow up information.

TABLE No. 1, 2, 3, 4 and 5**1) Study Information –**

- **State Protocol #** - State the protocol # as given on cover page of protocol
- **Study title** - State title of the study as given on cover page of protocol
- **Indication/Objective of Protocol** - Provide objective of the protocol
- **Type of study** - Tick the appropriate box(s) to indicate if study type is clinical, consumer, panel or combination
- **Study Originator/Monitor** – Mention the study Originator/Monitor's name and Contact number
- **Centre Name** - Complete the Centre details such as name and investigator details
(E.g. name, contact details, occupation, etc.)

2) Subject Information -

- **Section A)** Provide demographic details of subject.
- **Section B)** Complete section **only** if subject is pregnant female.

3) Reporter Information –

- This section to be filled **only if Reporter is different from Investigator** named in section 1) Study Information
- **Sender/Reporter Name:** If investigator is reporter mention – “Same as given in Section 1”.
If reporter is different than Investigator, mention name and fill rest of the reporter information (Address, country, email, telephone, etc.)
- **Healthcare Professional/non-Healthcare Professional** - Tick the applicable box whether the reporter is a Health Care Professional or not. If Healthcare Professional, specify occupation (Physician, Dentist, Dental Surgeon, Pharmacist, Nurse, Hygienist...).

4) Phase of study the earliest event (s) occurred during–

Mark the appropriate box to specify the phase in which the earliest event occurred (E.g. After consent, wash-out, pre-randomization, randomization, etc.)

5) Study products -

- **Product Name** - Provide information of all products relevant to the study which the subject received (including washout products, test product, blinded, placebo, comparator, etc.).

- **Lot No/Batch No/Serial No (If MOCD)** – Write the batch number that is printed on the pack or outer packaging of product. Serial number is applicable for Mechanical Oral Cleaning Devices (MOCD) like Toothbrushes or Dental Floss.
- **Route of administration** – Provide how the product is used. E.g. oral, topical application
- **Dosage & Frequency** – Provide amount of product used and the frequency of usage.
Dosage examples: pea size, cap full, 10 ml, etc.
Frequency examples: daily, 2 times/day, weekly, at bedtime, etc.
- **Start Date (DD-MMM-YY)** – The date when the subject has started using the study product. Partial dates are accepted (MMM-YY)
- **Stop Date (DD-MMM-YY)** – The date when the subject has stopped using the study product.
- **Action taken with Product** – Select the appropriate action taken after subject experienced the adverse event from the dropdown list. Action could be anyone of these:
 - Withdrawn permanently - Discontinued
 - Withdrawn temporarily - Stopped for some time
 - Dosage decreased - The amount of product used is decreased
 - Dosage increased - Increase in amount of product taken during usage.
 - No Action Taken – Continued as before
 - Unknown - No info provided
- **Death** – In case of death of subject, mention the date and cause of death (if known)
- **Autopsy** – Tick mark to specify if autopsy was done or status is unknown. State the outcome of the autopsy if done.

TABLE No. 6, 7 and 8

- 5) **Adverse Event (AE)/Reaction Information** – Provide the information related with the adverse events reported.

For non-serious events leave the field blank

- **Seriousness Criteria:** Choose or write any of the below mentioned seriousness criteria for the reported event
 - Death
 - Life-Threatening
 - Hospitalization/Prolongation of hospitalization
 - Persistent or significant disability/incapacity
 - Congenital Anomaly/Birth defect
 - Medically Significant – If AE is mentioned as medically significant by HCP.
 - Suspected transmission - Suspected transmission **via a medicinal product** of an infectious agent
 - Any malfunction or deterioration in the characteristics and/or performance of a medical device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to any of the other seriousness criteria here above.
 - Temporary functional incapacity for Cosmetics (only applicable to studies conducted in EU)
- **Causality** - Tick the most appropriate box based on investigator's assessment.
 - Definite – Adverse event/reaction is incontrovertibly related to study product.
 - Probable - Adverse event/reaction is considered related to study product with a high degree of certainty.
 - Possible – A connection to the study product appears unlikely, but cannot be ruled out with certainty.
 - Unlikely - Adverse event/reaction is considered unrelated to study product.
 - Not related - Adverse event/reaction is clearly and uncontrovertibly due to causes other than the study product.

-
- **Severity** – Tick the most appropriate box.
 - **Outcome** – Select the outcome of the adverse event from the dropdown list.
 - Fatal - The event resulted in death of subject.
 - Recovered - If AE is resolved.
 - Recovered with Sequelae - The AE has resolved, but subject still experiences effects of the event (e.g. subject suffered a stroke and continues to have right arm weakness).
 - Recovering - when the AE is resolving slowly
 - Continuing/ Ongoing -- If event is still present at the time of reporting.
 - Unknown – No information was provided
 - **Death** – In case of death of subject, mention the date and cause of death (if known)
 - **Autopsy** – Tick mark to specify if autopsy was done or status is unknown. State the outcome of the autopsy if known..
 - **Describe event (s)/reactions(s) in detail:** Provide the description of events in sequence as occurred. Including treatment received.
 - **Protocol status of subject** – Tick the appropriate box to specify if subject is continued/discontinued in the study.
 - **Was the subject treated for the event(s)/reaction(s) (Medical Intervention)?** Tick as yes or no depending on if the subject was treated for the adverse event experienced. If yes, specify the treatment given.
 - **Event/Reaction abated after study product(s) stopped or dose reduced?** Provide information as Yes, No or N.A. if the event/reaction subsided on stopping or reducing the dose.
 - **Event/Reaction reappeared after study product(s) reintroduced?** Provide information as Yes, No or N.A. if the event/reaction reappeared on reintroducing the dose.
 - 7) **Subject Medical History** – Include information on any past medical illness, condition, or surgeries. If there is no past medical history select the “None” checkbox. If no medical history was provided select the “Unknown” checkbox.
 - 8) **Other Medications/ Products used simultaneously** -Provide information of all other medications or products the subject used or was exposed to during or prior to the onset of AE.
 - 9) **Laboratory data & other test procedure(s) relevant to the AE(s)** - Include information on laboratory data and other test procedures those are relevant to the AE(s).

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Instructions: Refer to the General Instructions & Supplemental Guidance pages for specific details on completing sections of the form. Additional pages may be added, if necessary, to report all information.

Awareness date – Colgate-Palmolive:		Awareness Date- Investigator:	
1) Study Information			
Protocol #:		Centre Name:	
Study Title:		Investigator:	
Indication /Objective of Protocol:		Address:	
Study Type: ☐ Clinical Trial (Interventional) ☐ Consumer ☐ Panel ☐ Other Clinical ☐ Other Specify		Tel.: Fax:	
Study Originator/Monitor:		Email:	
Contact #		Health Care Professional : ☐ Yes ☐ No Specify occupation:	

2) Subject Information				
A)	Subject's ID #:	Gender ☐ Male ☐ Female	Age/(Age Group): _____	Weight _____
	Initials:		Or Date of Birth: _____ - _____	☐ LB ☐ KG
B)	If subject is pregnant, how many months?			

3) Reporter Information (Complete only if different from Investigator named above)	
Sender/Reporter Name:	
Address	Country:
Email:	Telephone: _____ Fax: _____
☐ Healthcare Professional Specify occupation:	☐ Non-Healthcare Professional

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4) Phase of study the earliest event (s) occurred during:

- ☐ After consent ☐ Wash-out ☐ Pre-randomization ☐ Randomization: no product
☐ Randomization: product exposure ☐ Other:

5) Study products (Please indicate if Test product, Blinded Product, Comparator (control product) or Placebo was used by subject)

Product Name	Lot No/ Batch No/ Serial No (If MOCD)	Route of administ ration	Dosage & Frequenc y	Start Date (DD- MMM- YYYY)	Stop Date (DD- MMM- YYYY)	<u>Action taken with Product</u>
				- -	- -	
				- -	- -	
				- -	- -	
				- -	- -	

6) Adverse Event/Reaction Information

Adverse Events (AEs)	Start Date of AEs (DD-MMM- YYYY)	Stop Date of AEs (DD-MMM- YYYY)	Seriousness Criteria	<u>Causality</u>	<u>Severity</u>	<u>Out come</u>
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related	☐ Mild ☐ Moderate ☐ Severe	
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related	☐ Mild ☐ Moderate ☐ Severe	
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible	☐ Mild ☐ Moderate ☐ Severe	

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6) Adverse Event/Reaction Information						
Adverse Events (AEs)	Start Date of AEs (DD-MMM-YYYY)	Stop Date of AEs (DD-MMM-YYYY)	Seriousness Criteria	Causality	Severity	Outcome
				☐ Unlikely ☐ Not Related		
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related	☐ Mild ☐ Moderate ☐ Severe	
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related	☐ Mild ☐ Moderate ☐ Severe	
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related	☐ Mild ☐ Moderate ☐ Severe	
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related	☐ Mild ☐ Moderate ☐ Severe	
	- -	- -	Choose an item.	☐ Definite ☐ Probable ☐ Possible ☐ Unlikely ☐ Not Related	☐ Mild ☐ Moderate ☐ Severe	

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8) Other Medications/ Products used simultaneously: ☐ None ☐ Unknown					
Other Medications/ Products	Start Date (DD-MMM-YYYY)	Stop Date (DD-MMM-YYYY)	Indication	Dosage & Frequency	Route of administration
	- -	- -			
	- -	- -			
	- -	- -			
	- -	- -			
	- -	- -			
	- -	- -			
	- -	- -			

9) Laboratory data & other test procedure(s) relevant to the AE/AER(s)		
Test	Date (dd/mm/yyyy)	Result (Specific value, normal, abnormal, clinically)

Investigator/Designee Signature:	Date (dd/mm/yyyy):

APPENDIX XV
PERIODIC/END OF STUDY REPORT FORM

Instructions:

- For Periodic reporting (study lasting >1 month):
 - Complete monthly with all *serious and non-serious adverse reactions* reported.
 - Submit monthly to Study Originator if form is completed by an individual other than the Study Originator/Manager.
 - Study Originator submits form monthly to globalpcv@colpal.com and scrp@colpal.com
- For End of Study reporting:
 - Complete upon study completion with all *serious and non-serious adverse events (AE) and adverse reactions (AR)* reported. If no AE/AR is reported, form must be completed indicating such information.
 - Submit within 2 weeks of study completion to Study Originator if form is completed by an individual other than the Study Originator.
 - Study Originator submits form within 2 weeks of receipt or study completion to globalpcv@colpal.com and scrp@colpal.com
- All dates must be in dd/MMM/yyyy format (e.g. 01Dec1980).
- All fields in **Section A** must be completed. If information is unknown, please record “Unknown” in field. If field is not applicable, please record “N/A”.
- **Section C Guidance:**
 - If a subject experienced multiple adverse events or reactions, record only 1 event/reaction per row in table.
 - Causality: This is an assessment of the relationship between study product use and the adverse event/reaction experienced. Based on assessment, note in field one of the following:
 - Definite – Adverse event/reaction is incontrovertibly related to study product.
 - Probable - Adverse event/reaction is considered related to study product with a high degree of certainty.
 - Possible – A connection to the study product appears unlikely, but cannot be ruled out with certainty.
 - Unlikely - Adverse event/reaction is considered unrelated to study product.
 - Not related - Adverse event/reaction is clearly and uncontrovertibly due to causes other than the study product.
 - Severity: This is the investigator’s assessment of the adverse event/reaction intensity. Note in field either “mild”, “moderate”, or “severe”.
 - Serious: Note “Yes” if adverse event/reaction resulted in hospitalization/hospitalization was prolonged, temporary/permanent disability, congenital anomaly, was life threatening, fatal or medically significant. Note “No” if none of the prior criteria is met.
 - Other Products Used: Note any products used concomitantly with the study product (e.g. medications, other personal care products, etc.).
 - Outcome with Date: Note either “Resolving”, “Resolved”, “Resolved w/Sequelae”, “Not Resolved”, “Fatal”, or “Unknown”. Provide date if adverse event/reaction is resolved or fatal.
 - Comments: Please note any additional relevant clinical information (e.g. medical history, diagnostic tests, treatment received due to event/reaction, etc.).

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Section A: Study Information

Study Title:	Study Type: Clinical ☐ Consumer ☐ Panel ☐ Other ☐ Specify if selecting Other:
Protocol #:	Ref #:
Indication/Objective of Protocol:	
Primary Study Product/PDM#:	
Study Start Date (dd/MMM/yyyy):	Country where study was conducted:
Investigator Name:	Study Originator Name:

Investigator/ Designee Signature: _____ Date dd/mmm/yyyy: _____

Section B: Report Type

Check applicable report type

☐ Periodic Report

☐ End of Study report

Were any adverse events/reactions reported during the study? If 'Yes' is checked, please complete section C

☐ Yes ☐ No

Section C: Adverse Event/Reaction Information

Protocol #:

Investigator Name:

Complete the table below *only* if an adverse event/reaction was reported during the study.

Case ID No.	Study Site Aware Date	Subject Information			Study Product Information			Adverse Events/Reactions				Other Products Used	Outcome with Date	Comments
		ID No.	Age/Date of Birth	Gender	Product Name	Dose & Frequency	Duration of Use	Description	Causality	Severity	Serious (Yes/No)			

Note: If needed attach additional pages of Section C to document all events/reactions reported during the study.

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APPENDIX XVI**CLINICAL PRODUCTS RETURN LOG SHEET**

Organization _____

Principal Investigator _____

Date	Subject #	Product Code	1)Tube Before Use (Weight_g)	2)Tube After Use (Weight_g)	Weight Difference 1) – 2)

Print Name of Person Weighing Products

[Signature][Date]

APPENDIX XVII**REFERRAL/NOTICE FORM**

Patient Name: _____ Patient DOB: _____

Patient Referred By: _____

- ☐ We did not find any condition that needs immediate treatment, but we recommend that you visit your dentist every 6 months
- ☐ During your next visit to the dentist you should let him/her know that you may have a dental problem
- ☐ You should visit the dentist as soon as possible
- ☐ You should visit the dentist for an emergency visit

Comments:

Doctor Signature: _____

Date: _____

APPENDIX XVIII**STOPPING RULE****Fresh Mint**

The following are the expected, mild to moderate, non-serious adverse events that have been documented via post-marketing surveillance for Fresh Mint flavor toothpaste formulations in descending order of frequency:

Adverse Events
Mouth Irritation
Nausea / Gagging / Vomiting
Canker Sores / Mouth Ulcers / Boils
Allergic Reaction
Gastrointestinal disorder
Throat Irritation
Tooth Sensitivity
Coughing
Mouth Swelling
Oral Numbing
Skin Irritation
Oral Exfoliation
Diarrhea
Accidental Injury
Cracked / Lost Tooth / Filling
Effect on Sleep
Headache
Human Ingestion
Toothache
Vertigo / Dizziness
Dermal Cut / Scratch
Dermal Staining
Dermatological disorder
Difficult / Irregular Breathing
Dry Mouth

Effect on Taste
Mouth Bleeding
Oral Staining
Respiratory disorder

Mouth Irritation is predominantly the leading reported adverse events. Mouth Irritation is the leading reported adverse event for toothpaste globally regardless of the type and concentration of the flavor. It can plausibly be explained by the mechanism of brushing one's teeth, gums and tongue; the sheer nature of the physical contact of repeated movement of brushing over the oral cavity will cause irritation and can be compounded by the texture of toothpaste used to remove plaque.

