CONFIDENTIAL

PROTOCOL NUMBER: C3J16-S205-00

PROTOCOL TITLE: A Phase 2, Single-blind, Randomized, Placebo-controlled Study to Evaluate the Microbiology, Safety and Tolerability of C16G2 Strip Administered in Multiple Doses to Adolescent and Adult Dental Subjects

STUDY DRUG: C16G2

DOSAGE FORM: C16G2 Strip

IND NUMBER: IND# 112,547

SPONSOR:
C3 Jian, LLC
4503 Glencoe Avenue
Marina del Rey, California 90292
Contact: Siegfried Rogy, PhD
Office: (310) 665-2928 X 232;
Mobile: (818) 618-5774

MEDICAL MONITOR:
Marilyn R. Carlson, DMD, MD, RAC
Agility Clinical, Inc.
6005 Hidden Valley Road
Carlsbad, CA 92011
Mobile: (858) 945-7189

DATE: January 25, 2017

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PROTOCOL SIGNATURE SHEET

The undersigned have reviewed the format and content of this protocol and have approved Protocol No. C3J16-S205-00 for issuance:

Marilyn R. Carlson, DMD, MD, RAC
Medical Monitor

25 Jan 2017
Date

Siegfried Rogy, PhD
Sr. Director of Clinical Operations

26 JAN 2017
Date

Brian C. Varnum, PhD
Chief Development Officer

27 Jan 2017
Date

INVESTIGATOR SIGNATURE SHEET

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and the Investigator's Brochure on the study drug, which was furnished to me by the Sponsor, to members of the study team responsible to me who participate in the study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB), I will not modify this protocol without obtaining prior approval from the Sponsor and the IRB. I will submit the protocol modifications and/or any Informed Consent Form (ICF) and assent modifications to the Sponsor and the IRB, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the Code of Federal Regulations, the principles of Good Clinical Practice (current International Conference of Harmonization [ICH] guidelines), and the Declaration of Helsinki (1964) including all amendments up to and including the Fortaleza, Brazil revision (2013).

_____ _____

Investigator's Signature Date

_____ _____

Investigator's Name and Title (print) Date

PROTOCOL SYNOPSIS FOR C3J16-S205-00

Protocol Number:	C3J16-S205-00
Protocol Title:	A Phase 2, Single-blind, Randomized, Placebo-controlled Study to Evaluate the Microbiology, Safety and Tolerability of C16G2 Strip Administered in Multiple Doses to Adolescent and Adult Dental Subjects
Study Design:	A single-blind, randomized, placebo-controlled, phase 2 study to evaluate oral microbiology and safety of multiple C16G2 Strip applications in male and female dental subjects 12-75 years of age. The study will compare multiple study drug administrations of 9.2 mg, 18.4 mg, and 36.8 mg C16G2 Strip or Placebo in Study Arms 1 through 3, respectively. Enrollment of subjects in Study Arms 1 through 3 will occur sequentially in an ascending dose-escalation manner. Before dosing of study drug, eligible subjects will receive professional dental prophylaxis between Days -7 and -2. Subjects will receive 11 doses administered over approximately two weeks. Each subject will receive a single dose on Day 0, followed by 5 days of AM and PM dosing starting on Day 7. To evaluate the durability of *S. mutans* suppression, study subjects will be followed for microbiology for up to 1 month after the last study drug administration. Clinic visits include Visit 1 (Screening/Days -30 to -1), Visit 2 (Prophylaxis/Day -7 to -2), Eligibility Confirmation & Baseline Visit 3, Follow-up Visits 4-7 (Safety and Microbiology), Visits 8-17 (Study Drug Administration), Follow-up Visits 18-20 (Safety and Microbiology) and Follow-up Visits 21-22 (Microbiology only). Subjects enrolled in all study arms will be assessed for safety and microbiology parameters. For details on study schedules including dosing and microbiology information refer to Appendix A. Details on study assessments & procedures for all study arms are provided in Appendix B. For microbiology assessments in all study arms refer to Appendix C.
Objectives:	Primary Objectives • To assess the targeted antimicrobial activity of C16G2 Strip administration as measured by a reduction in *Streptococcus mutans* in saliva and dental plaque • To assess total bacteria in saliva and dental plaque post study drug administration Secondary Objective • To evaluate the safety and tolerability of multiple C16G2 Strip administrations in adolescent and adult dental subjects
Subject Population:	Approximately 30 male and female subjects 12-75 years of age, inclusive at the time the Informed Consent Form or Assent is signed.

<table>
<tr><td>Duration of Study:</td><td>Estimated duration of study from first subject in (FSI) to last subject out (LSO) is approximately 3.5 months. The maximum subject's duration of participation will be 2.5 months.</td></tr>
<tr><td>Study Arms / Treatment / Randomization</td><td>The study will enroll subjects into three study arms. Approximately 30 subjects will receive three doses of study drug (9.2 mg, 18.4 mg, 36.8 mg C16G2 Strip or Placebo), for details see Table below. Subjects who do not return for assessments after study drug administration for any reason may be replaced at the Sponsor's discretion.

Study subjects will be randomized to receive C16G2 or Placebo Strip, in a 4:1 allocation ratio (8 C16G2 Strip subjects: 2 Placebo Strip subjects) for each of the three study arms. Subjects will be enrolled into one of the three study arms and the arms will enroll sequentially. Each study arm will be fully enrolled (i.e., the last subject in an arm has completed Visit 3) before enrollment is initiated in the next study arm.

After confirmation of study eligibility, subjects will be randomized at Visit 3 (Day 0) by authorized study staff according to the master randomization schedule from the Sponsor's study statistician. The randomization schedule and associated documentation will be kept in a secure location.

C3J16-S205-00 Study Drug Schedule
<table>
<tr><th></th><th>C16G2 Subjects</th><th>Placebo Subjects</th><th>Mode of Application</th><th>Days of Study Drug Admin.</th><th>C16G2 milligram (mg)</th></tr>
<tr><td>Study Arm 1</td><td>8</td><td>2</td><td>Strip</td><td>1</td><td>9.2</td></tr>
<tr><td>Study Arm 2</td><td>8</td><td>2</td><td>Strip</td><td>1</td><td>18.4</td></tr>
<tr><td>Study Arm 3</td><td>8</td><td>2</td><td>Strip</td><td>1</td><td>36.8</td></tr>
</table></td></tr>
<tr><td>Blinding/Unblinding</td><td>The study will be conducted in a single-blind, placebo-controlled manner. All study subjects will be blinded to the treatment assignment, while the Investigator, study staff/clinicians and the Sponsor's assigned team members (e.g., the Clinical Monitor and the Medical Monitor) will be unblinded as to whether subjects are receiving C16G2 or Placebo.</td></tr>
<tr><td>Microbiology:</td><td>All stimulated saliva and dental plaque samples obtained in this study will be tested for S. mutans using mitis-salivarius bacitracin (MSB) agar plating and total bacteria testing using Todd Hewitt (TH) agar plating. Samples will be stored for S. mutans and total bacteria testing using quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) and bacterial community analysis.

At the screening visit, only stimulated saliva samples will be collected and tested for S. mutans Colony Forming Units (CFUs) to determine the inclusion criterion of ≥ 1 x 10^5 CFU/mL at Screening using MSB agar plating. At all other visits both stimulated saliva and dental plaque samples will be obtained for microbiology assessments. Samples will be collected at</td></tr>
</table>

	the following visits: Screening Visit, prior to the dental prophylaxis at Visit 2, prior to study drug administration at Visits 3, 8-10, follow up visits 4-7 and 18-22. For details refer to Appendix C. Samples will be shipped overnight to the Sponsor's microbiology laboratory for analysis. Screening *S. mutans* results will be provided to the study center within 5 days of sample receipt.
Inclusion Criteria:	Subjects are eligible to participate if they meet the following criteria: 1. Males and females, 12-75 years of age 2. Adults subjects provide written informed consent and adolescent subjects give written or verbal assent, as appropriate, and parent(s) or legal guardian(s) give written informed consent 3. Female subjects of childbearing potential must agree to use one of the following forms of contraception from screening through the last study visit: hormonal (oral, implant, or injection) begun >30 days prior to screening; barrier (condom, diaphragm, or cervical cap with spermicide); intrauterine device (IUD). Acceptable contraceptive options may also include abstinence, relationship with a same sex partner or partner who has had a vasectomy at least six (6) months prior to the screening visit 4. Negative urine pregnancy test in all females of childbearing potential (past menarche) 5. Male subjects of sexual activity age: willing to use contraception or abstain from sexual activity beginning with the first exposure to study drug and continuing until discharged from the study due to completion or Early Termination *6.* Healthy, as determined by the Investigator (in consultation with the Medical Monitor, as needed), based on medical and dental history, concurrent illnesses, laboratory results, concomitant medications, oral cavity assessment, and targeted physical examination (general, extraoral, head and neck) during Screening *Note: Subjects on a stable dose of medication may be eligible for screening and will be assessed by the medical monitor on a case-by-case basis.* 7. Have a minimum of 12 bicuspids and molars with a minimum of 8 molars and bicuspids NOT having restorations, crowns or sealants 8. Demonstrated ability to expectorate ≥2 mL of stimulated saliva in 5 minutes 9. Have a salivary *S. mutans* of 1.0 x 10^5 CFUs/mL or greater at Screening using MSB agar plating 10. Willing to refrain from using non-study dentifrice and other non-study oral care products (oral care rinses, fluoride products, etc.) during the study 11. Willing to postpone elective dental procedures (e.g., dental cleanings) between Screening and final post-treatment visit (End of Study or Early Termination) 12. Willing and able to comply with oral hygiene and diet instructions