Serious Case Discussion

Only one case was identified as serious during the relevant time period. A 63 year old male consumer in Finland reported experiencing 'breathing difficulty, felt like choking, difficulty in talking, saliva in mouth' and the healthcare professional in the ambulance mentioned that he had a life-threatening hypersensitivity reaction and was treated with antihistamine and cortisone. It was reported the consumer experienced these events right away after using the product Colgate Maximum Protection Caries Whitening Toothpaste; it was reported that he never needed allergy medications before. There was limited information regarding previous exposure to the suspect product, concomitant medications or use of other products with the toothpaste. In this case temporal relation is positive and causality may not be excluded; however, it could not be attributed to a specific ingredient in the product or to any other product to which he might have been exposed to at the same time.

Cool Mint

The following are the expected, mild to moderate, non-serious adverse events that have been documented via post-marketing surveillance for Cool Mint flavor toothpaste formulations in descending order of frequency:

Adverse Events
Mouth Irritation
Tooth Sensitivity
Mouth Bleeding
Canker Sores / Mouth Ulcers / Boils
Mouth Swelling
Dry Mouth
Allergic Reaction
Oral Exfoliation
Oral disorder / Undefined
Oral Staining
Gastrointestinal disorder
Effect on Taste
Toothache
Accidental Injury

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Oral Numbing
Dermal Cut / Scratch
Nausea / Gagging / Vomiting
Skin Irritation
Throat Irritation
Oral Discoloration
Eye Irritation
Oral Cut / Scratch / Pinch
Dermal Numbing
Diarrhea
Headache
Nasal Passage Irritation
Accidental Exposure
Coughing
Cracked / Lost Tooth / Filling
Dermatological Misc / Undefined
Difficult / Irregular Breathing

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Human Ingestion
Respiratory disorder
Vertigo / Dizziness

Mouth Irritation is the leading reported AE. It can plausibly be explained by the mechanism of brushing one's teeth, gums and tongue; the repeated action of brushing over the oral cavity may cause irritation and can be compounded by the texture of the toothpaste.

There has been no spontaneous, post-market reporting of adverse events for Cool Mint toothpaste formulations that have been assessed as serious.

Superseded

CLINICAL TRIAL PROTOCOL

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Investigator's Agreement

I understand that all documentation supplied to me by the sponsor concerning this study, which has not been previously published, will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

The study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the sponsor, and the IRB, except where necessary to eliminate an immediate hazard to the subjects.

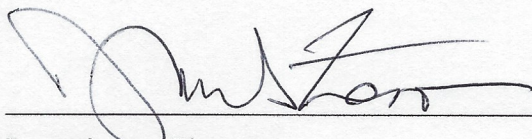
I agree to monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority (ies) as required.

I understand that there is nothing in this document which is intended to limit my authority as a dentist to provide emergency care under applicable regulations.

I have read and approved this protocol. My signature confirms my agreement that the clinical study will be conducted in full compliance with the protocol and all applicable laws, regulations and regulatory requirements including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki and all applicable country-specific and local regulations. All required study information will be archived as required by regulatory authorities.

I have read, understood, and do agree to abide by all the conditions and instructions contained in this protocol, "A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children."

Protocol # CRO-2020-CAR-ARG-ED



Investigator Signature

09 FEB 2020

Date

Domenick T. Zero, DDS, MS
School of Dentistry
Indiana University

Sponsor Agreement

TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-carries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

STUDY NO.: *CRO-2020-CAR-ARG-ED*

SPONSOR: Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

The signatures of the Sponsor's representatives below constitute the Sponsor's agreement:

- a) to all provisions of the protocol;
- b) to comply with ICH GCP Guidelines and all applicable country-specific and local laws, regulations and guidelines.



Maria E Ryan, DDS, PhD, Vice President, Chief Dental Officer
Oral Care Research & Development
Colgate-Palmolive Technology Center

1/29/2020

Date

COLGATE-PALMOLIVE

Clinical Study Protocol

Title: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

Protocol No. *CRO-2020-CAR-ARG-ED*

IND # 140794

Investigational Medicinal Product (IMP) COL101 (arginine)

Indication Reduction in dental caries

Sponsor: Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

Medical Director: Maria E Ryan, DDS, PhD
VP and Chief Dental Officer
Oral Care Research & Development
Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08854

Study Investigators: Details of participating Study Investigators, clinical study sites and other study personnel is contained in the Clinical Trials Master File and may be obtained from the Sponsor

PROTOCOL SYNOPSIS

Protocol Title:	A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children
Protocol Number:	<i>CRO-2020-CAR-ARG-ED</i>
Study Phase:	Phase II
Rationale for the Study:	Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia <i>et al.</i>, 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and also creates an environment that disfavors cariogenic bacteria and their deleterious activities. The present study is intended to evaluate anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year in 10 to 14 year old children. The outcome of this study may lead to an alternative method of caries prevention.

Study Design:

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in Section 5 of this protocol. At each study site, each enrolled subject will be randomized in a 1:1:1:1 ratio into one of four parallel study groups.

Group 1 dentifrice	1.5% arginine
Group 2 dentifrice	4.0% arginine
Group 3 dentifrice	8.0% arginine
Group 4 dentifrice	0.24% sodium fluoride with no arginine

Subjects will be required to brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice for one year. Measurements for safety and product use compliance will be conducted after 3 months, 6 months, 9 months and 12 months of assigned product use. In addition, caries examinations using the International Caries Detection and Assessment System (ICDAS) will be conducted at Baseline and at the 6 months and 12 months' time points. All subjects will be monitored for adverse events (AEs) during the course of the study.

Objectives:

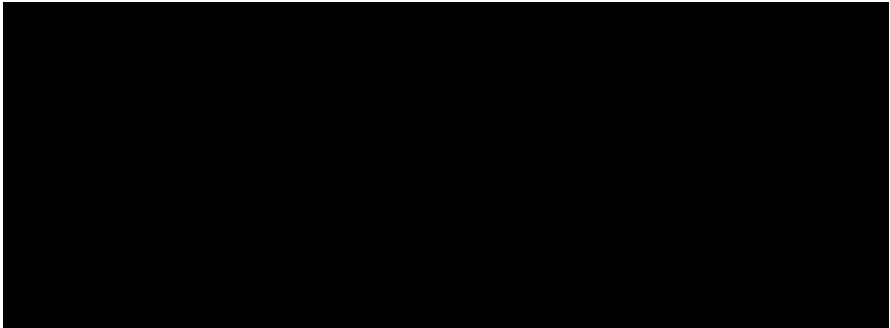
The objective of this study is to assess the safety and to evaluate the anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices containing 1.5%, 4% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10-14 year-old children over a one year period.

Main Endpoints:

Primary Endpoint: The primary efficacy endpoint will be the incremental subject-wise DMFS score after one-year of product use

Secondary Endpoints:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use.

- Clinically significant change in ICDAS severity scores between the baseline and the six-month and one-year examinations and between the six-month and one-year examinations.
 - Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6.
 - Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.
- 

Study Population:

Healthy school children 10 to 14 years of age with the presence of second permanent molars or evidence of erupting permanent second molars and evidence of previous caries experience.

Number of Subjects Planned:

2000 children (10-14 years of age) will be enrolled with the expectation that at least 1,800 subjects will complete the clinical trial at the end of a one-year period (10% annual attrition).

Number of Centers:

This study will be conducted by Study Investigators that are faculty from U.S. dental schools with standing approval from the Commission on Dental Accreditation and a Clinical Research Organization. Nine sites are planned.

Main Criteria for Inclusion:	• Healthy children 10-14 years of age of either sex. Subjects must be in good general health as evidenced by a review of their medical history • Subjects must have presence of second permanent molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through. • Subjects must have evidence of previous caries experience (DMFT >1). • Subjects must have two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth.
Test Products:	COL101 (arginine) dentifrices: 1.5%, 4.0%, and 8.0% arginine.
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Reference Therapy:	Positive control dentifrice: 0.24% sodium fluoride (1100 ppm F)
Dose and Route of Administration:	Dosage: Full ribbon on adolescent size toothbrush Route of Administration: Oral topical/toothbrushing
Duration of Treatment:	For all dentifrices, subjects will be instructed to brush their teeth for two minutes twice daily using their assigned dentifrice for one year.
Efficacy Parameters:	Increments in Decayed Missing or Filled Surfaces (DMFS) over the one-year duration of the study. Caries threshold at the “moderate” cavitation caries level of ≥ 3 in the International Caries Detection and Assessment System (ICDAS).
Safety Parameters:	Safety will be assessed by an evaluation of all reported/observed adverse events during the course of the study and by hard and soft-oral tissue examinations conducted at Baseline, 3 months (± 1 month), 6 months (± 1 month), 9 months (± 1 month) and at 1 year (± 1 month).

Primary Objective:

The objective of the study is the estimation of the effectiveness on the reduction of caries of each of the three test products (1.5%, 4.0%, and 8.0% Arginine) relative to the positive control (0% arginine/sodium fluoride 0.24%).

Study Monitoring (Data Safety Monitoring Board):

The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. Specific for this trial, the incidence of caries progression in each of the Study Product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DSMB can recommend removal of individual subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor.

Statistical Methods:

Efficacy of each of the four treatment groups will be estimated by the mean 1-year DMFS increment. Associated 95% confidence intervals will also be calculated. Generalized linear models will also be used to compare the DMFS increments statistically. Hard- and soft-tissue findings will be summarized by treatment group. Adverse events will be summarized by treatment group.

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LIST OF ABBREVIATIONS

ADA	American Dental Association
AE	Adverse Event
ANCOVA	Analysis of covariance
CRF	Case Report Form
CFR	Code of Federal Regulations

CPI	Community Periodontal Index
DMFS	Decayed Missing Filled Surfaces
DMFT	Decayed Missing Filled Teeth
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
ICCMS	International Caries Classification and Management System
ICDAS	International Caries Detection and Assessment System
ICH	International Conference on Harmonisation
IND	Investigational New Drug (Application)
IRB	Institutional Review Board

MRTD	Maximum Recommended Therapeutic Dose
NaF	Sodium Fluoride
NSAE	Non Serious Adverse Event

PSR	Periodontal Screening and Recording
SAE	Serious Adverse Event
US	United States
WHO	World Health Organization

1 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

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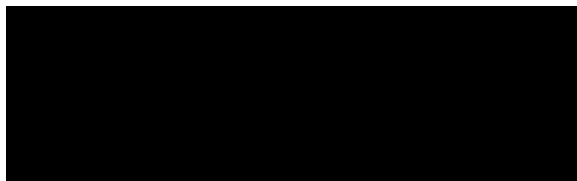
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2 INTRODUCTION AND BACKGROUND

Traditional caries prevention strategies have focused on making the tooth stronger by allowing for the replacement of the hydroxyl ions in hydroxyapatite-forming fluorapatite and maximizing the stability of the tooth mineral. This mode of action has a favorable outcome on mineral balance. Fluoride modulates calcium phosphate chemistry at the tooth surface with little to no effect on causative plaque bacteria (Santarpia *et al.*, 2014)¹. An alternative preventive strategy to address the cause has been identified through the use of arginine toothpaste to mimic our mouths' natural defense mechanism against caries. Unlike fluoride, arginine is utilized by beneficial bacteria to produce alkali, which helps maintain a pH favoring mineral repair and creates an environment that disfavors cariogenic bacteria and their deleterious activities.

2.1 Rationale for the Study

The present study is intended to evaluate anti-caries efficacy of COL101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10-14 year old children for a period of one year. The outcome of this study may lead to an alternative method of caries prevention

2.2 Risk-Benefit Assessment

L-arginine is a semi-essential amino acid that can be obtained through dietary sources such as dairy products, beef, pork, soybeans, poultry, and granola among other sources. The normal intake of L-arginine from dietary sources is orders of magnitude higher than incidental ingestion from dentifrice. This amino acid is considered semi-essential because it can be synthesized *de novo* from glutamine, glutamate, and proline. Endogenous synthesis of arginine can, however, be insufficient e.g. during periods of growth, in inflammatory disease states or during infections.

L-arginine is generally recognized as safe (GRAS) by the US FDA when used in accordance with good manufacturing practice (21CFR 582.5145) and has been approved for use as a food additive permitted for direct addition to food for human consumption (21CFR 172.320 – amino acids). Although a Recommended Daily Allowance (RDA) has not been set, a Maximum Recommended Therapeutic Dose (MRTD) has been provided and set at 500 mg/kg body weight/day for L-arginine supplementation by the US FDA. The expected exposure to arginine from the use of dentifrice (maximum exposure, 2 yr old = 14 mg) is well below both the MRTD and the normal dietary intake.

Arginine has a good safety profile and is currently marketed in the United States (US) as an ingredient in dentifrice. Proven clinical benefits include the reduction of dentin hypersensitivity. There has been no observed pattern of adverse events (AEs) associated with its regular use.

2.3 Compliance Statement

The study will be conducted according to the protocol and in compliance with, International Council for Harmonization Good Clinical Practice (GCP) guidelines and other applicable local regulatory requirements and laws^{2,3}.

3 OBJECTIVES

The objective of this one-year study is to assess the safety and to evaluate the anti-caries efficacy of non-fluoride dentifrices containing 1.5%, 4% or 8.0% arginine each compared to a 0.24% sodium fluoride dentifrice in 10 to 14 year old children.

4 OVERALL DESIGN AND PLAN OF THE STUDY

For this study, approximately 2,000 children will be enrolled, according to the criteria detailed in Section 5 of this protocol. At each study site, each enrolled subject will be randomized into one of four parallel study groups (1.5% arginine dentifrice, 4.0% arginine dentifrice, 8.0% arginine dentifrice or 0.24% sodium fluoride dentifrice with no arginine). Voluntary participants will brush their teeth twice daily at home (unsupervised use) with the assigned dentifrice. Measurements for efficacy, safety and assessment of product use compliance will be conducted at baseline, 6 months (± 1 month) and 1 year (± 1 month). Additional safety evaluations including evaluation of oral soft and hard tissues, as well as and product use compliance assessment will be performed at 3 months and 9 months (± 1 month). All subjects will be monitored for adverse events (AE) during the course of the study.

Subjects who are discontinued cannot reenter treatment and will not be replaced. Adverse events will be monitored for up to 30 days following study conclusion, until the AE is resolved or it is determined by the Study Investigator and Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) to be stable.

4.1 Overview

4.1.1 Screening and Selection of Subjects

Candidates will be screened by a trained and calibrated study examiner to identify those subjects who meet the inclusion/exclusion criteria (Section 5) and the findings will be recorded on an Inclusion/Exclusion case report form (CRF). Parents or legal guardians of participating children will be informed about all aspects of the study and informed consent/assent forms will be completed by each participating subject and by their parent or legal guardian.

At each site, subjects who, in addition to meeting the inclusion criteria, assent to voluntarily participate and whose parents or legal guardian have signed the informed consent form will be enrolled.

4.1.2 Baseline Clinical Examinations of Soft and Hard Tissue

The following evaluations will be performed at Baseline:

Soft and Hard Tissues will be examined and abnormalities will be noted in corresponding CRFs.

The soft tissue structures examined will include the soft palate, hard palate, gingival mucosa, buccal mucosa, mucogingival folds, tongue, sublingual and submandibular areas, salivary glands, tonsillar and pharyngeal areas. Observations will be listed as “Normal” and “Abnormal” and abnormalities will be described.

The hard tissue structures examined will include assessing for enamel irregularities, tooth fracture, pathologic tooth wear, cavitated caries lesions, residual roots, faulty restorations and implants. Observations will be listed as “Normal” or “Abnormal” and conditions noted as abnormal will be described.

The International Caries Detection and Assessment System (ICDAS) will be used to determine caries severity and the caries lesion activity and to establish subject eligibility^{4,5,6}. As the subjects are recruited, baseline caries examinations will be performed by trained and calibrated study examiners who will carry out the examinations according to ICDAS Criteria. All examinations will be conducted after subjects have brushed their teeth with water and, if necessary, brushed again and possibly flossed by the study examiner or study personnel.

The severity criteria used in the ICDAS diagnostic system are as follows:

Code 0 Sound tooth surface

There should be no evidence of caries (either no or questionable change in enamel translucency after prolonged air drying (suggested drying time 5 s). Surfaces with developmental defects such as enamel hypoplasias; fluorosis; tooth wear (attrition, abrasion and erosion), and extrinsic or intrinsic stains will be recorded as sound. The examiner should also score as sound a surface with multiple stained fissures if such a condition is seen in other pits and fissures, a condition which is consistent with non-carious habits (e.g. frequent tea drinking).

Code 1 First visual change in enamel

Code 1: Pits and fissures

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air drying (approximately 5 s is suggested to adequately dehydrate a carious lesion in enamel) a carious opacity or discoloration (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel.

OR

When there is a change of color because of caries which is not consistent with the clinical appearance of sound enamel and is limited to the confines of the pit and fissure area (whether seen wet or dry). The appearance of these carious areas is not consistent with that of stained pits and fissures as defined in code 0.

Code 1: Smooth tooth surfaces

When seen wet there is no evidence of any change in color attributable to carious activity, but after prolonged air-drying a carious opacity (white or brown lesion) is visible that is not consistent with the clinical appearance of sound enamel. This will be seen from the buccal or lingual surface.

Code 2 *Distinct visual change in enamel*

The tooth must be viewed wet. When wet there is a (i) carious opacity (white spot lesion) and/or (ii) brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel (Note: the lesion must still be visible when dry)

Code 3 *Localized enamel breakdown because of caries with no visible dentin or underlying shadow*

The tooth viewed wet may have a clear carious opacity (white spot lesion) and/or brown carious discoloration which is wider than the natural fissure/fossa that is not consistent with the clinical appearance of sound enamel. Once dried for approximately 5 s there is carious loss of tooth structure at the entrance to, or within, the pit or fissure/fossa. This will be seen visually as evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the fissure or pit, and although the pit or fissure may appear substantially and unnaturally wider than normal, the dentin is NOT visible in the walls or base of the cavity/discontinuity.

If in doubt, or to confirm the visual assessment, the WHO/CPI/PSR probe can be used gently across a tooth surface to confirm the presence of a cavity apparently confined to the enamel. This is achieved by sliding the ball end along the suspect pit or fissure and a limited discontinuity is detected if the ball drops into the surface of the enamel cavity/discontinuity.

Code 4 *Underlying dark shadow from dentine from dentin with or without localized enamel breakdown*

This lesion appears as a shadow of discolored dentin visible through an apparently intact enamel surface which may or may not show signs of localized breakdown (loss of continuity of the surface that is not showing the dentin). The shadow appearance is often seen more easily when the tooth is wet. The darkened area is an intrinsic shadow which may appear as grey, blue or brown in color. The shadow must clearly represent caries that started on the tooth surface being evaluated. If in the opinion of the examiner, the carious lesion started on an adjacent surface and there no evidence of any caries on the surface being scored then the surface should be coded '0'.

Code 5 *Distinct cavity with visible dentine*

Cavitation in opaque or discolored enamel exposing the dentin beneath.

The tooth viewed wet may have darkening of the dentin visible through the enamel. Once dried for 5 s there is visual evidence of loss of tooth structure at the entrance to or within the pit or fissure – frank cavitation. There is visual evidence of demineralization [opaque (white), brown or dark brown walls] at the entrance to or within the pit or fissure and in the examiner judgment dentin is exposed.

The WHO/CPI/PSR probe can be used to confirm the presence of a cavity apparently in dentin. This is achieved by sliding the ball end along the suspect pit or fissure and a dentin cavity is detected if the ball enters the opening of the cavity and in the opinion of the examiner the base is in dentin. (In pits or fissures the thickness of the enamel is between 0.5 and 1.0 mm. Note the deep pulpal dentin should not be probed).

Code 6 *Extensive distinct cavity with visible dentine*

Obvious loss of tooth structure, the cavity is both deep and wide and dentin is clearly visible on the walls and at the base. An extensive cavity involves at least half of a tooth surface or possibly reaching the pulp.

**Classification of the restoration, sealant, or missing status in the ICDAS
(Ismail et al., 2007)⁴**

- 0 = Unrestored or unsealed
- 1 = Sealant, partial
- 2 = Sealant, full
- 3 = Tooth colored restoration
- 4 = Amalgam restoration
- 5 = Stainless steel crown
- 6 = Porcelain or gold or PFM crown or veneer
- 7 = Lost or broken restoration
- 8 = Temporary restoration
- 9 = Tooth does not exist or other special cases.

Used in as the following:

9–6 = Tooth surface cannot be examined because of access problem to visualize the tooth surface

9–7 = Tooth missing because of caries (all tooth surfaces are coded 97)

9–8 = Tooth missing for reasons other than caries (all tooth surfaces are coded 98)

9–9 = Un-erupted (all tooth surfaces care coded 99)

Caries Lesion Activity Assessment (ICCMS Guide)⁶:

Code 0 Signs of Inactive Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located near the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing. Surrounding enamel has polished edges and may be shiny and hard and smooth when the ball-ended probe is moved gently across the surface.

Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning. The adjacent gingival tissue may show signs of inflammation or bleed upon probing.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.

A study examiner (dentist) will evaluate the condition of every surface of every tooth and will verbalize the findings to a trained recorder who will enter the data on to a CRF.

4.1.3 Subsequent Soft and Hard Tissue Examinations

Subsequent 6-month and 12-month clinical examinations will be conducted following the same examination criteria and procedures employed at baseline. Additional soft and hard tissue examinations will be conducted at 3 and 9 months for safety reasons. Examinations 3, 6 and 9 months will coincide with resupply of assigned toothpaste and toothbrush.

4.1.4 Calibration of Examiners

For each cohort, a didactic training session will be held to the participating examiners prior to the actual ICDAS clinical calibration session by a gold standard examiner (the Principal Investigator). This didactic session will include: 1) Review of ICDAS depicting the dental status examination criteria; 2) Evaluation of participating examiners' knowledge of the criteria; 3) Clinical Training with demonstration examinations; and 4) Practice Examinations.

On training session day one, examiners from one cohort will see the first few qualifying screening subjects together and discuss their scores with the gold standard examiner and among each other. On calibration session (days 2 and 3) the participating examiners will conduct the examinations independently. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each permanent tooth surfaces will be scored. On day 4, approximately 3-5 willing subjects from calibration session (day 2) will be asked to return to the clinic for a repeat session. Examiners will perform the ICDAS examination and record any findings on the corresponding case report forms (CRF's). Teeth will be charted as present or missing and each surface of permanent teeth will be scored.

Each tooth will be categorized into one of seven categories (0-6) based on its ICDAS score. A tally of counts and percentages will be maintained during screening to determine

the frequency of teeth qualifying under each ICDAS category. Analyses will be performed at the tooth level and the subject level. Intra and inter-examiner reliability will be assessed using weighted kappa scores. A kappa score of 0.61 or higher will be considered substantial agreement. If an examiner fails to achieve the said mark, the exercise may be repeated on some of the same subjects if they're willing to come back for future dates.

Prior to the one-year exam examination of clinical trial, a new calibration will be done to determine intra- and inter-examiner agreement to prevent any drift of the examiners.

4.1.5 At-Home Product Use

After the baseline examinations are completed, dental study personnel (non-examiners) will give subjects tubes of their assigned dentifrice and adolescent size soft bristled toothbrushes. Subjects will be instructed to brush their teeth by applying a full ribbon of their assigned dentifrice to their assigned toothbrush head, and brush their teeth for 2 minutes twice daily. Subjects will also be requested to use no other dental products, such as other toothbrushes, mouth rinses or other dentifrices during the course of the study, however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with the dentist. Subjects that routinely use dental floss may continue to do so during the study period.

The assigned toothpaste and a new toothbrush will be re-supplied every three months.

4.1.6 Dental Treatment During the Study

Subjects will be instructed to continue regular visits to the dentist and routine dental treatment during the course of the study. In addition, at every scheduled study examination, subjects will receive a referral for dental care, if needed.

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects meeting all criteria below will be included in the study:

1. Subject assent and parental/guardian informed consent for voluntary participation.
2. Willingness and ability to use the assigned products according to instructions, availability for all appointments and likelihood of completing the clinical trial.
3. Children ages 10-14 years at baseline.
4. Presence of permanent second molars or evidence of at least one permanent second molar erupting as indicated by cuspal break through the mucosa.
5. Good general health as evidenced by a review of the medical history.
6. Subjects who, at study entry, have present two or more active caries lesions (ICDAS scores of 2 or greater) in permanent teeth and previous caries experience (DMFT >1).

5.2 Exclusion Criteria

Subjects presenting any of the criteria below will be excluded from the study:

1. Presence of fixed or removable prosthetic appliance or orthodontic treatment involving more than four permanent teeth.
2. Use of medication that could increase the risk of developing dental caries, i.e. medications that reduces saliva flow and those with high sugar content.
3. Long-term antibiotic therapy.
4. Children with a confirmed diagnosis of cognitive and/or motor impairment.
5. Severe malocclusion.
6. Subjects who, at study entry, have present severe caries (ICDAS 5 or 6) on five or more teeth.
7. Evidence of moderate to severe periodontal disease.
8. Participation in any other clinical study within the 30 days preceding the start of the clinical study.
9. Known history of allergies or other adverse reactions to arginine, or oral care products, or their ingredients.

5.3 Withdrawal and Replacement of Subjects

A genuine effort will be made to determine the reason(s) why a subject fails to report to the scheduled examinations or has been dropped from the study. A subject will be dropped from the study if any of the following occurs:

1. Subject fails to report for the examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.

4. Subject experiences a serious adverse reaction to the test products. Withdrawal of the subject is at the discretion of the Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendation of the Medical Monitor). (See Section 7.5.7 for SAE reporting procedures).
5. Subject is determined to be non-compliant by the Site PI in consultation with the Sponsor.

Subjects discontinued from the study for any reason will not be allowed to re-enter the study and will not be replaced. Subjects withdrawn due to AEs will receive follow-up as outlined in Section 7.5.8

5.4 Statistical Basis for Sample Size

The sample size requirement was determined based on the precision of the efficacy estimate for each treatment group. Details regarding this determination are provided in Section 10.2 of this protocol.

5.5 Subject Identification, Randomization, and Blinding

Enrolled subjects at each study site will be assigned subject numbers specific to that site. An un-blinded biostatistician will generate a separate randomization listing for each study site, ensuring that the study biostatistician will remain blinded to the treatment assignments until the study has been completed. The randomization listings will be transferred to a designated un-blinded individual at each study site, who will manage randomized assignment, product dispensing and resupply. In addition to utilizing this information for the dispensing to treatment to enrolled subjects, this individual will also be on call to provide emergency un-blinding information for an individual subject if such a need should arise during the study. Each study site will maintain a list of all individuals who are privy to the randomization listing. At the conclusion of the study, after all data cleaning and statistical analyses have been programmed and completed (based on the blinded study data), the investigator at each study site will indicate that un-blinding can proceed. Un-blinding of the study data will not take place until this indication has been received from all study sites.

5.6 Un-blinding

If the Study Investigator determines that some event, such as a serious adverse event (SAE) has occurred and the treatment should be un-blinded for that subject, the Study Investigator should contact the Colgate Study Monitor. The Study Investigator in consultation with the Colgate Study Monitor (who will consult with and represent the recommendations of the Medical Monitor) will then make a decision about breaking the blind for the subject. The Colgate Study Monitor will then contact the study code un-blinder, and the subject will be un-blinded and documented accordingly.

6 STUDY PRODUCT

6.1 Identity

Study Product 1 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 1.5% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 2 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 4.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 3 (Test Product) Name: Dosage form: Manufacturer: Description:	Dentifrice containing 8.0% arginine Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube
Study Product 4 (Control Product) Name: Dosage form: Manufacturer: Description:	Dentifrice 0.24% sodium fluoride (1100 ppm F) Dentifrice Colgate-Palmolive Dentifrice in a 4.7 oz tube

6.2 Packaging, Labeling, and Storage

The packaging and labeling will be performed by the sponsor according to all local legal requirements.

All supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to subjects, the study dentifrices will be stored in a securely locked area, only accessible to authorized personnel.

The study products will be coded and the identity of the products will be concealed.

The sponsor will provide the study dentifrices to the site.