	13. Able to communicate with the Investigator/study center personnel, understand and comply with the study requirements, and willing to return for protocol-specified visits at the appointed times
Exclusion Criteria:	Subjects are <u>excluded</u> from participation if any of the following apply: 1. Advanced periodontal disease 2. Active caries lesion(s) within 30 days prior to study drug administration (confirmed by comprehensive caries examination including standard radiographs). Subjects presenting with insipient, non-cavitated lesion(s) are not excluded *Note: If radiographs are deemed appropriate for the study and taken within 6 months prior to the Screening visit, these may be used for determining eligibility and are not required to be repeated at Screening* 3. Partially erupted teeth where the entire crown is not erupted or an operculum is present 4. Medical condition (e.g., artificial heart valve, history of infective endocarditis, cardiac transplant with valvular dysfunction, congenital heart disease or total joint replacement) for which antibiotics are recommended prior to dental visits and/or procedures 5. Pathologic lesions of the oral cavity (suspicious or confirmed) 6. Full dentures or permanent orthodontic appliances, e.g., braces, buccal or lingual brackets. *Note: Partial dentures, removable retainers and night guards are not excluded, provided that they are cleaned regularly throughout the duration of the study* 7. Use of systemic antibiotics, topical oral antibiotics, or use of other drugs, which in the opinion of the Investigator could influence the study outcome, beginning 30 days prior to Screening until the end of study participation 8. Medical history indicating the woman is pregnant, breastfeeding/lactating or has a positive urine pregnancy test 9. Participation in a clinical trial or receipt of a non-FDA approved therapy within 30 days prior to study drug administration (depending on the specifics, participation in an observational study is not necessarily excluded) 10. Presence of any condition or concurrent illness, which in the opinion of the Investigator, would compromise normal immune function (e.g., diabetes, rheumatoid arthritis, lupus, liver disease, organ transplant, etc.), interfere with the use of study dentifrice and oral care products, or interfere with the ability to comply with study requirements, or jeopardize the safety of the subject or the validity of the study results
Study Assessments & Procedures:	See Appendices A through D for detailed study information. **<u>Clinic Visit Schedules</u>** For clinic visit schedules refer to Appendix D **<u>Assessments & Procedures</u>**

Clinic Visit 1 (Screening, Days -30 to -1)

Subjects will be scheduled for this visit between 6AM and 10AM.

- Informed Consent/Assent & Assign Subject ID
- Inclusion/Exclusion
- Medical/Surgical/Dental History and Concurrent Illnesses
- Salivary Flow Assessment
- Concomitant Medications
- Demographics
- Dental status and comprehensive caries examination including standard radiograph
  Note: If radiographs are deemed appropriate for the study and taken within 6 months prior to the Screening visit, these may be used for determining eligibility and not required to be repeated at Screening
- Screening Laboratory Testing
- Urine Pregnancy Test (females of childbearing potential only)
- Oral Cavity Assessment
- Targeted Physical Exam (general, extraoral, head & neck)
- Vital Signs (blood pressure, heart rate, temperature)
- Microbiology (stimulated saliva ONLY)
  Note: Screening Microbiology sample will be collected on Days -30 to -8 prior to Visit 2
- Discharge

Clinic Visit 2 (Prophylaxis, Day -7 to -2)

Subjects will be scheduled for this visit between 6AM and 10AM.

- Microbiology (Stimulated Saliva and Dental plaque collection)
  Note: Samples need to be obtained prior to oral hygiene training and professional dental prophylaxis
- Professional Dental Prophylaxis (prophylaxis will include removal of bulk plaque and supragingival scaling)
  Note: NO fluoride treatment as part of the procedure, NO subgingival scaling as part of the prophylaxis
- Oral Hygiene Training:
  - Flossing (string): instructions are provided in Appendix E
  - Manual toothbrush technique for routine dental hygiene using a manual toothbrush provided by the sponsor and toothpaste containing fluoride (for instructions refer to Appendix F)
- Oral Hygiene Product Distribution
- Discharge

Clinic Visits 3, 8-17 (Baseline Day 0, Days 7-11)

AM visits will be scheduled 6AM to 10AM. PM visits will be scheduled 6PM to 10PM.

Subjects should not be exposed to study drug if they present with any

	disruption or loss of integrity in the oral cavity mucosa, gingiva or have lip lesions, (e.g. aphthous stomatitis, active herpetic sores, cheek bites, or severely chapped or cracked lips, etc.). Pre-Dose o Confirmation of eligibility (Visit 3 ONLY) o Medical/Dental History & Concurrent Illness Update (Visit 3 ONLY) o Study Arm Assignment and Randomization (Visit 3 ONLY) o Urine Pregnancy Test (females of childbearing potential only) (Visit 3 ONLY) o Targeted Physical Exam (Visit 3 & 8 ONLY) o Concomitant Medications Update o Oral Cavity Assessment: AM Visits 3, 8, 10, 12, 14, & 16 only o Vital Signs (blood pressure, heart rate, temperature taken in supine or sitting position) (Visits 3, 8 & 17 only) o Microbiology (Stimulated Saliva & Dental Plaque) ***Note: Microbiology samples will only be collected at Visits 3, 8, 9 and 10*** o Brushing and flossing with the dental material provided by the Sponsor Study Drug Administration: Instructions for the application of C16G2 Strips or Placebo are provided in the Study Manual and in Appendix G. o Subjects will have C16G2 Strip (9.2 mg, 18.4 mg, or 36.8 mg in Study Arms 1 through 3, respectively) or Placebo applied to molars and bicuspids. Strips will be applied and remain on the subjects teeth for up to 90 minutes. Subject will not eat, swish or drink during study drug administration. Post-Dose o C16G2 and Placebo strips will remain on the subject's teeth for 30 minutes (do not manipulate strips during that time) o Remove strips that have fully self-detached starting 30 minutes after application o Remove all strips that have not fully self-detached 90 minutes after application *Note: Dental strips will in most cases fully detach prior to 90 minutes. Only remove strips that fully detach earlier than 90 minutes after application. Subjects will not eat, swish, or drink for one hour after the removal of study drug* o Photograph imaging immediately after study drug application (Visit 3 ONLY) o Oral Cavity Assessment: AM Visit 3 and PM Visits 9, 11, 13, 15, & 17 only o Vital Signs (blood pressure, heart rate, temperature) within 20 minutes of removal of the last strip, taken in supine or sitting position (Visits 3, 8 & 17 only) Prior to Discharge

	○ Adverse Events ○ Oral Hygiene Product Distribution (as needed) ○ Discharge **Clinic Visits 4-7 and 18-20** On visits 7, 19 & 20 subjects will be scheduled between 6AM and 10AM. Remaining visits will be scheduled as appropriate, according to clinic visit schedule in Appendix D. ○ Concomitant Medication Update ○ Oral Cavity Assessment ○ Targeted Physical Exam (Visits 5, 18 and 20) ○ Microbiology (stimulated saliva and dental plaque collection) ○ Adverse Events ○ Discharge **Clinic Visits 21 & 22** Subjects will be scheduled for this visit between 6AM and 10AM. ○ Microbiology (stimulated saliva and dental plaque collection) ○ Discharge ○ End of Study (Visit 22 ONLY)
Subject Instructions:	Subjects enrolled in all study arms will be instructed to abstain from eating food and drinking beverages that contain a high sugar content (e.g., candy, soda with refined sugar, sugary snacks, dried fruit, fruit rolls) from Screening to the last day of study drug administration (Visit 17, Day 11, PM). While smokers are not excluded from study participation, subjects should abstain from using chewing tobacco or similar products throughout the study. **a) Oral Hygiene Instructions** Beginning at Visit 2 and during the entire study subjects will not be allowed to use any dental products besides the materials provided by the study center. Prior to attending the study center for any visit (Visits 1-22), subjects will not be allowed to perform oral hygiene at home. In addition, subjects will be advised not to use any mouth rinse for approximately 24 hours before the Screening visit. Prior to discharge at Visit 2 (Days -7 to -2), subjects will receive a manual toothbrush, a regular toothpaste containing fluoride, and dental floss provided by the Sponsor to take home. Subjects will be instructed to use these dental products in the morning and evening at home during the remaining study duration, including the evening of Day 0. In addition, subjects will be resupplied with these dental products as needed. **b) Diet Instructions** Subjects in all study arms will be instructed as follows:

	All Visits: • Do not eat for 1 hour prior to the appointment time • No liquids, other than plain water, 1 hour prior to the appointment time *Note: Subjects will be allowed to drink water up to 10 minutes prior to dental plaque and saliva collection, and will be instructed not to swish or rinse* **Visits 3, 8-17 (Study Drug Administration Days)** • Do not eat or drink anything besides plain water within 1 hour prior to the appointment time • Do not eat, drink anything or swish during the study drug administration period and for 1 hour after the removal of the strips *Note: Subjects will be under the supervision of study staff to ensure that they do not consume any food or drink anything during and 1-hour post study drug administration*
Safety Monitoring:	All subjects that receive study drug will be included in the safety analysis. Safety will be evaluated on the entire study population of 30 subjects. Subjects in all study arms will be followed for safety assessments for 1 week after dosing. Safety monitoring will include vital signs, intraoral assessments of hard and soft tissues, targeted physical examination, and collection of adverse events during study visits and unscheduled telephone contacts. Subjects will be instructed to inform the Investigator and/or a member of the study staff of any adverse events that occur at any time during the study. Subjects will be asked a general health question at each clinic visit up to and including Visit 20 and with each unscheduled telephone contact to identify changes in their state of health since their last communication with the study center or their last study visit. All subjects will be closely monitored for safety for 1 week after the last administration of study drug. After that time point, all ongoing adverse events will be followed in accordance with good medical practice until resolution or the condition has stabilized.
Statistical Methods:	<u>Sample Size:</u> The total number of subjects planned for this study is 30. There are no data on which to base formal sample size calculations for this study. The data generated in this study will assist with ongoing clinical development of C16G2 Strip. Subjects' data in the three study arms will provide information on the safety and microbiology of multiple administrations of C16G2 Strip or Placebo. Subjects may be replaced at the Sponsor's discretion. <u>Data Analysis:</u> Analysis Sets: There will be two analysis sets; the safety analysis set and the microbiology analysis set

	• The safety analysis set will be defined as those subjects who received any amount of study drug (C16G2 Strip or Placebo) • The microbiology analysis set will be comprised of two subsets, the saliva microbiology and dental plaque microbiology subset. These subsets will be based on the subjects who received study drug and have at least one baseline and one post-baseline dental plaque and saliva sample, respectively. Safety: All safety-related interventions, adverse events (AEs), and findings will be summarized. The incidence and duration of treatment emergent AEs (TEAEs) will be summarized by study arm. An AE will be considered treatment emergent if the onset date and time occur on or after the recorded clock time of the administration of study drug (C16G2 Strip or Placebo). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The severity of each adverse event will be determined using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. All adverse events (AEs) will be classified by the relationship of the event to study drug as 1) None, 2) Unlikely, 3) Possible or 4) Probable. All AEs will be followed in accordance with good medical practice until resolved or fully characterized. All serious AEs (SAEs) will be followed until the outcome is known or the subject's condition has stabilized. Other safety assessments include vital signs, oral cavity assessments, and targeted physical exams. These safety parameters will be presented by study arm using descriptive statistics. Microbiology: All saliva and dental plaque samples will be analyzed for *S. mutans* and total bacteria present in each sample and relative to the different doses in the 3 study arms. Samples will also be tested by qRT-PCR and bacterial community analysis at appropriate time points based on plating assessments. Descriptive statistics utilizing mean, standard deviation, median and range of *S. mutans* and total bacteria at each time point for Study Arms 1 through 3 will be determined and compared to Baseline samples.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	alkaline phosphatase
BMI	body mass index
BUN	blood urea nitrogen
C16G2	antimicrobial peptide (investigational study drug)
CFR	Code of Federal Regulations
CFU	colony forming units
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
°C	degrees Celsius
ECG	electrocardiogram
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
FSI	first subject in
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IUD	intrauterine device
LLOQ	lower level of quantitation
LSO	last subject out
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MSB	mitis salivarius-bacitracin
µM	micromolar
mL	milliliter
NCI	National Cancer Institute
ng	nanogram
NOAEL	no observed adverse effect level
PHI	Protected Health Information
PK	pharmacokinetic
qRT-PCR	quantitative real-time polymerase chain reaction

RBC	red blood cells
SAE	serious adverse event
SAR	suspected adverse reaction
SAP	Statistical Analysis Plan
S. mutans	*Streptococcus mutans*
Sponsor	C3 Jian, LLC (C3J)
SSAR	suspected serious adverse reaction
Study Drug	C16G2 or Placebo Strip
TEAE	treatment-emergent adverse event
TH	Todd Hewitt
WBC	white blood cells
WHO ATC	World Health Organization Anatomical Therapeutic Chemical

1. INTRODUCTION

Dental caries is a chronic disease of microbiological origin that affects populations worldwide. Caries arises from an imbalance in the indigenous microflora of the oral cavity: upon intake of dietary sugars (primarily sucrose), aciduric microbes produce lactic acid that damages tooth structure and enables these pathogenic bacteria to become dominant in the multispecies biofilms found on the tooth surface (known as dental plaque). The bacterium *Streptococcus mutans (S. mutans)* has been implicated in a wide body of historical and contemporary clinical and nonclinical data as being the major etiological agent responsible for the majority of caries (Loesche 1986; Tanzer, Livingston et al. 2001; Marsh 2006; Marsh 2010). Furthermore, in studies examining the endpoint, caries-free individuals were found to have lower *S. mutans* compared with caries-active subjects.

Controlling caries by reducing the total bacterial load in saliva and plaque through use of broad spectrum antibacterial agents can, in theory, reduce caries incidence; however, there is no clinical evidence supporting the long-term prevention of *S. mutans* re-infection and very few studies examining the impact on caries reduction (Tong, Dong et al. 2010; Vollmer, Papas et al. 2010; Young, Lyon et al. 2010). The reason for lack of long-term cavity protection is the persistence of *S. mutans* within the dental plaque and the dynamic balance of the biofilm community between a healthy state and cariogenic state. There is a need to develop a specific antimicrobial therapy that can substantially reduce or eliminate the primary agent of dental caries, *S. mutans*, from the oral biofilm while leaving the remaining organisms intact. If this can be achieved, a healthy biofilm may be established that provides long-term caries protection.

In response to the need for a focused *S. mutans* reduction, a series of novel synthetic molecules were designed and evaluated *in vitro* (Eckert, R., He J., et al., 2006; Kaplan, C. W., Sim, J.H., et al., 2011; Li, L. N., Guo, L. H., et al, 2010). The C16G2 antimicrobial peptide was shown to specifically kill *S. mutans*, and not other oral streptococci, in both planktonic and saliva-derived biofilm systems. Additionally, intact *S. mutans*-free biofilms created by a C16G2 intervention were resistant to colonization from exogenous *S. mutans* (Li, L. N., Guo, L. H., et al, 2010; Guo, L., McLean, J.S., et al, 2015).

Previous studies evaluated the safety, pharmacokinetics and microbiology of single and multiple C16G2 doses formulated as a mouth rinse, gel and varnish. In Study C3J16-S205-00 subjects will receive multiple C16G2 or Placebo strip administrations to evaluate the safety and microbiology of this mode of application.

1.1 Previous Clinical Experience

1.1.1 Phase 1

Study C3J11-101-01, a Phase 1, randomized, double-blind, placebo-controlled, dose escalation study was conducted at a single study center in the US. A total of 36 healthy adult subjects were enrolled, of which 24 subjects received C16G2, and 12 subjects received placebo. C16G2 was administered in a mouth rinse formulation as a single dose of three concentrations (4 mg [50 µM], 8 mg [100 µM] and 32 mg [400 µM]) by swishing for 40 seconds in the oral cavity and subsequent expectoration.

The objectives of this study were to evaluate the safety and pharmacokinetics of C16G2 in healthy adult subjects and to assess the targeted antimicrobial activity of C16G2 as measured

by a reduction in the number of salivary *S. mutans* and to assess the bacterial composition in the oral cavity over 28 days post-study drug administration in healthy adult subjects.

C16G2 was well-tolerated with no deaths and no other serious or severe AEs. No study drug-related treatment-emergent AEs were reported and no subject was discontinued due to an AE. No clinically significant changes in vital signs were observed in association with the administration of C16G2. Mean values for systolic and diastolic blood pressure and pulse showed only small fluctuations from baseline over the entire treatment period, and values were similar for the C16G2 dose cohorts and the placebo cohort. No clinically significant findings in the oral cavity were attributable to C16G2 administration and no clinically significant targeted physical exam and electrocardiogram (ECG) findings were reported. In addition, no clinically significant out-of-range clinical laboratory findings were observed. Immunogenicity assessments demonstrated that single dose C16G2 administrations up to a dose of 32 mg did not trigger the development of antibodies against C16G2.

C16G2 could not be detected above the lower level of quantitation (LLOQ 10 ng/mL) in any pharmacokinetic (PK) sample, with a single exception, which tested just above the LLOQ and was most likely the result of high background signal near the LLOQ. This suggests that there is minimal or no systemic absorption of C16G2 into the circulation after a single C16G2 administration up to a dose of 32 mg.

Microbiology assessments did not demonstrate an apparent reduction or increase in *S. mutans* and other bacterial species outside of the variation observed in the placebo cohort, indicating that single C16G2 doses formulated as a mouth rinse did not impact the oral microbiome.

Study C3J16-V102-00, a Phase 1, single-blind, randomized, placebo-controlled, dose-escalation study evaluated the safety and efficacy of single 13.6 mg, 27.2 mg, 54.4 mg C16G2 Varnish or Placebo administrations.

The objectives of this study were to evaluate the safety and microbiology of C16G2 Varnish formulation in healthy adult subjects and to assess the targeted antimicrobial activity of C16G2 as measured by a reduction in the number of salivary *S. mutans.* In addition, the study assessed the bacterial composition in the oral cavity over 28 days post single study drug administration in healthy adult dental subjects.

A total of 48 adult healthy subjects were enrolled, of which 30 subjects received C16G2 and 18 subjects received placebo. C16G2 was well-tolerated with no deaths and no other serious or severe AEs. No study drug-related treatment-emergent AEs were reported and no subject was discontinued due to an AE. No clinically significant changes in vital signs were observed in association with the administration of C16G2. Oral cavity assessments and targeted physical exams did not indicate any clinically relevant changes due to study drug administration. Microbiology evaluations demonstrated a significant decrease in *S. mutans* levels in saliva and plaque samples in each dose level. The 27.2 mg dose group showed the greatest decrease in *S. mutans* compared to Placebo and the other two dose groups. Total bacteria levels did not change significantly post study drug administration. The clinical study report for this study is currently in preparation.