Representative product labeling that will be placed on the outside box of each tube of toothpaste and on the tube of toothpaste itself can be found in Appendix IV.

6.3 Product Use Instructions

Subjects will be verbally instructed to brush their teeth twice daily (morning and evening before bed) for two minutes each time, using their assigned dentifrice and toothbrush. A timer will be provided to each participant as an aid to comply with 2-minute brushing. Subjects will also be instructed to dispense a full ribbon of toothpaste covering the full length of the toothbrush head for each tooth brushing. Study personnel will demonstrate this at the initial study visit. No oral hygiene products, other than the toothbrush and the dentifrice provided, should be used during the treatment period. Subjects that routinely use dental floss may continue to do so during the study period.

In addition to verbal product use instructions and essential information provided in product labels, subjects will be given written product use instructions to take home (Appendix V).

6.4 Study Product Dispensing

Kits containing dentifrices and toothbrushes shall be provided to the subjects every three months. All product dispensing and resupply will be handled by a study site individual un-blinded to product assignment.

The initial distribution of the study products will occur at the examination facility after completion of the baseline examinations. Subsequent product dispensing will then take place every three months at the 3-month, 6-month and 9-month examination visits. Subjects will receive at each of these product resupply visits a new adolescent-sized, soft-bristled toothbrush and sufficient dentifrice will be dispensed to last until the next scheduled visit (one tube (4.7 oz tube) for every month) of product use.

Should additional dentifrice be required between routine deliveries, the subject will contact the study coordinator. The coordinator shall immediately ensure resupply via appropriate study personnel, preserving the double-blind design.

6.5 Study Product Accountability

The Sponsor will provide each study site with sufficient amounts of the study products. The study site will confirm in writing receipt of all batches of study product.

The study site will administer/dispense study product only to subjects included in this study according to the procedures established in this study protocol. Each subject will be given only the dentifrice assigned to him/her. Each dispensed tube of dentifrice will be documented in the dispensing log.

All supplies must be accounted for at the end of the study. The study site must maintain accurate and adequate records, including dates dispensed, quantities received, subject dispensed to, date returned by the subject, amount returned by the subject, date returned to the sponsor and/or destroyed at the study site.

At the end of the study, no remaining supplies are to be in the study site's possession. The study monitor will procure and document that all remaining study supplies are properly discarded by the site.

6.6 Product Use Compliance

Subjects will be expected to return previously dispensed study dentifrice (empty, partially used or unused tubes of dentifrice included) to the site at each of the pre-established product resupply events and exchanged for new supply to last until the next scheduled visit (Appendix XV). Unused study dentifrice will also be collected at the site at the end of study participation. The study site will weigh all tubes of toothpaste at the time of dispensing and weigh the tubes when returned, maintaining a log of the gathered information on a subject per subject basis. For each individual, the amount of toothpaste used will be estimated by weight at each of the tube return/collection time points and compared to the expected use based on projection of using "two ribbons" per day. A timer will be provided to each participant as an aid to comply with 2-minute brushing.

6.7 Concomitant Medications

Any medication used during the study period, other than the study dentifrices specified in the protocol, is considered a concomitant medication. All concomitant medications must be recorded at the beginning of every study visit through completion of a health questionnaire.

7 SAFETY

7.1 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be appointed by the Sponsor as an independent multidisciplinary group that will assure subject safety and integrity of the clinical trial. The DSMB will include clinical research scientists and statistician not otherwise connected with the study that, collectively, have extensive experience in the management of clinical trials and in the conduct and monitoring of randomized clinical trials and will be competent in applying this experience to the study of children with dental caries. The DSMB will elect a chair under rules they define in their organizational meeting and review and approve a DSMB Charter provided by the Sponsor. The DSMB

will have access to un-blinded safety and effectiveness outcome data during the trial that will be provided by an un-blinded data manager. Specific for this trial, the incidence of caries progression in each of the study product toothpastes will be compared to the positive control fluoride toothpaste. In order to protect participants from unreasonable or unnecessary safety risks the DSMB can recommend removal of individual subjects from the trial or early termination of the trial if the data suggest significant adverse risk to participants. The DSMB will also review the timeliness of recruitment and the quality of the data and make recommendations to the Sponsor. The DSMB will meet at least every three months throughout the trial and distribute a report summarizing any safety concerns or serious adverse events that have occurred since the last three-month exam. This report will be submitted to the IRBs of each study site (or Central IRB), the Study Investigators and the Sponsor. Each report should contain an open section containing materials for blinded staff, and a closed section of treatment comparisons. Every precaution will be taken to maintain the blind from Study Investigators, study examiners, statisticians and the Sponsor. Interim conference calls may also be scheduled at the discretion of the board, Study Investigators or the Sponsor.

7.2 Stopping Rules

If an investigational product-related serious or unexpected AE occurs and it is determined to be an unacceptable risk to the health and safety of other investigational product recipients by the Study Investigator, Colgate Study Monitor, Medical Monitor, and DSMB, administration of investigational product will be discontinued until a thorough review of the events is undertaken by the Study Investigators, institutional review board (IRB) of record, and Colgate Monitor (who represents the recommendation of the Medical Monitor). The study may be resumed with the concurrence of the Medical Monitor (via Colgate Study Monitor), Study Investigators, and the US Food and Drug Administration (FDA).

7.3 Subject Safety Measures

Study subjects that have cavitated lesions (ICDAS 5/6) at their screening examinations will be referred to their dentist of record for necessary treatment. If the subject does not have a dentist, the study site will provide the names of three local dentists to the subject's parent/guardian.

7.4 Rescue Therapy

Any randomized subject that experiences pain, swelling, abscess or caries progression resulting in frank cavitation (ICDAS 5/6) during any follow up visit will be referred to their dentist of record for appropriate dental treatment. If the subject does not have a dentist, the study site will refer the subject to a local dentist or a dental school clinic.

7.5 Adverse Events (AEs)

Illnesses present at entry to the study are considered pre-existing conditions and will be documented on the Health Questionnaire (sample included as Appendix VII). AEs will be followed for up to 30 Days, until it resolves or is determined by the Study Investigator and the Medical Monitor (through the Colgate Study Monitor) to be stable.

All AEs must be reported and documented as described below.

7.5.1 Definitions

Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined by the ICH Guideline for Good Clinical Practice (ICH GCP) as follows:

Adverse Event: Any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include any clinically significant deterioration of a subject's medical status, after being enrolled in the study and signing an Informed Consent form. The AE may involve any organs or systems and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change from baseline, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring after the first administration of study medication is an adverse event. All such occurrences must be recorded and reported accordingly, whether they appear causally related to the study medication, or not.

Serious Adverse Event: Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening adverse event
- Inpatient hospitalization, or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience 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 important 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.

7.5.2 Assessment of Adverse Events

Volunteered, observed, and elicited AEs will be recorded. This includes those the subject reports spontaneously, those the study examiner observes, and those the study examiner

elicits in response to open-ended questions at the times indicated on the Schedule of Study Activities, Section 8.1.

All clinical complaints, symptoms, or signs that meet the adverse event definition will be recorded on the Adverse Events case report form (Appendix XIII) using a recognized medical term or diagnosis that accurately reflects the event. Source documentation should be maintained that allows for clear identification of each adverse event and the following parameters required for the CRF:

- AE description
- Date of onset
- Date of resolution
- Outcome
- Severity
- Seriousness
- Relationship to study drug (causality)
- Actions taken

Adverse events will be assessed by the investigator or designee for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification of the sponsor.

For CRF data collection purposes, the outcome of all adverse events recorded on the Adverse Event form should be reported within two (2) weeks of the study completion. The Investigator will include this information in the Site Report providing a line listing using the Periodic/End of Study Report Form (Appendix XIV) and attaching the individual adverse event form for each case reported. However, the Investigator is responsible for following all adverse events until resolution or until no longer of clinical concern, and providing these data to the Sponsor.

When protocol duration, is six (6) months or longer, a Periodic/End of Study Report Form must be completed and included as part of your Site Report every six (6) months for the duration of the protocol.

7.5.3 Serious Adverse Events (SAEs)

Federal law defines an SAE as any event, occurring at any dose, which suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, an SAE can be described as one or more of the following:

- Fatal:
This includes deaths that appear to be completely unrelated to study product (e.g., car accident). If a subject dies during the study and an autopsy is performed, autopsy results will become part of this subject's CRF. Possible evidence of organ toxicity and the potential relationship of the toxicity to the study product will be of particular interest. The autopsy report should distinguish the relationship between the underlying diseases, the study product's side effects, and the cause of death.

- Life-threatening:

A life-threatening AE is any adverse event during which the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered a life-threatening event though drug-induced hepatitis can be fatal.

- Permanently or significantly disabling
- Requiring/prolonging inpatient hospitalization
- A congenital anomaly/birth defect

AEs that fall outside of these categories are not considered serious.

7.5.4 Severity

Regardless of the classification of an AE as serious or not, its severity must be assessed according to the following categories:

Mild:	does not interfere with routine activities
Moderate:	interferes with routine activities
Severe:	impossible to perform routine activities

Note that a severe AE need not be serious and that an SAE need not, by definition, be severe.

7.5.5 Relationship to Study Product

The study examiner will assess the relationship between the study product and the AE.

The following definitions are used to determine the relationship between the study product and the AE.

Definite: (must have four of the following)

This category applies to those AEs that the study examiner feels are incontrovertibly related to study product. This relationship may be considered definite if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose and recurs with re-exposure to study product (Note: this is not to be construed as a requirement to re-expose the subject; however, a category of definitely related can only be used when recurrence is observed);
- follows a known pattern of response to study product;
- is associated with toxic levels of the study product in the blood or positive results on drug sensitivity tests (e.g., skin test).

Probable: (must have 3 of the following)

This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to study product. This relationship may be considered probable if or when the AE:

- follows a reasonable temporal sequence after administration of the study product;
- could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the study product, yet the event is clearly related to the study product (e.g., tardive dyskinesia);
- follows a known pattern of response to study product.

Possible: (must have two of the following)

This category applies to those AEs for which, after careful medical consideration at the time they are evaluated, a connection with the study product appears unlikely, but cannot be ruled out with certainty. This relationship may be considered possible if or when the adverse event:

- follows a reasonable temporal sequence after administration of the study product;
- could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- follows a known pattern of response to study product.

Unlikely: (must have two of the following)

In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study product. This may be considered unlikely if or when the adverse event:

- does not follow a reasonable temporal sequence after administration of the study product;
- could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
- does not follow a known pattern of response to study product;
- does not reappear or worsen when the study product is re-administered.

Not related:

This category applies to those AEs that, after careful consideration, are clearly and incontrovertibly due to causes other than the study product (e.g., disease or environment).

7.5.6 Recording Adverse Events (AEs)

All AEs, regardless of relationship to study product, must be recorded on the Adverse Events CRF. All AE reports should contain the date the AE occurred, a brief description of the event, time of onset, duration of event, intensity, treatment required, relationship to

study product, study product action taken, outcome, and whether the event is classified as serious.

7.5.7 Reporting Non Serious Adverse Events (NSAEs) and Serious Adverse Events (SAEs)

The Study Investigator must complete the Report of Adverse Event when an AE is identified. The Study Investigator must report any NSAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 72 hours of the event. The Study Investigator will provide the NSAE Report to Central IRB within 1 month of the event. The Colgate Study Monitor will then report the NSAEs to the DSMB within 1 month of discovering the event.

The Study Investigator must report any SAEs to the Colgate Study Monitor and Colgate Safety and Pharmacovigilance Group within 24 hours of the event. The Study Investigator will provide SAE Report to Central IRB no later than 2 weeks (10 business days) of the event. The Colgate Study Monitor will then report the SAEs to the DSMB within 5 days of discovering the event.

The Study Investigator must also follow local IRB guidelines for Adverse Event reporting. The Study Investigator may be asked to submit substantiating data, such as diagnostic test reports, to the Colgate Study Monitor.

The Study Investigator and the Colgate Study Monitor (who consults with and represents the recommendations of the Medical Monitor) will review each Serious Adverse Event Report and evaluate the relationship of the event to study product.

Based on the Investigator and Sponsor's assessments of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new AE related to arginine raises concern over the safety of continued administration of the study product to subjects, the Sponsor will take immediate steps to notify the Federal Food and Drug Administration (FDA) and all investigators participating in clinical trials with arginine.

Further action that may be required includes the following:

- Modification of the protocol
- Discontinuation or suspension of the study
- Modification of the existing consent/assent form and informing current study participants of new findings
- Addition of any newly identified arginine-related AEs to the list of expected AEs.

7.5.8 Follow-Up of Adverse Events (AEs)

The Investigator must continue to follow all SAEs and those non-serious events possibly related to study product until they resolve or until the Study Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

Any SAE occurring within 30 days after the end of the study and considered to be at least possibly caused by the study product, and therefore a possible adverse product reaction, must be reported as above.

7.5.9 Reporting Safety Information

The Study Investigator must promptly report to the Colgate Study Monitor, Central IRB, his or her Institutional Review Board (IRB), according to the specific guidelines of that IRB, all unanticipated problems involving risks to subjects. The Clinical Study Monitor will provide all unanticipated problems involving risks to subjects to the DSMB. This includes death from any cause and all SAEs associated, or possibly associated, with the use of the study product.

7.5.10 Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis, only in the event of an emergency. The Study Investigator or other physician in attendance in such an emergency must contact the Colgate Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Study Investigator will decide, in consultation with the Colgate Monitor (who consults with and represents the recommendations of the Medical Monitor), whether the subject should continue to participate in the study. All protocol deviations and the reasons for such deviations must be recorded.

8 STUDY CONDUCT

8.1 Schedule of Study Activities

Assessment	Baseline	3 Month (±1 Month)	6 Month (±1 Month)	9 Month (±1 Month)	12 Month (±1 Month)
Informed Consent/Assent	X				
Baseline Medical History/ Concomitant Medications	X				
Hard and Soft Tissue Examinations	X	X	X	X	X
Conformance with Entry Criteria	X				
Caries Examination	ICDAS	Visual Monitoring for Safety	ICDAS	Visual Monitoring for Safety	ICDAS
Medical History Update/Concomitant Medications		X	X	X	X
Visit Form (Continuance)		X	X	X	X
Dentist Notice/Referral (when Necessary)	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X
Randomization, Study Group Assignment and Initial Toothpaste and Toothbrush Supply	X				
Study toothpaste and toothbrush re-supply		X	X	X	
Collection of previously dispensed study toothpaste and toothbrush		X	X	X	X
Assessment of Product Use Compliance		X	X	X	X
Periodic/End of Study Report Form for Non-interventional Studies on Humans			X		X

8.2 Observations by Visit

8.2.1 Baseline Examination

- * Obtain parental written informed consent and participant assent
- * Verify conformance with entry criteria (inclusion/exclusion criteria).
- * Medical history/concomitant medications
- * Hard and soft tissue evaluation
- * ICDAS Caries Examinations
- * Randomization
- * Adverse Events
- * Dentifrice and toothbrush distribution and written and oral instructions for use
- * Dentist Notice/Referral (if necessary)

8.2.2 3 Month Examinations (±1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * Adverse Events
- * Dentifrice and brush collection and resupply
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)

8.2.3 6 Month Examinations (±1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * ICDAS Caries Examinations
- * Adverse Events
- * Dentifrice and brush collection and resupply
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)
- * Periodic/End of Study Report Form for Non-interventional Studies on Humans

8.2.4 9 Month Examinations (±1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * Adverse Events
- * Dentifrice and brush collection and resupply
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)

8.2.5 12 Month Examinations (±1 Month)

- * Medical history update/concomitant medications
- * Visit Form (Continuance)
- * Hard and soft tissue evaluation (including caries safety monitoring)
- * ICDAS Caries Examinations
- * Adverse Events
- * Dentifrice and brush collection
- * Compliance assessment (assessment of returned product use)
- * Dentist Notice/Referral (if necessary)
- * Periodic/End of Study Report Form for Non-interventional Studies on Humans

8.2.6 Follow-Up Procedures

Subjects will be followed for AE resolution, as defined in Section 7.5.8

8.3 Site / Study Termination

If the Sponsor, or the Investigator discovers conditions arising during the study that indicate that the study should be halted, it must be terminated after appropriate consultation between the study Sponsor, project manager, and Investigator. Conditions that may warrant termination include, but are not limited to:

- * The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- * Failure of the Study Investigator to enter subjects at an acceptable rate.
- * Insufficient adherence to protocol requirements.
- * A decision on the part of the sponsor to suspend or discontinue development of the study product.

9 DATA HANDLING AND RECORD KEEPING

9.1 Data Quality Assurance

Colgate Study Monitors will conduct a site visit to verify the qualifications of the Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

An Investigator's meeting will be held to introduce the Investigators and their key personnel to the study protocol, CRFs, procedures, and regulatory requirements.

The Study Investigator is required to prepare and maintain adequate and accurate case histories, designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRFs for this study must be consistent with the subject's source documentation (i.e., medical records).

9.2 Case Report Forms (CRFs) and Source Documentation

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

In this clinical trial visit forms, confirmation of enrollment, randomization, study group assignment, log of product dispensing, data from soft tissue examinations, data from caries examinations, and administration of [REDACTED] will be captured on electronic case report forms (eCRFs). Direct data entry into eCRFs will be

captured and stored in Veeva Vault Clinical Suite. Paper case report forms (paper CRFs) will be used to capture all other data that will not be directly entered into the Veeva system, such as report of adverse events and documentation of product use compliance. Paper CRFs will be retained as original source documents and will be scanned and uploaded to the Veeva Vault Clinical Suite.

Veeva Vault is a cloud-based Content Management System (CMS) developed by Veeva Systems. The Vault Clinical Suite includes Vault eTMF and Vault CTMS. Vault Clinical enables increased compliance of clinical processes, inspection readiness, and permits a unified and connected view of clinical operations business functions. In addition, Veeva Vault produces secure and compliant audit trails in accordance with the FDA 21 CFR Part 11 Electronic Records, Electronic Signatures, and Eudralex Annex 11: Computerized Systems regulations. All data collected from the web based EDC hosted on a private Google Cloud Platform (GCP) cloud will be verified before being sent through encoded HTTP POST requests to the Veeva Vault cloud hosted on Amazon's Web Services cloud (AWS).

A study coordinator, designated by the study center Investigator will be responsible for overseeing management principles including validated data entry at the point of data generation, data storage in one comprehensive relational database and data security.

9.3 CRF Fields as Database Entry Sources

CRFs should be considered the only source for database entry. Data should not be entered on any other form. Should an AE occur that requires clinical laboratory or electrocardiogram (ECG) data, the original printout should be attached to the Adverse Event CRF.

9.4 Direct Access to Source Data

During the course of the study, the Colgate Study Monitors will make site visits to review protocol compliance, compare CRFs and individual subject's medical records/study records, assess product accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records/study records will be performed in a manner to ensure that subject confidentiality is maintained.

Reviewing the CRFs for completeness and clarity, and cross-checking with source documents will be required to monitor the progress of the study. Moreover, regulatory authorities and/or the Sponsor's clinical quality assurance group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

9.5 Documentation of Consent, Privacy Notice and Storage of Study Documents

All informed consent/assent forms and privacy notices will be administered in either English or Spanish, whichever is most appropriate, and will be kept as source documentation. Informed Consent/Assent forms will be stored in a secure locked room designated for research charts storage in the clinical site. The Study Investigator will

provide each subject's parent with a clear and understandable Privacy Notice (Appendix I-A presents the Sponsor's standard privacy notice) regarding the processing in connection with the study of personal data (i.e., any information relating to an identified or identifiable individual) by the Study Investigator, Sponsor and other persons involved in the study. The Study Investigator will obtain parental signature to this privacy notice. The original signed copy of the privacy notice for each subject participating in the study will be retained in the Investigator's study records. Each subject's parent will be given a copy of the privacy notice and the privacy notice will be referenced in and form a part of the overall study informed consent/notice process.

A baseline privacy notice is included in this protocol for that purpose. Any deviation to the privacy notice as regards processing by the Sponsor (including its vendors, monitors and other representatives) must be agreed with the Sponsor. In addition, The Study Investigator is responsible for ensuring that all study subjects' parents receive a copy of the privacy notice, and that the privacy notice includes any local requirements regarding data security and privacy laws and regulations applicable to the study and the subjects. Should the privacy notice provided by the Sponsor fail to meet any applicable local requirements, the Study Investigator is responsible for amending the privacy notice to bring it into compliance with local applicable regulations and the Study Investigator agrees to indemnify and be liable to the Sponsor for any damages resulting from such non-compliance. Subjects' study charts will be stored in a secure locked room designated for research charts storage in the clinical site. The chart room is a limited- access area and only delegated study personnel will have access to the study charts and subjects' data.

9.6 Archiving Study Records

Essential documents should be retained for a minimum of 5 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or for at least 5 years since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local regulations.

10. STATISTICAL METHODS

10.1 Study Objectives and Hypotheses

10.1.1 Primary Study Objective

The primary objective of the study is the estimation of the effectiveness of the three test products (1.5%, 4.0%, and 8.0% Arginine) each relative to the positive control (0% arginine/sodium fluoride 0.24%).

Toward this end, the following null hypothesis will be considered for each of the three test products (1.5%, 4.0%, and 8.0% Arginine) in the analysis of the data:

- H_0 : There is no difference between the anti-caries efficacy of the test product and that of a dentifrice containing 0% arginine/ sodium fluoride 0.24% (1100 ppm F).

These hypotheses will each be tested through a comparison of the mean caries DMFS increments for the respective dentifrices. The secondary efficacy endpoints, counts of clinically significant changes in ICDAS severity (progression and regression) and caries lesion activity scores between the baseline and the 6-month and one-year examinations and between the 6-month and one-year examinations will also be compared among the four dentifrices. The analysis methods are described in section 10.6.

10.2 Sample Size Considerations

The sample size determination was based on the expected half width of the 95% confidence interval for the one-year DMFS increment for each treatment group. Based on past data we expect a standard deviation of approximately 3.0. Using the normal approximation and 450 subjects per group at one year, the confidence interval half-width would be ± 0.28 . These estimates will provide data to be used in planning the next (pivotal) study.

10.3 Randomization

Separate randomization listings for each study site will be provided. Within each randomization, subjects will be assigned to each of the 8.0% arginine/0 ppm F dentifrice, 4.0% arginine/0 ppm F dentifrice, the 1.5% arginine/0ppm F dentifrice and the 0% arginine/ sodium fluoride 0.24% (1100 ppm F), in a 1:1:1:1 ratio.

10.4 Analysis Populations

Analysis populations for this study are as follows:

- Intent to Treat (ITT): The ITT population will consist of all subjects randomized and dispensed treatment.
- Safety: The Safety population will consist of all randomized subjects who received at least one administration of the study treatment
- Per-Protocol (PP): The PP population will consist of those subjects in the ITT population who completed all study examinations, and who experienced no serious protocol violations.

For the purpose of this determination, serious protocol violations:

1. Subject fails to report for examinations.
2. Subject elects to terminate participation in the study.
3. Sponsor elects to terminate the study.
4. Subject is treated with medications that may affect the parameters under investigation during the study.

All analyses performed on the ITT population will be based on treatments as randomized. Analyses performed on both the Safety and PP populations will be based on treatments actually received. Analyses performed to investigate safety will be performed on the Safety population. Analyses to investigate efficacy will be performed on both the ITT and PP populations; however, the primary efficacy analyses will be those based on the PP population.

10.5 Planned Interim Analyses

No interim analysis is planned for this study.

10.6 Final Analysis Plan

10.6.1 Procedures for Handling Missing, Unused, and Spurious Data

All analyses performed on the Safety and PP populations will be based on data as observed. For the ITT population, multiple imputation methodology will be employed to impute missing values for subjects who have missed visits, or who have dropped out of the study. Multiple imputation will be implemented using baseline subject characteristics to randomly impute each data point five times. The five complete data sets will be analyzed and then combined to incorporate both the estimated within and between data set error terms.

10.6.2 General Statistical Considerations

Data summaries for continuous variables will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

Baseline values for all parameters will be the most recent value prior to the first administration of study treatment.

10.6.3 Analyses for Efficacy

Based on the caries assessments performed on each tooth surface at each examination, subject-wise DMFS and DMFT scores will be calculated.

The primary efficacy endpoint will be the incremental subject-wise DMFS score after one year of product use.

Secondary efficacy endpoints will include:

- Incremental subject-wise DMFS score after 6-months of product use;
- Incremental subject-wise DMFS score between 6-months and one year of product use;
- Incremental subject-wise DMFT scores after 6-months and after one year of product use.
- Clinically significant change in ICDAS severity scores between the baseline and the six-months and one-year examinations and between the six-months and one-

year. Clinically significant changes indicating caries progression are changes in ICDAS severity values from 0 to 2 or higher, from 1 or 2 to 3 or higher, or from 3 or 4 to 5 or 6. Clinically significant changes indicating caries regression are changes in ICDAS severity values from 2 or higher to 0 or 1.

A score summary of all efficacy endpoints will be provided at each assessment time point.

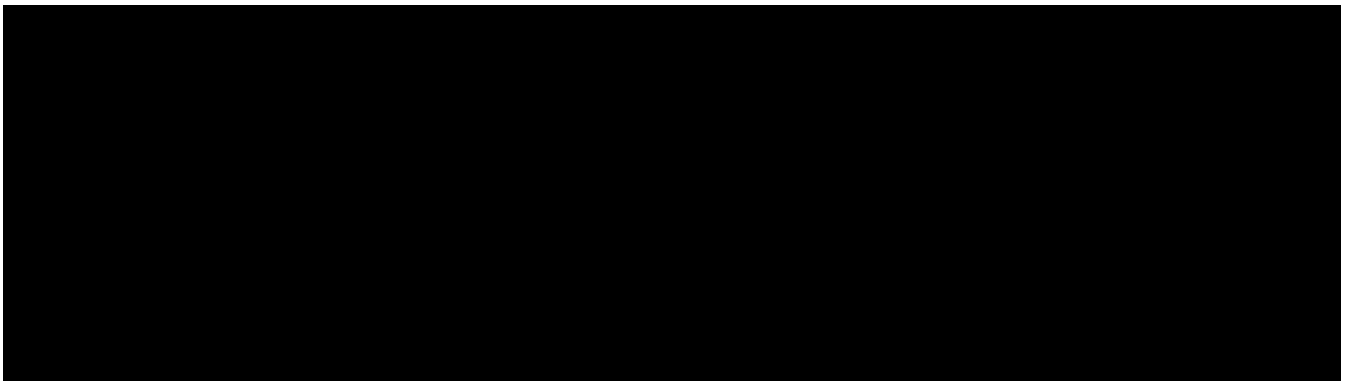
The analysis of the primary endpoint (DMFS increment) will consist of the estimation of the mean and 95% confidence interval for each treatment group. This will allow the sponsor to make an informed decision on the choice of the treatment to pursue in a pivotal study.

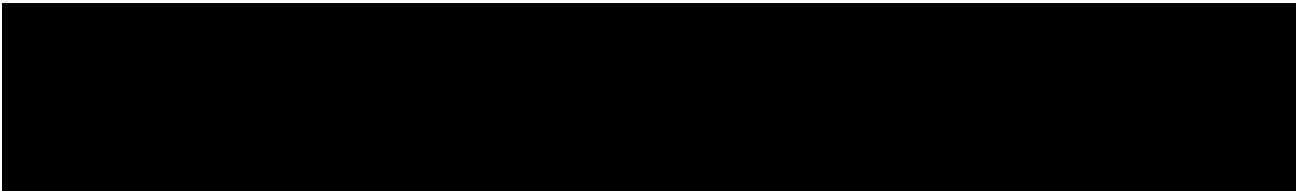
The analyses of the secondary efficacy endpoints will consist of the preparation of descriptive summaries, which will include 95% confidence intervals.

Although the study is not powered to detect differences among the treatment groups, statistical models will still be implemented for the primary and secondary efficacy endpoints. Generalized linear models (GLIM) will be used for all analyses. For analyses of DMFS and DMFT increments, we anticipate that a normal error term will be appropriate. For counts of clinically significant changes, Poisson regression will be the most appropriate GLIM with the number of teeth at risk as the offset. This model is appropriate for analysis of progression or regression although the number of teeth at risk will differ. For changes in activity scores the GLIM will be in the form of a multinomial logistic regression with four categories (0 at both times, 0 to 1, 1 to 0 and 1 at both times) that compares the distributions among the treatment groups. All statistical tests will be performed using a two-tailed 5% significance level. 95% confidence intervals for the differences between treatments will also be calculated based on the models. In addition, the models will yield estimates of the pooled within group variance which can be used for planning further studies.

Analyses as described above will be performed on both the PP population, and the ITT population.

Listings of data will be provided for DMFS scores and for all efficacy endpoints.





10.6.5 Analyses for Safety

A summary of the hard- and soft-tissue findings will be provided, showing the incidence of findings in each treatment group.

Adverse events will be summarized by treatment group.