1.1.2 Phase 2

To enhance the targeted *S. mutans* killing activity of C16G2 in dental plaque, C3 Jian formulated the drug product for both mouth rinse and gel application. C3J13-201-01, a double-blind, placebo-controlled study, evaluated different combinations of multiple C16G2 Gel and/or C16G2 mouth rinse administrations at two dose levels. To determine the most effective mode of gel application, gel was applied by manual toothbrush, Sonicare™ toothbrush and upper and lower custom dental trays.

A total of 60 adult healthy subjects were enrolled, of which 48 subjects received C16G2, and 12 subjects received placebo. Subjects received study drug for 7 consecutive days and were followed for safety and microbiology assessments for 14 days post first study drug administration. The C16G2 concentrations were 3.2 mg/mL (800 µM) in gel formulation and 1.6 mg/mL (400 µM) in liquid formulation.

C16G2 was well-tolerated with no deaths and no other serious or severe adverse events (AEs). A total of 43 TEAEs were reported, 38 AEs in 19 subjects receiving C16G2, 5 AEs in 3 subjects receiving placebo. The majority of AEs were deemed mild in severity and unrelated to study drug administration and study procedures. In Study Arm 3, in which subjects received gel administrations with a Sonicare™ toothbrush, followed by a single rinse, the number of subjects with one or more AEs and the number of AEs was greater compared to the other three study arms. Since the majority of these AEs were mild irritation related to the oral cavity, use of the Sonicare™ toothbrush for longer than recommended by the manufacturer (four minutes versus two) and the rinsing schedule are possible procedure-related explanations.

Two subjects discontinued from the study due to adverse events. The first subject, a 32 year old Asian female, was enrolled in Study Arm 1 and randomized to C16G2 study drug. She received six C16G2 mouth rinses on the first day of study drug administration. She subsequently developed a mild rash on both arms and mild pruritus on her arms and her jaw. She withdrew from the study the next day. Both AEs resolved within a few hours and were assessed as possibly related to study drug administration and study procedures by the Investigator. The second subject, a 22 year old Caucasian female enrolled in Study Arm 4, developed tonsillitis and pyrexia at the end of the treatment period (subject completed 5 of 7 study drug administration days). Both AEs were assessed as moderate in severity and unrelated to study drug administration and study procedures by the Investigator and resolved after 5 days.

Clinically significant findings in the oral cavity and targeted physical exam were reported as adverse events. No clinically significant changes in vital signs were observed in association with administration of C16G2. Mean values for systolic and diastolic blood pressure, pulse and temperature showed only small fluctuations from baseline over the entire treatment period, and values were similar for the four active C16G2 Study Arm groups and combined placebo group.

The majority of subjects receiving C16G2 via a custom dental tray demonstrated an average 1 $\log_{10}$ CFU/mL *S. mutans* reduction in saliva 1 day after the last 7-day study drug administration period and this reduction was maintained in some subjects 1 week after the last study drug administration, demonstrating the durability of effect for 7 days. The majority of subjects receiving C16G2 Gel via a manual toothbrush demonstrated an *S. mutans* reduction in occlusal dental plaque 1 day after the last 7-day study drug administration period, with fewer subjects having an impact in salivary *S. mutans*. At the end of the study, only a portion of subjects in the manual brush arm showed a substantial reduction in *S. mutans* occlusal dental plaque and the effect was less pronounced in saliva, indicating that the response observed on Day 7 may decrease over time post-treatment. Other modes of application (mouth rinse, gel administered via Sonicare™ toothbrush) were less effective.

In the open-label study C3J14-201B-00, subjects received 400 µM and 800 µM C16G2 Gel, administered either by custom dental trays once daily for 5 consecutive days (Part A) or via manual toothbrush only compared to a combination of manual toothbrush and custom dental trays (Part B), with four study drug administrations on the first day of dosing followed by AM and PM dosing for 6 consecutive days. Results from Part A of the study demonstrated that C16G2 administered once daily for 5 days via dental trays for up to 4 hours did not suppress *S. mutans* efficiently. Results from Part B of the study showed a 1 $\log_{10}$ CFU/mL suppression of *S. mutans* when C16G2 was applied via a manual toothbrush and custom dental tray combination and at the higher concentration (800 µM).

Pharmacokinetic data from study C3J14-201B-00 indicated no detectable systemic levels of C16G2 (all samples below the LLOQ of 10 ng/mL). PK samples were obtained: 1) during and after a 4 hour gel tray administration of 3.2 mg/mL C16G2 in gel (C16G2 administered after manual brushing with conventional toothpaste without C16G2), and 2) immediately after 3 manual brushings with C16G2 and one 30 minute tray administration with C16G2 (3.2 mg/mL C16G2 in gel).

Study C3J15-202-00, a Phase 2, multi-center, randomized, double-blind, placebo-controlled study evaluated the safety and microbiology of C16G2 (gel formulation) in adolescent and adult dental subjects. The study evaluated the treatment regimen and schedule previously assessed in Study C3J14-201B-00, Part B and assessed the durability of *S. mutans* suppression over a longer period of time (up to 4 months compared to 7 days in previous studies), evaluated the safety and microbiology of two 7-day study drug administration periods, and compared 2 mL (Study Arm 1) versus 4 mL (Study Arm 2) 800 µM C16G2 Gel/Placebo administrations.

A total of 64 subjects were enrolled into this study, of which 41 were randomized to receive active drug. A total of 104 AEs were reported in 36 subjects, with a similar distribution over the two study arms and the placebo group (Study Arm 1: 9 subjects; Study Arm 2: 16 subjects; placebo group: 11 subjects). AEs related to study drug were reported for 3 subjects receiving C16G2 (all in Study Arm 2) and 2 subjects treated with placebo. AEs deemed related to the study drug in Study Arm 2 were gingival swelling, oral discomfort, and sensitivity of teeth, all assessed as mild in severity. There were no serious adverse experiences (SAEs) or severe AEs, no deaths, and no discontinuations due to AEs.

No clinically significant changes in vital signs were observed in association with administration of C16G2. Assessments of the oral cavity and body areas examined as part of the targeted physical exams did not reveal any treatment-related safety issues. Thus, the dosing regimens and modes of application evaluated in this study were safe in healthy adults and adolescents.

Results for salivary *S. mutans* samples during the first and second study drug administration period suggest that either 2 or 4 mL volumes of 800 µM C16G2 delivered via MBGA and TGA over 7 days, with an intensive first day, are sufficient to suppress *S. mutans* for 12 hours following the cessation of therapy compared to placebo.

Results for occlusal dental plaque during the first study drug administration period suggest that 800 µM C16G2 administered as either 2 or 4 mL volumes via MBGA and TGA over 7 days, with an intensive first day, are sufficient to suppress *S. mutans* in dental plaque for up to 12 hours after the last dose as compared to placebo. During the second study drug administration only the 4 mL volume appeared sufficient to suppress *S. mutans* up to 12 hours in both plaque and saliva, while 2 mL suppressed *S. mutans* in saliva.

In both study drug administration periods total bacterial loads were not reduced by study treatments at 1 week post last study drug administration. The magnitude of the *S. mutans*

reduction in the first study drug administration period was modest, yet selective, since there was no change in total bacterial levels.

Study C3J15-203-00, a Phase 2, multi-center, randomized, double-blind and open-label, placebo-controlled study, evaluated the safety and microbiology of C16G2 administered in multiple oral gel doses to adult and adolescent dental subjects. The study evaluated different dosing regimens and different doses of C16G2 and Placebo Gel. There were no significant safety findings and the safety profile of C16G2 was consistent with previous studies and generally safe in majority of the subjects. Microbiology results did not show a significant durable response in reduction of *S. mutans* in stimulated saliva and dental plaque samples. The clinical study report for this study is currently in preparation.

The ongoing Phase 2 study C3J16-V204-00 will evaluate the safety and microbiology of C16G2 varnish administered in multiple doses to adolescent and adult dental subjects in a single-blind, randomized, placebo-controlled manner. The study is will enroll approximately 33 subjects into 3 dose groups (13.6 mg, 27.2 mg, and 54.4 mg C16G2 Varnish or Placebo). Subjects in each cohort will receive three doses over one week and will be followed up for safety and microbiology for up to 1 month post last study drug administration.

1.1.3 Non-US Pilot Studies

Three C16G2 pilot studies that evaluated the safety and microbiology of C16G2 mouth rinse administrations were conducted in China. These studies demonstrated a safety profile similar to the one observed in the US clinical studies. Only one of these three studies showed a short-term decrease in *S. mutans* levels that returned to baseline after 24 hours. For detailed information refer to the C16G2 Investigator's Brochure.

1.2 Rationale for Development of C16G2

The rationale for developing C16G2 as a product to prevent dental caries in adults, adolescents and younger children is based on the following:

- Acid production by *S. mutans* is implicated as a major factor in the initiation of dental caries and eventual cavitation of the tooth (Tanzer, Livingston et al. 2001). The selective reduction of *S. mutans* from within the oral cavity may reduce the likelihood of developing dental caries by reducing acid production and providing long term protection through preservation of the non-cariogenic oral flora that maintain protective colonization benefits.

- C16G2, a novel antimicrobial peptide, has demonstrated efficacy and selectivity for *S. mutans* and not other bacteria.

Refer to the Investigator's Brochure for additional information.