Data listings will be provided for all adverse event data, and for all soft- and hard-tissue findings.

10.6.6 Modifications to Statistical Methodology

Any modifications made to the analysis methodology described here will be clearly presented and explained in an amendment.

11. ETHICS, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1. Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Study Investigators abide by the principles of the GCP guidelines of the ICH. Also, the study will be carried out in accordance with local legal requirements.

The Study Investigator confirms the above by signing this study protocol.

11.2. Informed Consent/Assent

Before being enrolled in the study, informed consent will be obtained from the parent or legal guardian of each subject and assent will be obtained from the subjects according to the regulatory and legal requirements of the state. The consent and assent forms must be signed and dated and retained by the Study Investigator as part of the study records.

Should a protocol addendum be made, the consent/assent forms may be revised to reflect changes in the protocol.

The Study Investigator will not undertake any investigation specifically required by the protocol until valid consent/assent has been obtained.

11.3. Approval of Study Protocol

Before the start of the study, the study protocol and/or other appropriate documents will be submitted to the IRB and/or the authorities, in accordance with local legal requirements.

The Sponsor and the Study Investigator must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study.

11.4. Amending the Protocol

This protocol is to be followed exactly. Alterations and amendments must be written, receive approval from all persons who approved the original protocol, and receive FDA and IRB approval prior to implementation. Administrative changes (not affecting the patient benefit/risk ratio) may be made by the clinical monitor without any further approvals. All amendments will be distributed to all protocol recipients with instructions to append them to the protocol.

11.5. Confidentiality

All records of subject participation in this study are confidential and these records are available only to the investigator, specifically trained site personnel, supervising dentist/examiner, potentially the Sponsoring Company, Ethics/Institutional Review Board (IRB), the Food and Drug Administration of the United States (FDA) or other local regulatory agency. The results of this study may be published in a scientific journal or a government public clinical database. If any publication occurs, only the subject's study number/ID, gender and/or age may be used. They will agree to verify, by letter, that they participated in this study, if called upon to do so.

In addition, the identity of participating subjects must be protected. Only investigators (and specifically trained clinical site staff) will collect and have access to a subject's private information (e.g., name, medical records, etc.). Investigators will assign a study number to subjects which will be used to conceal their identity on all case report forms and other documents prior to their sharing with the broader study team, including the sponsor. Documents that identify the subject by name (e.g., the signed informed consent form or health questionnaire) will not be transferred or submitted to the sponsor, and will be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate national or local authorities or to sponsor personnel to verify subject, product safety and study compliance.

Parents or legal guardians of participating subjects will be asked to review a participant privacy notice (Appendix I-A) and will be given a copy of the accepted and signed notice.

11.6. Advertising

No newspaper, radio, or television advertising will be used for recruitment purposes. If needed, a flyer may be created to recruit participants. If used, the flyer will be approved by an Institutional Review Board prior to posting or dissemination.

11.7. New Findings

Subjects will be informed of any significant new findings related to study products or procedures when they become known during the course of this clinical research study. Such information may affect the subject's decision to continue participation in the study.

11.8. Publication Policy

Colgate discourages any individual investigator from publishing his/her own results independently. An investigator shall not publish any data (poster, abstract, paper, etc.) without having received permission in advance from Colgate-Palmolive. The above procedure also applies to information on prematurely discontinued and other non-completed studies. Results from the investigator shall not be made available to any third party by the investigating team outside the publication procedure as set out above. Colgate-Palmolive will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

12. REFERENCES

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6. ICCMST™ Guide for Practitioners and Educators, 2014 <https://www.iccms-web.com/uploads/asset/59284654c0a6f822230100.pdf>
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APPENDIX I

SAMPLE PARENTAL/LEGAL GUARDIAN INFORMED CONSENT FORM

PAGE ONE OF SEVEN

PARENTAL/LEGAL GUARDIAN CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

STUDY TITLE: A Phase 2 randomized, double-blind, active-controlled multi-center clinical trial to assess the safety and the anti-caries efficacy of COL 101 (arginine) non-fluoride dentifrices with 1.5%, 4.0% and 8.0% arginine each in comparison with 0.24% sodium fluoride (1100 ppm F) dentifrice control in 10 to 14-year-old children.

STUDY SPONSOR: This clinical study is sponsored by Colgate-Palmolive Company

STUDY INVESTIGATOR:

Name of Investigator _____
ADDRESS _____
_____, USA.

Taking Part in this Study is Voluntary

Your son or daughter is invited to voluntarily participate in a one-year clinical research study.

Before agreeing to your child's participation in this research study, it is important that you read this form. This form, called a consent form, describes the purpose, procedures, benefits, risks and discomforts expected from participation in this research study. It also describes your right to withdraw consent for your child to participate in this research study at any time. No promises or guarantees can be made as to the results of this research study. Please ask as many questions as you want in order to decide whether you want your child be in this research study. This consent form may contain words that you do not understand. Please ask the research study doctor or the research study staff to explain any words or information that you do not clearly understand.

Please review the rest of this document for more details about this study and the things you should know before making a decision about whether to allow your child to participate in this study.

Why is this Study Being Done?

The purpose of the study is to compare the effectiveness in reducing tooth cavities of a commercially available fluoride toothpaste to nonfluoride dental toothpastes containing arginine (a safe and essential amino acid that is naturally found in saliva and produced by the human body).

How Many People Will Take Part?

If you decide to allow your son/daughter to participate, know that he/she will be one of about 2,000 (two thousand) participants in the study. The study will be conducted simultaneously in many sites across the United States and Puerto Rico.

What Will Happen During the Study?

In order to be in this study your child must meet the following criteria.

1. Your son/daughter must be in the age range of 10 to 14 years at the start of the study and in good general health and absent of allergies.
2. The study examiner must find that conditions of your child's teeth and gums are satisfactory for the study and meet other teeth criteria that will be considered.

During your child's initial examination, the study examiner will evaluate your child's teeth and gums. If your child qualifies for the study, he/she will be assigned, using a procedure similar to flipping a coin, to one of four study groups. You, your child or the study examiner will not know to which toothpaste your child will be assigned to use for the one (1) year duration of the study. Every three (3) months, your child will be provided with toothpaste and a new toothbrush and he/she will be expected to return the previously dispensed tubes of toothpaste (no matter if full or empty). During the course of the study your child will be asked to not use any other oral hygiene products; however, there will be no restrictions on diet or restrictions on continued regular treatment and checkups with your child's dentist.

Your child will be examined every three (3) months for one (1) year.

Examination 1 (Screening)

You will be asked to read and sign this consent form and also fill out some other documents about the study. Your child will be provided with an assent form providing him/her with opportunity to choose if he/she wants to participate in the study.

The study examiner will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study examiner will also check his/her teeth to see if there are any cavities.

After this examination, it will be decided if your child can be in this study.

Examination 2 (Baseline)

This examination may take place the same day of the screening examination. A study examiner will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study examiner will also check his/her teeth to see if there are any cavities. Your child will be asked to brush his/her teeth with water before he/she sees the study examiner.

Your child will also be given a short questionnaire for him or her to share how he or she feels about his/her oral health and his/her self-perception about oral function, social and emotional well-being. Similar questions will be asked after six (6) months and after twelve (12) months of assigned product use.

PAGE THREE OF SEVEN

Your child will be given the first supply of toothpaste and a toothbrush to take home. Your child will be instructed to brush his or her teeth twice per day (morning and evening) for two minutes each time, once in the morning and once before going to bed and not to use any other toothpastes or mouth rinses. A timer will also be provided to aid your child with the duration of brushing.

Your child will be asked to return the tubes of toothpaste provided (empty or not) at the next scheduled examination.

If the study examiner finds a cavity you will be notified and you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one.

Examinations after three (3) months of product use

A study examiner will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. He/she will also check your child's teeth to see if there are any cavities.

Your child will be given a re-supply of toothpaste and a new toothbrush to take home. Your child will be instructed to brush twice per day for two minutes each time, once in the morning and once before going to bed and not to use any other toothpastes or mouth rinses. Your child will also be asked to return the tubes of toothpaste provided (empty or not) at the next scheduled examination.

If the study examiner finds a cavity you will be notified and you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one.

Examinations after six (6) months of product use

The study examiner will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study examiner will also check his/her teeth to see if there are any cavities. Your child will be asked to brush his/her teeth with water before he/she sees the study examiner.

Your child will be given a re-supply of toothpaste and a new toothbrush to take home. Your child will be instructed to brush twice per day for two minutes each time, once in the morning and once before going to bed and not to use any other toothpastes or mouth rinses. Your child will also be asked to return the tubes of toothpaste provided (empty or not) at the next scheduled examination.

If the study examiner finds a cavity you will be notified and you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one.

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Examinations after nine (9) months of product use

A study examiner will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. He/she will also check your child's teeth to see if there are any cavities.

Your child will be given a re-supply of toothpaste and a new toothbrush to take home. Your child will be instructed to brush twice per day for two minutes each time, once in the morning and once before going to bed and not to use any other toothpastes or mouth rinses. Your child will also be asked to return the tubes of toothpaste provided (empty or not) at the next scheduled examination.

If, at any of these examinations, the examiner finds a cavity you will be notified and you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one.

Examinations after twelve (12) months of product use

The study examiner will look at your child's gums, lips, cheeks, tongue and all other areas inside of his/her mouth. The study examiner will also check his/her teeth to see if there are any cavities. Your child will be asked to brush his/her teeth with water before he/she sees the study examiner.

If the study examiner finds a cavity you will be notified and you will be asked to bring your child to his/her regular dentist or if your child does not have a dentist you will be referred to one.

After this examination, your child will be finished with the study.

What are the Risks of Taking Part in the Study?

The risk of your child getting a cavity is reduced by participating in this study because your child will receive an exam of their teeth and gums every (3) months and by the fact that the study progress will be closely monitored by an independent committee known as a Data Safety Monitoring Board.

The risks associated with minor and rare irritations from dental examinations will be minimized by having trained and licensed oral care professionals conduct the oral examination, following standard clinical procedures.

There is a risk of possible loss of confidentiality while maintaining all research observations and data.

Any significant findings will be communicated to you and, when necessary, will include a referral to a dentist or a note to his/her dentist. If your child experiences any problems, you should contact Dr. _____ at 24-hour phone number _____.

What are the Potential Benefits of Taking Part in the Study?

It is expected that your child will receive a direct dental benefit from participation in this study. Although it cannot be guaranteed for every child, a cavity reduction benefit is expected from all toothpastes in the study. Your child's teeth and gums will be monitored by examinations every three (3) months. Any significant findings will be communicated to you and, if necessary, will include a referral to a dentist or a note to his/her dentist. Participation in this clinical study does not replace the need for your son or daughter to visit his or her dentist on a regular basis. The results of this study may help the sponsor improve the product and help dental professionals provide proper advice to their patients.

How will your Child's Information be Protected?

Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information may be disclosed if required by law. No information which could identify your child will be shared in publications about this study.

Organizations that may inspect and/or copy your child's research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, NAME OF IRB, Colgate Palmolive], and any state or federal agencies who may need to access your medical and/or research records (as allowed by law).

Will my Child's Information be used for Research in the Future?

Information collected from your child for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify your child will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

Will there be a Cost to Participate?

There is no cost to you or your child for the oral examinations and the use of toothpaste, toothbrush or any other study related product. Your child may receive an incentive for participation in the clinical study consisting of _____ (SITE TO DETERMINE IF APPLICABLE, ETC).

Who will Pay for my Child's Treatment if he/she gets Injured?

In the event of physical injury resulting from your child's participation in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your child's health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

Who Should I call with Questions of Problems?

For questions about the study or a research-related injury contact the study investigator, Dr. _____ at 24-hour phone number _____.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about the study, or to obtain information or to offer input, please contact the IRB _____ at phone number _____.

Can my Child Withdraw from the Study?

Your child's participation is voluntary, and you may refuse to participate and/or withdraw your child at any time without penalty or loss of benefits to which your child would otherwise be entitled up to the point of withdrawal. Your child's study dentist has the right to withdraw your child from the study at any time if he or she feels that it is in your child's best interest or if your child fails to comply with the terms of the study.

Your child's participation may be terminated by the investigator without regard to your consent in circumstances when the investigator feels it may not be beneficial to your child.

You will be told about new information that may affect your child's health, welfare, or willingness to stay in the study.

Study Sponsor

This clinical research study is sponsored by the Colgate-Palmolive Company. Study Site _____ will receive financial support and material for this study. The study staff and Investigators have no financial interest in the Colgate-Palmolive Company.

Informed Consent Statement

I have read the contents of the consent form and have listened to the verbal explanation given by the investigator. My questions concerning this study have been answered to my satisfaction. I hereby give voluntary consent for my child to participate in this study. Signing this consent document does not waive my child's rights nor does it release the investigators, institution, or sponsors from their responsibilities.

PAGE SEVEN OF SEVEN

I voluntarily agree for my child to participate in this study. I understand that I will be been given a copy of this consent form after signing it.

CHILD'S NAME _____

Signature of Parent or Legal Guardian

Print Name of Parent or Legal Guardian

Date

I attest that the requirements for informed consent from the research project described in this form have been satisfied, that I have discussed the research project with the participant's parent or legal guardian and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Signature of Person Obtaining Consent

Printed Name of Person Obtaining Consent

Date: _____

APPENDIX I-A SPONSOR'S PRIVACY NOTICE

PAGE ONE OF TWO

In addition to the informed consent that explains the clinical study in which your child may participate in, this authorization gives you additional detailed information about how your child's health information will be protected. By signing this document you are allowing Colgate Palmolive Co. to disclose personal health information to outside organizations or people involved with the processing of this study.

What personal health information is collected and used in this study and might be shared?

1. name, address and telephone number
2. medical history
3. current medications
4. procedures performed in this study such as: Oral health exams

Why is your personal information being used?

So the research team may contact you during the study. Your child's health information is used to ensure your child's safety while selecting subjects for the study. Results and data are collected for the advancement of medicine, dentistry and clinical care.

Which of our personnel may use or disclose your child's personal health information?

The following individuals and organizations may use or disclose your child's personal health information for this research project:

1. The principal investigator and associated research team
2. The Institutional Review Board
3. Safety and Regulatory departments at Colgate Palmolive Co.
4. Authorized members of the clinical site who may need your information in the performance of their duties associated with this research (i.e. to provide treatment, ensure integrity of the research, accounting, scheduling etc.)
5. The Data and Safety Monitoring Board

Who outside Colgate Palmolive Co. or the Principal Investigator might receive your child's personal health information?