1.3 Rationale for Selection of Dose & Mode of Application

In prior clinical trials using C16G2 mouth rinse and gel formulations, C16G2 was administered at an 400 µM (1.6 mg/mL) and 800 µM (3.2 mg/mL) dose with a maximum daily exposure of 115.2 mg resulting in approximately 1 $\log_{10}$ suppression of *S. mutans* while study drug was administered. The current study is designed to evaluate a C16G2 strip formulation. The proposed doses of C16G2 are 9.2 mg, 18.4 mg, or 36.8 mg of C16G2 applied via 4 tooth strips that will extend over molars and bicuspids. Release of the peptide from the film is achieved through mixing of the layer of the tooth strip containing C16G2 with saliva on the tooth surface

resulting in a 4-fold increase in peptide release from the 9.2 to 36.8 mg dose. The strip will be hydrated by saliva during the administration period resulting in continuous dissolution of C16G2 from the strip during the treatment period. In this study the tooth strips will remain on the tooth surface for a minimum of 30 minutes and during this timeframe it is expected that the majority of peptide will be released. An average salivary flow rate of 0.4 mL/min over the course of the 30 minutes application time results in the production of approximately 12 mL of saliva and an average peptide concentration for the three doses from lowest to highest of 0.77, 1.53 and 3.07 mg/mL C16G2, respectively. The highest concentration of 3.07 mg/mL is similar to a prior gel formulation that delivered 3.2 mg/mL in a dental tray. The three proposed doses were evaluated and each demonstrated a similar level of selective antimicrobial activity against *S. mutans* in a multispecies *in vitro* biofilm assay. Due to the well-known limitations of effective penetration into biofilms, the higher concentrations of C16G2 were selected to achieve a greater effective concentration beyond the surface of the biofilm.

The proposed clinical program dose range, as well as the multiple dosing schedule, was not selected based on safety issues, but rather based on 1) a reasonable expectation that this dose range will cover the bactericidal potential of C16G2, 2) a product profile that targets the highest flexibility for C16G2 administration (at home or professional) and 3) results from prior C16G2 clinical studies that demonstrated an unremarkable safety profile with no serious or severe adverse events assessed as related to study drug administration by the Investigator.

The non-clinical toxicity and clinical safety and tolerability profile of orally administered C16G2 mouth rinse and gel formulations is very benign, which is consistent with the peptide not being orally bioavailable. Pharmacokinetic and toxicokinetic studies did not detect C16G2 after oral administration, either by gavage to rats and dogs or buccal administration to hamsters. Furthermore, *in vitro* studies in simulated gastric and intestinal fluids show that C16G2 is quickly destroyed and undetectable, and thus swallowing of C16G2 is not expected to result in any systemic exposure. None of the ingredients in the strip formulation raise safety concerns because they are currently used in commercial products.

A large safety margin exists between the proposed clinical doses and the no observed-adverse-effect levels (NOAEL) determined after administration of C16G2 to rats and dogs by oral gavage daily for 14 days. The NOAELs in these nonclinical studies were at least 150 mg/kg/day in rats and at least 50 mg/kg/day in dogs, respectively, which converts to a human equivalent dose (HED) of 24 to 28 mg/kg/day. The maximum daily dose proposed in Study C3J16-S205-00 is 1.05 mg/kg/day (assuming a 70 kg subject), which equates to 22.9 to 26.7-fold below the HED values at the NOAELs derived from the oral gavage toxicology studies.

In addition, a study to assess the potential for C16G2 Gel to produce local irritation in the oral mucosa of hamsters did not reveal any adverse findings or delays in wound healing following daily buccal administration at a concentration of 16 mg/mL for up to 28 days in intact and abraded cheek pouches.

1.4 Rationale for the Length of Safety Follow-up

Given the lack of systemic exposure at clinical doses, the short half-life, and the unremarkable clinical safety profile at the doses studied, safety follow-up for subjects enrolled in any study arm of Study C3J16-S205-00 will be 1 week after the last administration of study drug. After that time point, all ongoing adverse events will be followed in accordance with good medical practice until resolution or the adverse event or condition has stabilized. All SAEs will be followed until the outcome is known or the subject's condition has stabilized. The shorter follow-up period compared to earlier C16G2 studies is supported by the following data:

The maximum daily C16G2 exposure in this study will be up to 73.6 mg, (a 36.8 mg strip applied twice daily), in Study Arm 3. The completed Phase 2 Study C3J13-201-01 had a maximum daily C16G2 exposure of 115.2 mg, and demonstrated an unremarkable safety profile with no serious or severe adverse events. In completed C16G2 clinical studies, the majority of adverse events reported were mild in severity and assessed by the investigators as unrelated to study drug. In addition, all adverse events that were assessed as related to study drug administration were assessed as mild in severity. In Study C3J14-201B-00, one serious adverse event (acute abdominal pain – infarcted sigmoid appendix epiploica) was reported and assessed as unrelated to study drug by the investigator.

Pharmacokinetic evaluations in two clinical studies demonstrated minimal or no measurable systemic absorption of C16G2. In the Phase 1 Study, Protocol No. C3J11-101-01, C16G2 could not be detected after a single C16G2 administration of up to 32 mg with a single exception. One sample tested just above LLOQ, which may have been the result of high background signal near the LLOQ. In a Phase 2 Study (Protocol No. C3J14-201B-00), C16G2 administered at a concentration of 3.2 mg/mL could not be detected above the LLOQ (10 ng/mL) in any pharmacokinetic sample after multiple manual brush gel applications and during and after tray gel applications. The clinical PK evaluations are consistent with nonclinical data that demonstrate a lack of systemic exposure after sublingual, buccal, and oral gavage. After parenteral administration of C16G2 to rats and dogs for 28 days, C16G2 was rapidly cleared from circulation ($t_{1/2}$ = 1.1 to 3.92 hours). In vitro stability studies performed with C16G2 diluted in human saliva indicated degradation occurs within 1 hour ($t_{1/2}$ = 18.8 minutes). Furthermore, in vitro studies in simulated gastric and intestinal fluids demonstrated that C16G2 is quickly destroyed and undetectable, and thus swallowing of C16G2 is not expected to result in any systemic exposure.

1.5 Study Assessments and Procedures

Laboratory assessments will be performed at Screening to determine eligibility. Evaluations of safety include oral cavity assessments, targeted physical examinations, vital sign measurements, and collection of adverse events as set forth in the Schedule of Study Assessments and Procedures in Appendix B.

1.5.1 Screening Laboratory Assessments

Laboratory assessments will be performed at a local laboratory to determine eligibility at screening. Any out-of-range hematology or chemistry test result may be repeated, in consultation with the Medical Monitor as needed, to evaluate eligibility.

Hematology: White blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils.

Serum Chemistries: Sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT).

1.5.2 Adverse Event Collection and Review

Adverse events (AEs) will be collected and reviewed to evaluate the safety of C16G2 or Placebo Strip. The safety follow-up for subjects enrolled in any study arm of Study C3J16-S205-00 will be 1 week after the last administration of study drug. After that time point, all ongoing

adverse events will be followed in accordance with good medical practice until resolution or the adverse event or condition has stabilized. AEs that occur after exposure to study drug will be classified as treatment-emergent AEs (TEAEs).

All AEs, whether observed by the Investigator and/or study staff or reported by the subject, will be entered in the source records and electronic data capture (EDC) system.

AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 and coded according to Medical Dictionary of Regulatory Activities (MedDRA).

1.5.3 Vital Signs

Vital signs (blood pressure [systolic and diastolic], heart rate and temperature) will be obtained for safety monitoring at time points specified in Section 6 and Appendix B, and will be obtained while the subject is in a supine or sitting position.

1.5.4 Oral Cavity Assessments & Targeted Physical Exam

At the scheduled time points, according to the Schedule of Study Assessments and Procedures in Appendix B, investigators will perform a comprehensive oral exam consisting of an evaluation of oral hard and soft tissue structures for each subject. Oral hard tissue assessments will be performed with a dental mirror on the teeth and bony structures. Oral soft tissues will be performed by examining each subject's mouth and pharynx, including lips, tongue, floor of the mouth, palate, gingiva, alveolar mucosa, buccal mucosa, oropharynx, tonsils, uvula, and salivary glands using palpation techniques and visualization. Targeted extraoral examination of the head and neck regions will also be performed by visualization and palpation.

At Screening and prior to the first study drug administration, any abnormal examination findings should be documented and evaluated for clinical significance. If, in the opinion of the Investigator, the findings are not clinically significant and/or do not disqualify a subject from participation in the study, this clinical impression should be documented and the findings should be adequately described to allow comparison at subsequent visits. If there are questions about the clinical significance of any finding(s), a discussion with the Medical Monitor is recommended.

The types of abnormalities that should be recorded include, but may not be limited to, amalgam tattoos, bony exostoses, Fordyce granules, and extrinsic tooth stains.

At the time of study drug administration or post-dose, should an AE be reported, the Investigator will determine if an oral hard/soft tissue exam should be performed. All findings will be recorded on the respective source document and in the EDC system.

Any non-clinically significant and clinically significant findings, signs or symptoms that are present at Screening and worsen in severity or frequency during or after study drug administration, will be recorded as adverse events in the source record and EDC system.

1.5.5 Salivary Flow Assessment

Stimulated whole salivary flow rates will be used to measure salivary function. The stimulated whole saliva test will be administered for 5 minutes.

With study staff present, subjects will be instructed to chew on parafilm (a 50/50 mixture of paraffin wax and polyolefin) and to drain saliva into a tube which is to be held near their mouth. At the end of 5 minutes, subjects will be instructed to collect all remaining saliva in their mouth and expectorate it into the test tube. Subjects who are able to expectorate ≥2.0 mL of stimulated saliva within a 5 minute period are eligible to continue screening for participation in the study. Subjects that pass the salivary flow assessment will be instructed to continue to collect saliva until a minimum of 5 mL have been collected at the first screening visit.