1. Institutional Review Board
2. Food and Drug Administration (your child will be identified only by his/her first name and last initial)
3. The Data and Safety Monitoring Board

How long will Colgate or the Clinical Site be able to use or disclose your child's personal health information?

Your authorization for this specific study does not expire however the information may not be re-used or re-disclosed for another purpose other than the research described in this document unless you give written permission to do so. The Institutional Review Board may grant permission to the Principal Investigator or others to use your child's information for another purpose after ensuring that appropriate privacy safeguards are in place. The Institutional Review Board is a committee whose job it is to protect the safety and privacy of research subjects. Results of tests and procedures are done solely for this research study and will not be included in your child's dental record.

APPENDIX I-A SPONSOR'S PRIVACY NOTICE

PAGE TWO OF TWO

Will you be able to access your child's records?

You will be able to access your child's dental record when the study is completed. During the study you will not have access to prevent knowledge of study results from affecting the reliability of the study. Should an emergency or need for care arise that would require your child's treating physician or dentist to know this information the records would be provided.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your child's personal information for research but you must do so in writing to the Study Investigator at the address provided in your parental informed consent. Even if you withdraw your permission, the Study Investigator may still use your child's personal information that was collected prior to your written request if that information is necessary to the study. If you withdraw your permission to use your child's personal health information that means your child will also be withdrawn from the research study.

By signing this document you are permitting Colgate Palmolive Co or the Clinical Site to use and disclose personal health information collected about your child for research purposed as described above.

CHILD'S NAME _____

Signature of Parent or Legal Guardian

Print Name of Parent or Legal Guardian

Date

Signature of Person Obtaining Authorization

Printed Name of Person Obtaining Authorization

Date: _____

APPENDIX II

SAMPLE ASSENT FORM

PAGE ONE OF THREE

Dear Child:

You are invited to join in a research study that is described below:

WHAT IS THIS STUDY ABOUT?

We would like to find out if new toothpastes can prevent cavities as well as a fluoride toothpaste. If you qualify for the study and you agree to participate in the study, you will be assigned to one of four (4) study groups. The toothpaste to be assigned to you will be determined using a procedure similar to flipping a coin. You will not know what toothpaste you will be assigned to use. During the study, which will last one (1) year, you will be asked to brush your teeth with the toothpaste assigned to you and not use any other toothpastes or mouth rinses; however, you should continue with treatment and checkups with your regular dentist.

If you decide to participate, you will be one of about 2,000 (two thousand) other children participating in the study.

WHAT WILL HAPPEN TO ME IN THIS STUDY?

If you decide that you want to be in this study, you will be examined by the study examiner six (6) times in the one (1) year-long study. Here is what will happen at each of these examinations:

First Examination (Screening)

You will be asked to read and sign this form and also fill out some other documents about the study. Your parents will also need to sign a permission form.

A study examiner will look at your lips, cheeks, tongue and all other areas inside of your mouth. The examiner will also check your teeth to see if you have any cavities.

After this examination, the study examiner will decide if you can be in this study.

Second Examination (Baseline)

This second examination may happen the same day as the first examination. You may be asked to brush your teeth with water before you have this more detailed second examination. If the study examiner wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

If the study examiner decides that you will be in the study, you will be given a toothbrush and the toothpaste assigned to you. You will be asked to brush your teeth for two (2) minutes, two (2) times a day, once in the morning and once before going to bed. You will be asked not to use any other toothpastes or mouth rinses.

PAGE TWO OF THREE

You will be asked to return the tubes of toothpaste provided (empty or not) at your next scheduled examination.

If the study examiner finds a cavity, you will be asked to see your regular dentist or if you don't have one, the study dentist will recommend one.

Examinations three (3), four (4), five (5) and six (6)

You will be examined again every three (3) months after you start brushing with the toothpaste and the toothbrush that you will be given. During these examinations, the study examiner will look at your lips, cheeks, tongue and all other areas inside of your mouth. The study examiner will check your teeth to see if you have any cavities. Sometimes you may be asked to brush your teeth with water before you see the study examiner. If the study examiner wants to get a better look at your teeth, he/she might need to brush (and maybe floss) them again for you.

You will be asked to return the tubes of toothpaste provided (empty or not) at your next scheduled examination.

If the study examiner finds a cavity, you will be asked to see your regular dentist or if you don't have one, the study dentist will recommend one.

CAN ANYTHING BAD HAPPEN TO ME IN THIS STUDY?

We will try to be as careful as we can during the examinations but there is a chance that something could happen such as getting a sore spot in your mouth.

WHAT IS GOOD ABOUT BEING IN THIS STUDY?

You may have a cavity reduction from the toothpaste you use in the study. Your mouth and teeth will be checked every three (3) months. You will be told if you have any problems in your mouth and you may be asked to see your dentist. The results of this study may help the company paying for the study to improve their toothpaste products and help dentists provide proper advice to their patients.

WHAT DO I HAVE TO TELL THE STUDY EXAMINER ABOUT?

If you choose to join this study, the study examiner may ask you questions about your health and medicines that you may be taking. We ask that you tell the study examiner about your health and answer any questions the best you can.

You also need to tell your parents or guardian and the study examiner if you do not feel well after your examinations.

DO I HAVE TO BE IN THIS STUDY?

You do not have to be in this research study if you do not want to. You can say "yes" or you can say "no". You can stop later if you change your mind. No one will be angry with you if you say "no". Your regular doctor and dentist will still take care of you.

WHO CAN I TALK TO ABOUT THE STUDY?

You can ask questions about the study at any time. If you feel sick, you or your mom or dad can call the study examiner.

PAGE THREE OF THREE

DO YOU WANT TO PARTICIPATE?

- ☐ Yes, I will be in this study.
- ☐ No, I do not want to do this.

If you have any questions about the study, you may ask the dental team at any time. Your parent/guardian will be given a copy of the consent letter that has telephone numbers of people to call when you have questions. If you want to be in this study, read the next paragraph and sign and date in the space below.

Sincerely,

XXXX,
Study Investigator (person in charge)

I agree to participate in this research study. I may decide to stop at any time without hurting my chances of being in future dental studies.

Child's Name (Please Print)

Child's Signature

Date

Signature of Study Personnel Obtaining Assent

Date

APENDIX III

FORMULATIONS

CONTROL DENTIFRICE

This product is a commercially-available dentifrice of the Colgate-Palmolive Company under the commercial name Colgate Ultra Brite Anti-cavity Fluoride Toothpaste which is in compliance with the OTC Anti-caries Drug Monograph. It contains 0.24% sodium fluoride (1100 ppm F) in a silica base.

TEST DENTIFRICE 1

[1.5% Arginine in a calcium base]

This is a dentifrice containing 1.5% arginine in a calcium base.

TEST DENTIFRICE 2

[4.0% Arginine in a calcium base]

This is a dentifrice containing 4.0% arginine in a calcium base.

TEST DENTIFRICE 3

[8.0% Arginine in a calcium base]

This is a dentifrice containing 8.0% arginine in a calcium base.

APPENDIX IV

PRODUCT LABEL INFORMATION

Caution: New Drug - Limited by Federal (or United States) law to investigational use. Not for sale.

Protocol Number: CRO-2020-CAR-ARG-ED

Product Code_____ Subject #_____

Brush your teeth twice daily (morning and evening) for two minutes each time. Apply a full ribbon of toothpaste on the toothbrush head. Use only the toothpaste and toothbrush provided.

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study

For study-related questions call:

Dr. _____ at phone number (____) ____ - ____.

In case of emergency call:

Dr. _____ at phone number (____) ____ - ____.

APPENDIX V

PRODUCT USE INSTRUCTIONS

Important Product Information

Colgate Palmolive Sponsored Clinical Study (Protocol Number: *CRO-2020-CAR-ARG-ED*)

Caution:

For Investigational Use Only. Not for sale.

- **Brush your teeth twice daily in the morning and in the evening before bed**
- **Brush for two minutes each time. Use the timer as aid.**
- **Apply a full ribbon of toothpaste on the toothbrush head just like it was demonstrated at the beginning of the study.**
- **Use only the toothpaste and toothbrush provided.**
- **The study products are only for your use.**

Return all tubes of toothpaste to the study site at the time of your next examination.

For investigational use only by participants in the study

For study-related questions call:

Dr. _____ at phone number (____) ____-____.

In case of emergency call:

Dr. _____ at phone number (____) ____-____.

APPENDIX VI

CONFORMANCE WITH ENTRY CRITERIA (SCREENING FORM)

Subject's initials _____ Subject # _____ Date _____

1. Is subject in good health? (At Investigator's discretion upon review of medical history)	Yes	No
2. Is the subject at least 10 years old to no older than 14 years old at the time of recruitment?	Yes	No
3. Is the child willing and able to use the assigned products according to instructions, available for all appointments and likely to complete the study?	Yes	No
4. Has the parental/ legal guardian provided informed consent for voluntary participation of the child and has the child provided written assent?	Yes	No
5. Does the subject have erupted permanent second molars or there is evidence of at least One permanent second molar erupting as indicated by cuspal break through the mucosa?	Yes	No
6. Does the subject have, at study entry, two or more active caries lesions (ICDAS scores of 2 or greater in permanent teeth and with a previous caries experience (DMFT >1).	Yes	No

If any answer to any questions 1-4 is No, subject is ineligible for study. Dismiss subject and complete question 16 below. If subject is eligible continue to questions 7-16.

7. Is subject is undergoing orthodontic treatment, wears intraoral appliance?	Yes	No
8. Does subject use medications that could increase the risk of development of soft tissue irritations?	Yes	No
9. Is the subject taking long-term antibiotic therapy or have a condition which would require antibiotic prior to a dental procedure?	Yes	No
10. Does the child have cognitive and/or motor impairment?	Yes	No
11. Does subject have severe malocclusion?	Yes	No
12. Presence, at study entry, of severe caries (ICDAS 5 or 6) on five or more teeth?	Yes	No
13. Evidence of moderate to severe periodontal disease?	Yes	No
14. Participating in any other clinical study within 30 days preceding the start of the clinical study?	Yes	No
15. History of allergies or other adverse reactions to arginine or oral care products, or their ingredients?	Yes	No
16. IS SUBJECT ELIGIBLE FOR ENTRY INTO STUDY?	Yes	No

Signature of Study Investigator

Date

APPENDIX VII

SAMPLE HEALTH QUESTIONNAIRE

Name: _____ Today's date: _____

Date of Birth: _____

Name of Physician: _____ Phone#: _____

Date of last visit: _____

Emergency contact? Name: _____

Phone #: _____

Your current physical health is: __ Good ____ Fair ____ Poor

Have you ever had any serious operations? [] Yes [] No

If yes, please explain: _____

Are you currently under the care of a physician? [] Yes [] No

If yes, please explain: _____

Please CIRCLE if you have been treated for or told that you have:

Abnormal bleeding	Anemia	Blood Disorders	Blood transfusion
Hemophilia	AIDS	Arthritis	Asthma or Hay fever
Cancer/Tumor	Chemo/Radiation therapy	Kidney/Liver disease	
Ulcers/Colitis	Diabetes or abnormal blood sugar	Glaucoma	
Hepatitis /Jaundice	Emphysema	Difficulty breathing/Lung problems	
Hearth problems	High/Low blood pressure	Rheumatic fever	
Drug addiction	Epilepsy/Seizures	Skin problems	

Please describe any of the above conditions:

Do you have a history of allergies to whitening oral care products, personal care consumer products, or their ingredients?

If yes, please fill explain: _____

Do you take any medications? If yes, please fill out following:

List any prescription or over the counter medications which you are taking:

Name of Medication	Start Date	End Date	Amount taken	How often	Reason

DENTAL HISTORY

Name of your dentist: _____ Phone#: _____

How often do you visit your Dentist? _____

Date of last visit: _____

I understand that the information that I have given today is correct to the best of my knowledge. I also understand that this information will be held in the strictest of confidence, and it is my responsibility to inform this office of any changes in my medical status. I understand that my participation on this study is voluntary and that I can drop from the study at any time.

Signature

Date

APPENDIX VIII

ORAL SOFT AND HARD TISSUE ASSESSMENT FORM

SUBJECT'S INITIALS _____

SUBJECT NUMBER _____ DATE _____

Examination Period:

<u>AREA</u>	<u>NORMAL</u>
1. Soft Palate	YES _____ NO _____
2. Hard Palate	YES _____ NO _____
3. Gingival Mucosa	YES _____ NO _____
4. Buccal Mucosa	YES _____ NO _____
5. Mucogingival Folds	YES _____ NO _____
6. Tongue	YES _____ NO _____
7. Sublingual and submandibular areas	YES _____ NO _____
8. Salivary glands	YES _____ NO _____
9. Tonsillar and pharyngeal areas	YES _____ NO _____

If answer to any of questions 1-9 is "NO", please explain.

Signature, Examiner

Date

APPENDIX IX
VISIT FORM (CONTINUANCE)

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

Examination Period:

1. Were there any unexpected or serious reactions since the previous examination? YES NO

If yes, describe _____

2. Was any treatment prescribed for above? YES NO

If yes, describe _____

3. Was any dental treatment received since previous examination? YES NO

If yes, describe _____

4. Is the subject still in compliance with applicable inclusion/exclusion criteria? YES NO

If no, describe _____

5. Do any of the responses to Questions 1-4 warrant exclusion of this subject's data from the statistical analysis? YES NO

If yes, explain _____

6. Will the subject continue participation / Did subject complete the study? YES NO

Signature, Examiner

Date

APPENDIX X

SAMPLE ICDAS EXAMINATION FORM

SUBJECT NUMBER _____ SUBJECT'S INITIALS _____ DATE _____

UPPER TEETH																					
	2			3			4			5			6			7			8		
Tooth #	Condi.			Condi.			Condi.			Condi.			Condi.			Condi.			Condi.		
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
V																					
P																					

	9			10			11			12			13			14			15		
Tooth #	Condi.			Condi.			Condi.			Condi.			Condi.			Condi.			Condi.		
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
V																					
P																					

LOWER TEETH																					
	18			19			20			21			22			23			24		
Tooth #	Condi.			Condi.			Condi.			Condi.			Condi.			Condi.			Condi.		
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
V																					
L																					

	25			26			27			28			29			30			31		
Tooth #	Condi.			Condi.			Condi.			Condi.			Condi.			Condi.			Condi.		
SURFACE	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act	Con	Car	Act
O																					
M																					
D																					
V																					
L																					

Calculations				
ICDAS Mean:				
DT	MT	FT	DMF-T	Total T
DS	MS	FS	DMF-S	Total S

Classification of the restoration, sealant, or missing status in the ICDAS (Ismail et al., 2007)

- 0 = Unrestored or unsealed
- 1 = Sealant, partial
- 2 = Sealant, full
- 3 = Tooth colored restoration
- 4 = Amalgam restoration
- 5 = Stainless steel crown
- 6 = Porcelain or gold or PFM crown or veneer
- 7 = Lost or broken restoration
- 8 = Temporary restoration
- 9 = Tooth does not exist or other special cases.