1.5.6 Microbiology Evaluations

1.5.6.1 Dental Plaque Sample Collection

A dental plaque sample will be collected using an interdental brush for the analysis of microbial populations and for quantification of *S. mutans* according to the Schedule of Microbiology Assessments in Appendix C.

Subjects will be instructed to swallow the saliva in their mouths. Subjects will be instructed to open their lips in a wide smile with teeth loosely together and suck in several times to remove bulk saliva from occlusal surfaces of the teeth. Study staff will sample the occlusal surface of molars and bicuspids in four quadrants of the subject's mouth with one interdental brush used for each quadrant. Plaque collected from each interdental brush will be dispersed into one tube containing TH media.

Immediately after collection, dental plaque samples will be stored at 2-8°C. At the end of each day, all samples will be placed in an insulated box with ice packs, and a temperature monitoring device then shipped overnight for next day early morning delivery to C3 Jian, LLC. The study center will provide C3 Jian with pre-notification of the upcoming shipment by supplying a sample inventory list via email to:

Chris Kaplan, PhD
Director of Product Development
C3 Jian, LLC
E-mail: ckaplan@c3jtherapeutics.com
Office Phone: 310-665-2928 Ext. 207
E-fax: 310-665-2963

A copy of the sample inventory list should also accompany the actual shipment. A template for preparation of the sample inventory list is provided in the Study Manual for the study. The minimum required sample shipping information includes; subject number, sample description, sample collection date & time, and the total number of samples in the shipment. Shipments of stimulated saliva and dental plaque samples will be combined.

For details on laboratory and shipping procedures refer to the Study Manual.

Upon arrival at C3 Jian, samples will be inventoried and entered into a database for tracking through the analysis process. Plaque samples will then be re-suspended and aliquoted for immediate processing for plating. Remaining plaque samples will be aliquoted in sterile labeled sample tubes and stored at -80°C for qRT-PCR analysis and/or bacterial community analysis.

1.5.6.2 Stimulated Saliva Sample Collection

A stimulated saliva sample (≥ 5.0 mL) will be collected by expectoration into sterile tubes for the analysis of microbial populations to confirm baseline *S. mutans* ≥ 1.0 x 10^5 CFU/mL in saliva for study eligibility, and for quantification of *S. mutans* according to the Schedule of Microbiology Assessments in Appendix C.

With study staff present, subjects will be instructed to chew on parafilm (a 50/50 mixture of paraffin wax and polyolefin) and to drain saliva into a tube which is to be held near their mouth until a minimum of 5 mL have been collected.

Immediately after collection, saliva samples will be stored at 2-8°C. At the end of each day, all samples will be placed in an insulated Styrofoam box with ice packs, and a temperature monitoring device, then shipped overnight for next day early morning delivery to C3 Jian, LLC. The study center will provide C3 Jian, LLC with pre-notification of the upcoming shipment by supplying a sample inventory list via email to:

Chris Kaplan, PhD
Director of Product Development
C3 Jian, LLC
E-mail: ckaplan@c3jtherapeutics.com
Office Phone: 310-665-2928 Ext. 207
E-fax: 310-665-2963

A copy of the sample inventory list should also accompany the actual shipment. A template for preparation of the sample inventory list is provided in the Study Manual for the study. The minimum required sample shipping information includes; subject number, sample description, sample collection date & time, sample volume, and the total number of samples in the shipment. Shipments of stimulated saliva and dental plaque samples will be combined.

For details on laboratory and shipping procedures refer to the Study Manual.

Upon arrival at C3 Jian, samples will be inventoried and entered into a database for tracking through the analysis process. Saliva samples will then be re-suspended and aliquoted for immediate processing for plating. Remaining saliva samples will be aliquoted in sterile labeled sample tubes and stored at -80°C for qRT-PCR analysis and/or bacterial community analysis.

1.5.6.3 Isolation & Analysis of *S. mutans* in Plaque & Saliva Samples

Dental plaque and stimulated saliva samples collected at protocol specified time points will be analyzed for *S. mutans* using mitis-salivarius bacitracin (MSB) agar plates (see Appendix C). Upon arrival at C3 Jian laboratories, plaque and saliva samples will be diluted in microbiology growth medium (TH Broth) and plated on MSB agar in triplicate. After anaerobic incubation at 37°C for 48-72 hours, all growth on the plates will be quantified by colony count. The use of microbiological media containing antimicrobial agents to selectively culture bacterial groups from mixed bacterial community is a standard method in microbiological identification of bacteria present in clinical analysis. Streptococcus species present in the oral cavity have been traditionally isolated from oral cavity samples using MSB agar plates. The antimicrobial activity of crystal violet dye, high sucrose content, sodium tellurite and bacitracin effectively prevent the growth of all bacteria except for streptococci. Further differentiation of streptococci is

accomplished by observing colony morphology. *S. mutans* grows in large blue colonies with dry frosted tops or pale blue gumdrops and can be differentiated from other bacterial colonies.

1.5.6.4 Analysis of Bacteria in Plaque & Saliva Samples by Non-selective Plating

Upon arrival at C3 Jian laboratories, plaque and saliva samples will be diluted in bacterial growth medium (TH Broth) and plated on non-selective media in triplicate at protocol-specified time points (see Appendix C) to enumerate total bacteria present in a sample. After anaerobic incubation at 37°C for 24-48 hours, all growth on the plates will be quantified by colony count.

1.5.6.5 Analysis of Bacteria in Saliva and Dental Plaque Samples by qRT- PCR

The qRT-PCR method has been successfully used to quantitate bacteria present in the oral cavity and their association with disease states, such as dental caries and periodontitis. Dental plaque and saliva samples will be used for *S. mutans* and total bacteria testing using qRT-PCR. Genomic DNA will be extracted from plaque and saliva samples that will be aliquoted and stored at -80°C. Bacterial genomic DNA samples will be analyzed by qRT-PCR for levels of bacteria present.

1.5.6.6 Bacterial Community Analysis

Metagenomic analysis using next-generation sequencing is a powerful tool to compare entire microbial communities and evaluate the bacterial community composition in healthy and diseased states. Genomic DNA extracted from dental plaque and saliva samples will be aliquoted and stored at -80°C for metagenomics analysis by next generation sequences (see Appendix C).

1.6 Potential Risks to Participants

Potential risks to subjects participating in this study are as follows:

- **Screening Laboratory Tests**

Venipuncture to obtain blood samples may cause some temporary discomfort. There is a minimal risk of surrounding nerve damage or wound infection. Some known risks, although rare, that can be associated with blood drawing are pain, burning, local infection, or the development of a bruise at the site where the needle is placed to draw the blood.

- **Oral Examinations:**

The oral examination will involve procedures that are routinely performed in dental practice. A licensed dentist/hygienist will perform the procedures. The risks from the oral examination include minor discomfort or pain during the procedures.

- **Biological Sample Collection:**

Dental plaque, stimulated saliva and urine (females only) will be collected. These collection processes confer minimal risk to the subject.

- **Radiographs**

Standard radiographs will be taken, unless radiographs that are deemed appropriate for the study and taken within 6 months prior to the screening visit are available. These may be used for determining eligibility and not required to be repeated at Screening. As planned, this procedure confers minimal risk to the subject.

- **Photographs**

Photographs will be taken to evaluate the application of the dental strips on the subject's molars and bicuspids immediately after study drug administration. The risks from taking these pictures include minor discomfort, and on rare occasions, minor bruising, cracking or bleeding of the lips.

- **C16G2 Administration:**

Phase 1

A total of 36 adult healthy subjects were enrolled, of which 24 subjects received C16G2, and 12 subjects received placebo. C16G2 was administered in mouth rinse formulation as a single dose of three concentrations (4 mg [50 µM], 8 mg [100 µM] and 32 mg [400 µM]) by swishing for 40 seconds in the oral cavity and subsequent expectoration.

C16G2 was well-tolerated with no deaths and no serious or severe AEs. No study drug related treatment emergent AEs were reported and no subject was discontinued due to an AE. No clinically significant changes in vital signs, ECGs, clinical laboratory results, targeted physical examinations and oral cavity assessments were attributable to C16G2 administration. Immunogenicity assessments demonstrated that single dose C16G2 administrations up to a dose of 32 mg did not trigger the development of antibodies against C16G2.

C16G2 was not detected above the lower level of quantitation (LLOQ 10 ng/mL) in any pharmacokinetic sample, with a single exception most likely related to a high background signal,, suggesting there is minimal or no systemic absorption of C16G2 into the circulation after a single C16G2 administration up to a dose of 32 mg.

Phase 2

In Study C3J13-201-01, a total of 60 adult healthy subjects were enrolled, of which 48 subjects received C16G2, and 12 subjects received placebo. Subjects received study drug for 7 consecutive days and were followed for safety and microbiology assessments for 14 days post first study drug administration. The C16G2 concentrations were 3.2 mg/mL (800 µM) in gel formulation and 1.6 mg/mL (400 µM) in liquid formulation.

C16G2 was well-tolerated with no deaths and no other serious or severe adverse events (AEs). The majority of AEs were deemed mild in severity and unrelated to study drug administration and study procedures. Two subjects discontinued from the study due to adverse events; one subject experienced a mild rash and pruritus, the other subject moderate tonsillitis and fever. All events resolved without sequelae. In the clinical study C3J14-201B-00, one serious adverse event (SAE) was reported (acute abdominal pain – infarcted sigmoid appendix epiploica resulting in an appendectomy), and assessed as unrelated to study drug administration by the investigator.

Pharmacokinetic data from study C3J14-201B-00 indicate no detectable systemic levels of C16G2 (all samples below the LLOQ of 10 ng/mL). PK samples were obtained: 1) during and after a 4 hour gel tray administration of 3.2 mg/mL C16G2 in gel (C16G2 administered after manual brushing with a conventional toothpaste without C16G2), and 2) immediately after 3 manual brushings with C16G2 and one 15 minute tray administration with C16G2 (3.2 mg/mL C16G2 in gel).

In an ongoing Study C3J15-202-00, subjects will receive 4 study drug administrations on the first day of dosing followed by AM and PM dosing for 6 consecutive days. 2 mL or 4 mL of 800 µM C16G2 Gel or Placebo will be administered via manual toothbrush and custom dental trays. The doses, duration of application and schedule of study drug administrations in Study C3J15-202-00 are well supported by the safety profile established in Study C3J13-201-01, which also administered multiple daily doses of C16G2 for 7 consecutive days, with a maximum daily exposure of 115.2 mg C16G2. The maximum daily exposure in this study will be 51.2 mg, which is approximately half of the exposure in Study C3J13-201-01.

In the completed Study C3J15-203-00, subjects received study drug ranging from a single day of dosing to 28 days of daily dosing. The C16G2 concentrations in this study will be 3.2 mg/mL (800 µM) and 6.4 mg/mL (1600 µM). The maximum daily exposure in this study was 102.4 mg, which is less than the exposure in Study C3J13-201-01.

In an ongoing Study C3J16-V204-00 subjects will receive 13.6 mg, 27.2 mg or 54.4 mg C16G2 Varnish or Placebo applied to all tooth surfaces. The maximum daily exposure will be 54.4 mg which is less than half of the exposure in Study C3J13-201-01.

In Study C3J16-S205-00 subjects will receive study drug on multiple days of dosing. Approximately 9.2 mg, 18.4 mg, and 36.8 mg C16G2 Strip or Placebo will be applied to molars and bicuspids. The maximum daily exposure in this study will be 73.6 mg, which is less than the exposure in Study C3J13-201-01.

Potential risks to subjects are minimized in this Phase 2 study by the following:

- Study arms will be enrolled in an ascending dose escalation manner (9.2 mg, 18.4 mg, and 36.8 mg C16G2 Strip or Placebo)
- Requirement that all women of child-bearing potential, defined as not surgically sterile or at least two (2) years postmenopausal, must agree to use one of the following forms of contraception from screening through the last study visit: hormonal (oral, implant, or injection) begun >30 days prior to screening; barrier (condom, diaphragm, or cervical cap with spermicide); intrauterine device (IUD). Acceptable contraceptive options may also include abstinence, relationship with a same sex partner or partner who has had a vasectomy at least six (6) months prior to the screening visit
- Requirement that women are not lactating or pregnant, as verified by urine pregnancy tests performed at screening and baseline
- Requirement for male subjects to use contraception or abstain from sexual activity during the study
- Selection of qualified Investigator and training of study personnel
- Monitoring by trained study staff during clinic and follow-up visits
- Utilizing guidelines for management of hypersensitivity and adverse events
- Collection of AEs

This study is being performed in compliance with the guidelines of the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP).

1.7 Subject's Duration of Participation

Approximately 30 male and female subjects 12 to 75 years of age will be enrolled in the study. The maximum subject's duration of participation will be 2.5 months. The estimated duration of the study from first subject in (FSI) to last subject out (LSO) is approximately 3.5 months.

2. STUDY OBJECTIVES

Primary Objectives

- To assess the targeted antimicrobial activity of C16G2 Strip administration as measured by a reduction in *Streptococcus mutans* in saliva and dental plaque
- To assess total bacteria in saliva and dental plaque post study drug administration

Secondary Objective

- To evaluate the safety and tolerability of multiple C16G2 Strip administrations in adolescent and adult dental subjects

3. STUDY DESIGN

A single-blind, randomized, placebo-controlled, phase 2 study to evaluate the oral microbiology and safety of multiple C16G2 Strip applications in male and female dental subjects 12-75 years of age.

The study will compare multiple study drug administrations of 9.2 mg, 18.4 mg, and 36.8 mg C16G2 Strip or Placebo in Study Arms 1 through 3, respectively. Enrollment of subjects in Study Arms 1 through 3 will occur sequentially in an ascending dose escalation manner. Before dosing of study drug, eligible subjects will receive professional dental prophylaxis between Days -7 and -2. Subjects will receive 11 doses administered over approximately two weeks. Each subject will receive a single dose on Day 0, followed by 5 days of AM and PM dosing starting on Day 7. To evaluate the durability of *S. mutans* suppression, study subjects will be followed for microbiology for up to 1 month after the last study drug administration.

Clinic visits include Visit 1 (Screening/Days -30 to -1), Visit 2 (Prophylaxis/Day -7 to -2), Eligibility Confirmation & Baseline Visit 3, Follow-up Visits 4-7 (Safety and Microbiology), Visits 8-17 (Study Drug Administration), Follow-up Visits 18-20 (Safety and Microbiology) and Follow-up Visits 21-22 (Microbiology Only).

Subjects enrolled in all study arms will be assessed for safety and microbiology parameters. For details on study schedules including dosing and microbiology information refer to Appendix A. Details on study assessments & procedures for all study arms are provided in Appendix B. For microbiology assessments in all study arms refer to Appendix C.

3.1 Blinding and Randomization

3.1.1 Randomization

The study will enroll approximately 30 subjects into three study arms. Approximately 10 subjects will receive one of three doses of study drug (9.2 mg, 18.4 mg, 36.8 mg C16G2 Strip or Placebo).

Study subjects will be randomized to receive C16G2 or Placebo Strip, in a 4:1 allocation ratio (8 C16G2 Strip subjects: 2 Placebo Strip subjects) for each of the three study arms. Subjects

will be enrolled in one of the three study arms and the arms will enroll sequentially in an ascending dose escalation manner. Each study arm will be fully enrolled (i.e., the last subject in an arm has completed Visit 3) before enrollment is initiated in the next study arm.

After confirmation of study eligibility, subjects will be randomized at Visit 3 (Day 0) by authorized study staff according to the master randomization schedule from the Sponsor's study statistician. The randomization schedule and associated documentation will be kept in a secure location.

3.1.2 Blinding

The study will be conducted in a single-blind manner. All study subjects will be blinded to the treatment assignment, while the Investigator, study staff/clinicians and the Sponsor's assigned team members (e.g., the Clinical Monitor and the Medical Monitor) will be unblinded as to whether subjects are receiving C16G2 or Placebo.

4. SELECTION CRITERIA

4.1 Inclusion Criteria

Subjects are eligible to participate if they meet the following criteria:

1. Males and females, 12-75 years of age
2. Adults subjects provide written informed consent and adolescent subjects give written or verbal assent, as appropriate, and parent(s) or legal guardian(s) give written informed consent
3. Female subjects of childbearing potential must agree to use one of the following forms of contraception from screening through the last study visit: hormonal (oral, implant, or injection) begun >30 days prior to screening; barrier (condom, diaphragm, or cervical cap with spermicide); intrauterine device (IUD). Acceptable contraceptive options may also include abstinence, relationship with a same sex partner or partner who has had a vasectomy at least six (6) months prior to the screening visit
4. Negative urine pregnancy test in all females of childbearing potential (past menarche)
5. Male subjects of sexual activity age: willing to use contraception or abstain from sexual activity beginning with the first exposure to study drug and continuing until discharged from the study due to completion or Early Termination
6. Healthy, as determined by the Investigator (in consultation with the Medical Monitor, as needed), based on medical and dental history, concurrent illnesses, laboratory results, concomitant medications, oral cavity assessment, and targeted physical examination (general, extraoral, head and neck) during Screening.

   Note: Subjects on a stable dose of medication may be eligible for screening and will be assessed by the medical monitor on a case-by-case basis.
7. Have a minimum of 12 bicuspids and molars with a minimum of 8 molars and bicuspids NOT having restorations, crowns or sealants
8. Demonstrated ability to expectorate ≥2 mL of stimulated saliva in 5 minutes
9. Have a salivary *S. mutans* of 1.0 x 10^5 CFUs/mL or greater at Screening using MSB agar plating
10. Willing to refrain from using non-study dentifrice and other non-study oral care products (oral care rinses, fluoride products, etc.) during the study
11. Willing to postpone elective dental procedures (e.g., dental cleanings) between Screening and final post-treatment visit (End of Study or Early Termination)
12. Willing and able to comply with oral hygiene and diet instructions
13. Able to communicate with the Investigator/study center personnel, understand and comply with the study requirements, and willing to return for protocol-specified visits at the appointed times

4.2 Exclusion Criteria

Subjects are excluded from participation if any of the following apply:

1. Advanced periodontal disease
2. Active caries lesion(s) within 30 days prior to study drug administration (confirmed by comprehensive caries examination including standard radiographs). Subjects presenting with insipient, non-cavitated lesion(s) are not excluded.