Used in as the following:

- 9–6 = Tooth surface cannot be examined because of access problem to visualize the tooth surface
- 9–7 = Tooth missing because of caries (all tooth surfaces are coded 97)
- 9–8 = Tooth missing for reasons other than caries (all tooth surfaces are coded 98)
- 9–9 = Un-erupted (all tooth surfaces care coded 99)

Caries Lesion Activity Assessment (ICCMS Guide):

Code 0 Signs of Inactive Lesions

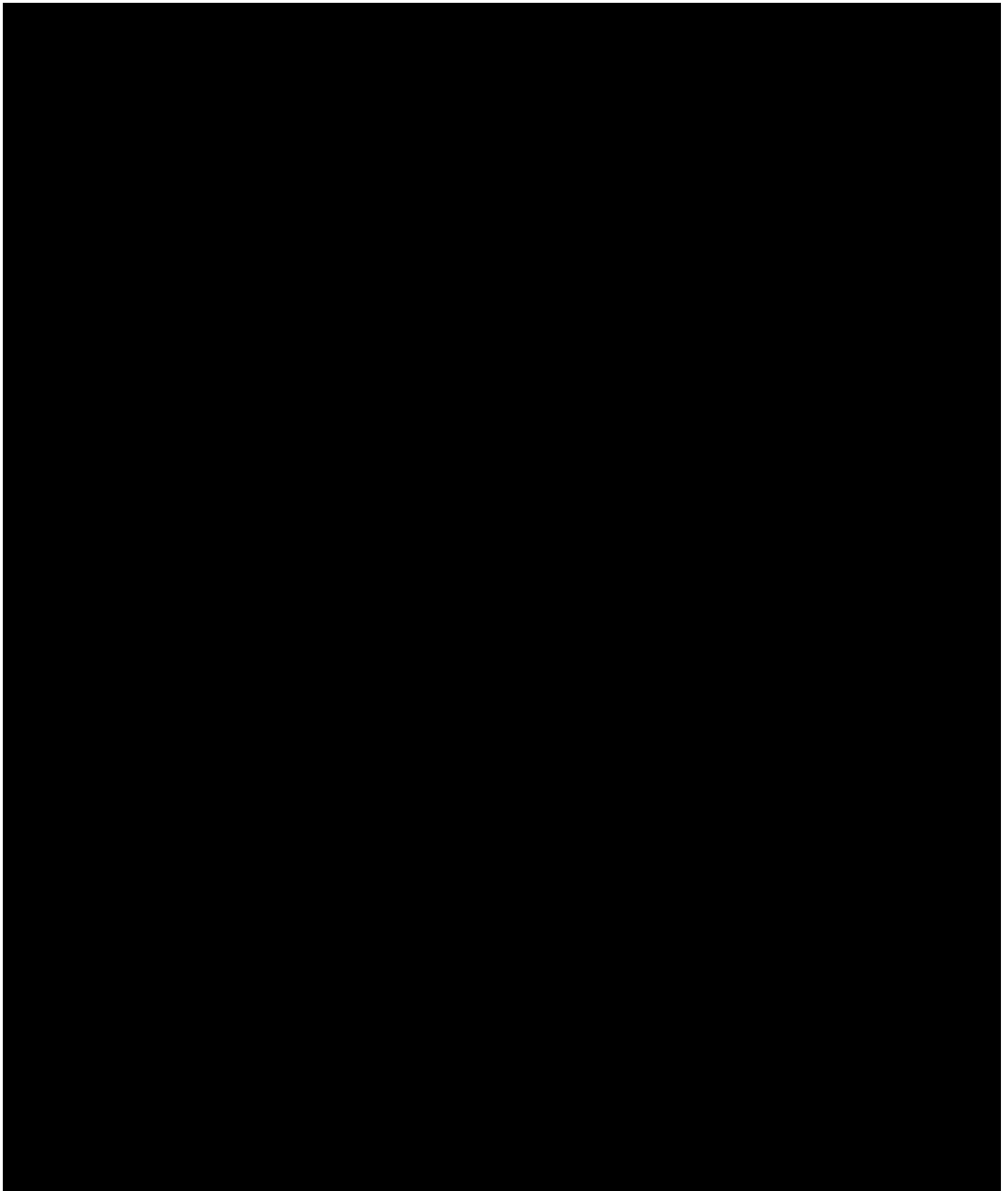
For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish, brownish or black. Enamel may be shiny and feels hard and smooth when the ball-ended probe is moved gently across the surface. For smooth surfaces, the caries lesion is typically located at some distance from the gingival margin. Lesion may not be covered by thick plaque prior to cleaning.

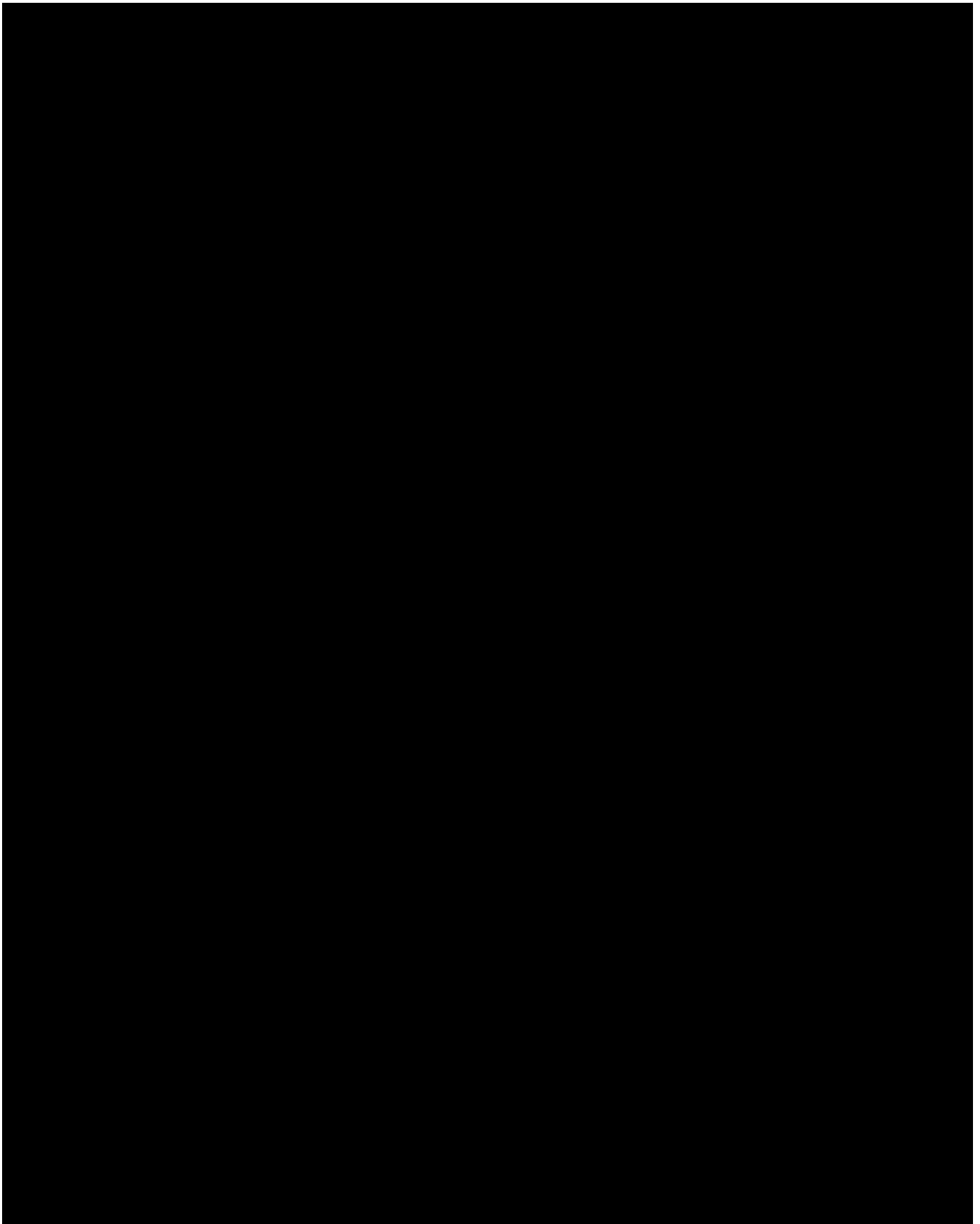
For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin is shiny and hard on gentle probing.

Code 1 Signs of Active Lesions

For Initial (ICDAS Codes 1 and 2) and Moderate Caries Stage (ICDAS Codes 3 and 4) - Surface of enamel is whitish/yellowish opaque; with loss of luster; feels rough when the tip of the ball-ended probe is moved gently across the surface. Lesion is in a plaque stagnation area, i.e. in the entrance of pits and fissures, near the gingival margin or, for proximal surfaces, below or above the contact point. The lesion may be covered by thick plaque prior to cleaning.

For Extensive Caries Stage (ICDAS Codes 5 and 6) – Dentin feels soft or leathery on gentle probing.





APPENDIX XIII **REPORT OF ADVERSE EVENT**

Instructions: Refer to the General Instructions & Supplemental Guidance pages for specific details on completing sections of the form. Additional pages may be added, if necessary, to report all information.

Awareness date – Colgate-Palmolive:	Awareness Date- Investigator:
1) Study Information	
Protocol #:	Centre Name:
Study Title:	Investigator:
Indication /Objective of Protocol:	Address:
Study Type: ☐ Clinical Trial (Interventional) ☐ Consumer ☐ Panel ☐ Phase II Clinical Trial ☐ Other Clinical ☐ Other Specify	Tel.: Fax:
Study Originator/Monitor:	Email:
Contact #	Health Care Professional : ☐ Yes ☐ No Specify occupation:

2) Subject Information			
Subject's ID #: Initials:	Gender ☒ Male ☒ Female	Age/(Age Group): _____ Or Date of Birth: _____ - -	Weight _____ ☒ LB ☒ KG
If subject is pregnant, how many months?			

3) Reporter Information (Complete only if different from Investigator named above)	
Sender/Reporter Name:	
Address	Country:
Email:	Telephone: Fax:
☐ Healthcare Professional Specify occupation:	☐ Non-Healthcare Professional

4) Phase of study the earliest event (s) occurred during:

☐ After consent ☐ Pre-randomization ☐ Randomization: no product ☐ Randomization: product exposure
☐ Baseline ☐ 3-Month ☐ 6-Month ☐ 9-Month ☐ 12-Month ☐ Other:

5) Study products (Please indicate if Test product, Blinded Product, Comparator (control product) was used by subject)

Product Name	Lot No/ Batch No/ Serial No (If MOCD)	Route of administration	Dosage & Frequency	Start Date (DD-MMM-YYYY)	Stop Date (DD-MMM-YYYY)	Action taken with Product
				- -	- -	
				- -	- -	
				- -	- -	
				- -	- -	

6) Adverse Event/Reaction Information

Adverse Events (AEs)	Start Date of AEs (DD-MMM-YYYY)	Stop Date of AEs (DD-MMM-YYYY)	Seriousness Criteria	Causality	Outcome
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	
	- -	- -	Choose an item.	☐ Related ☐ Unrelated ☐ Unable to assess	

Death (dd/mm/yyyy):	Autopsy: ☐ YES ☐ NO ☐ Unknown
Cause of death if known:	Outcome:
	☐ Related ☐ Unrelated ☐ Unable to assess

Describe event (s)/reactions(s) in detail:

Protocol status of subject:		
☐ Subject continued in protocol ☐ Unrelated	☐ Subject discontinued from protocol ☐ Unrelated	
Was the subject treated for the event(s)/reaction(s) (Medical Intervention)? ☐ YES ☐ No If yes, please specify or describe:		
Event/Reaction abated after study product(s) stopped or dose reduced?		
☐ YES	☐ NO	☐ N.A.
Event/Reaction reappeared after study product(s) reintroduced?		
☐ YES	☐ NO	☐ N.A.

7) Subject Medical History : ☐ None ☐ Unknown <i>(Provide the medical history including pre-existing medical conditions)</i>

8) Other Medications/ Products used simultaneously: ☐ None ☐ Unknown					
Other Medications/ Products	Start Date (DD-MMM- YYYY)	Stop Date (DD-MMM- YYYY)	Indication	Dosage & Frequency	Route of administration
	- -	- -			
	- -	- -			
	- -	- -			

	-	-	-	-			

9) Laboratory data & other test procedure(s) relevant to the AE/AER(s)

Test	Date (dd/mmm/yy)	Result (Specific value, normal, abnormal, clinically significant)

Investigator/Designee Signature:	Date (dd/mmm/yyyy):

APPENDIX XIV: Periodic/End of Study Report Form for Non-interventional Studies on Humans (Colgate-Palmolive 105362)

Section A: Study Information	
Study Title:	Study Type: Clinical ☐ Phase II ☐ Consumer ☐ Panel ☐ Other ☐ Specify if selecting Other:
Protocol #:	Ref #:
Indication/Objective of Protocol:	
Primary Study Product/PDM#:	
Study Start Date (dd/MMM/yyyy):	State where study was conducted:
Investigator Name:	Study Originator Name:

Investigator/ Designee Signature: _____ Date dd/mmm/yyyy: _____

Section B: Report Type

Check applicable report type

☐ Periodic Report

☐ End of Study report

Were any adverse events/reactions reported during the study? If 'Yes' is checked, please complete section C

☐ Yes ☐ No

Section C: Adverse Event/Reaction Information

Protocol #:

Investigator Name:

Complete the table below *only* if an adverse event/reaction was reported during the study.

Case ID No.	Study Site Aware Date	Subject Information			Study Product Information			Adverse Events/Reactions			Other Products Used	Outcome with Date	Comments
		ID No.	Age/Date of Birth	Gender	Product Name	Dose & Frequency	Duration of Use	Description	Causality	Serious (Yes/No)			

Note: If needed attach additional pages of Section C to document all events/reactions reported during the study.

APPENDIX XV
SAMPLE CLINICAL PRODUCTS RETURN LOG SHEET

Organization _____

Principal Investigator _____

Date	Subject #	Product Code	1)Tube Before Use (Weight_g)	2)Tube After Use (Weight_g)	Weight Difference 1) – 2)

Print Name of Person Weighing Products

[Signature][Date]