   Note: If radiographs are deemed appropriate for the study and taken within 6 months prior to the Screening visit, these may be used for determining eligibility and are not required to be repeated at Screening
3. Partially erupted teeth where the entire crown is not erupted or an operculum is present
4. Medical condition (e.g., artificial heart valve, history of infective endocarditis, cardiac transplant with valvular dysfunction, congenital heart disease or total joint replacement) for which antibiotics are recommended prior to dental visits and/or procedures
5. Pathologic lesions of the oral cavity (suspicious or confirmed)
6. Full dentures or permanent orthodontic appliances, e.g., braces, buccal or lingual brackets. *Note: Partial dentures, removable retainers and night guards are not excluded, provided that they are cleaned regularly throughout the duration of the study*
7. Use of systemic antibiotics, topical oral antibiotics, or use of other drugs, which in the opinion of the Investigator could influence the study outcome, beginning 30 days prior to Screening until the end of study participation
8. Medical history indicating the woman is pregnant, breastfeeding/lactating or has a positive urine pregnancy test
9. Participation in a clinical trial or receipt of a non-FDA approved therapy within 30 days prior to study drug administration (depending on the specifics, participation in an observational study is not necessarily excluded)
10. Presence of any condition or concurrent illness, which in the opinion of the Investigator, would compromise normal immune function (e.g., diabetes, rheumatoid arthritis, lupus, liver disease, organ transplant, etc.), interfere with the use of study dentifrice and oral care products, or interfere with the ability to comply with study requirements, or jeopardize the safety of the subject or the validity of the study results

5. STUDY TREATMENTS

Study subjects will receive a single dose of study drug on Day 0 followed by twice daily administrations on Days 7-11. Study drug will be administered by qualified study staff at the center. Study drug will be removed 90 minutes after application, unless the strips have self-detached prior to that time point.

	C16G2 Subjects	Placebo Subjects	Mode of Application	Days of Study Drug Admin.	C16G2 (mg)
Study Arm 1	8	2	Strip	1	9.2
Study Arm 2	8	2	Strip	1	18.4
Study Arm 3	8	2	Strip	1	36.8

5.1 Study Drug

5.1.1 C16G2 Tooth Strip Formulation

C16G2 Tooth Strip drug product is manufactured by C3 Jian, LLC (Marina del Rey, CA) for administration as a dental tooth strip. The C16G2 Tooth Strip product is provided in a clear pouch containing 4 tooth strips at doses of 9.2, 18.4, and 36.8mg of C16G2 per set of 4 strips.

5.1.2 Placebo Tooth Strip Formulation

Placebo Tooth Strip drug product is manufactured by C3 Jian, LLC (Marina del Rey, CA) with identical excipients as the C16G2 Tooth Strips but does not contain active ingredient. To maintain the study blind the Placebo product is manufactured, packaged, and labeled in the same manner as C16G2 Tooth strips.

5.1.3 Supply, Packaging, and Labeling

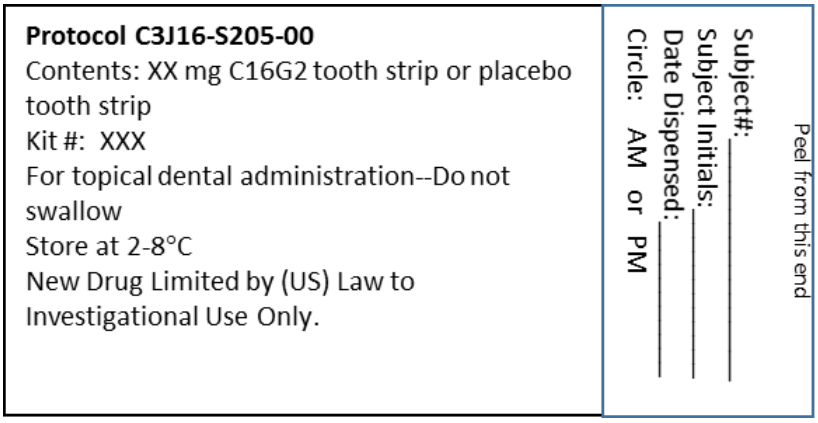
Each kit box will contain 13 clear pouches with 4 individually pouched strips each in a white, light protective pouch. The dosing schedule requires 11 clear pouches for each subject. Two additional clear pouches are provided in each kit box in the event that replacement strips are needed.

The tooth strip pouch labels will include the protocol number, caution statement “Investigational New Drug Limited by (US) Law to Investigational Use Only”, the kit number and the subject number/initials.

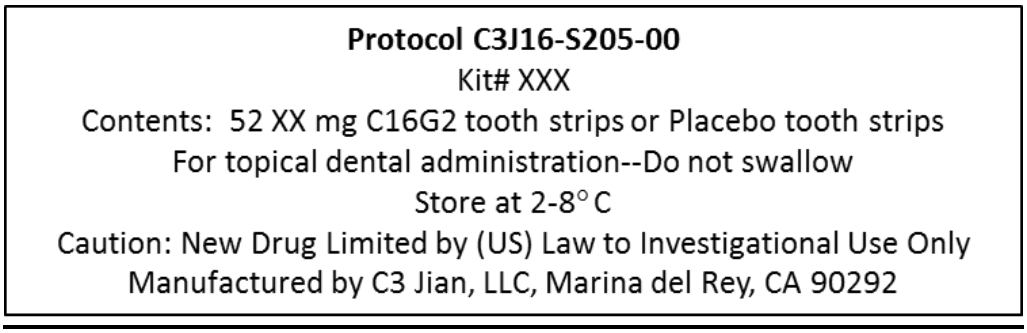
Individual strip white pouches will reflect the dose of individual strips. Total dose (9.2 mg, 18.4 mg, and 36.8 mg C16G2 or Placebo) is a total of 4 strips that will be used for a single dose as demonstrated in the table below.

Study Arm	Individual Strip Dose	Total Dose (4 Strips)
Study Arm 1	2.3 mg	9.2 mg
Study Arm 2	4.6 mg	18.4 mg
Study Arm 3	9.2 mg	36.8 mg

Sample C16G2 Strip or Placebo Strip Label



Sample Kit Box Label



The box label will include the protocol number, kit number, contents, subject number/initials, date of study drug administration, route of administration, storage temperature, caution statement "New Drug Limited by (US) Law to Investigational Use Only", and statement "Manufactured by C3 Jian, LLC, Marina del Rey, CA 90292"

For additional details on supply, packaging and labeling refer to the Study Manual for this study.

5.2 Storage of Study Drug

All study drug material will be stored under secured conditions with limited access. Study drug boxes containing C16G2 or Placebo Strip will be stored at 2-8°C.

Used tooth strips are discarded at the end of each treatment event, the pouches will need to be retained for study drug accountability purposes. Excess tooth strips will be replaced in the study drug box and re-stored at room temperature or 2-8°C. After dosing in the study is complete, box(es) will be sealed closed for future drug accountability by the authorized study staff and/or clinical study monitor (See Section 9.1.7).

5.3 Study Drug Preparation

5.3.1 C16G2 or Placebo Strip Preparation

For details on study drug preparation refer to the Study Manual for this study.

Study drug preparation involves the following steps:

- According to the randomization and study arm assignment, retrieve a study drug kit containing the assigned C16G2 or Placebo Strip dose
- Enter the subject identification and dispensation date on the appropriate study drug label and study records
- To avoid any potential damage to the strip, open the pouch on the side where the subject information was entered
- Apply one strip per quadrant per instructions in Appendix G

6. STUDY ASSESSMENTS & PROCEDURES

For details on study schedules and assessments, including dosing and microbiology information refer to Appendices B through D.

6.1 Screening and Re-screening

Subjects will be screened, including *S. mutans* assessment, within 30 days of planned dosing with the study drug. If a subject qualifies for the study based on screening results, but cannot be treated within 30 days due to scheduling problems, he/she may be re-screened at the Investigator's discretion. During re-screening, the following assessments will be repeated: re-signing of the consent form (if required by the IRB), oral cavity assessment, targeted physical exam, salivary flow assessment, local laboratory (hematology and chemistry) and pregnancy test (if applicable). If the informed consent is not re-signed, all screening procedures except for the informed consent need to be within 30 days. During re-screening, the *S. mutans* assessment does not need to be repeated if <60 days have elapsed since the initial procedures. For potential subjects that do not qualify for the study based on initial screening, re-screening is at the discretion of the Sponsor in consultation with the Investigator on a case-by-case basis. If re-screened within 30 days, not all screening procedures may need to be repeated. Also, subjects that were successfully screened for Study C3J16-V204-00, but not enrolled, may be enrolled into Study C3J16-S205-00 without repeating screening assessments if these are within 30 days of planned dosing (and within 60 days for *S. mutans* assessments).

6.2 Subject Instructions

Subjects enrolled in all study arms will be instructed to abstain from eating food and drinking beverages that contain a high sugar content (e.g., candy, soda with refined sugar, sugary snacks, dried fruit, fruit rolls) from Screening to the last day of study drug administration (Visit 17, Day 11, PM). While smokers are not excluded from study participation, subjects should abstain from using chewing tobacco or similar products throughout the study.

6.2.1 Oral Hygiene Instructions

During the entire study subjects will not be allowed to use any dental material besides the material provided by the study center. Prior to attending the study center for any visit (Visits 1-22), subjects will not be allowed to perform oral hygiene at home. In addition, Subjects will be advised not to use any mouth rinse for approximately 24 hours before the Screening visit.

Prior to discharge at Visit 2/Day -7 to -2, subjects will receive a manual toothbrush, a regular toothpaste containing fluoride, and dental floss provided by the Sponsor to take home. Subjects will be instructed to use these dental products in the morning and evening at home during the remaining study duration, including the evening of Day 0. In addition, subjects will be resupplied with these dental products as needed.

6.2.2 Diet Instructions

Subjects in all study arms will be instructed as follows:

All Visits:

- Do not eat for 1 hour prior to the appointment time
- No liquids, other than plain water, 1 hour prior to the appointment time
  Note: Subjects will be allowed to drink water up to 10 minutes prior to dental plaque and saliva collection, and will be instructed not to swish or rinse

Visits 3, 8-17 (Study Drug Administration Days)

- Do not eat or drink anything besides plain water within 1 hour prior to the appointment time
- Do not eat, drink anything or swish during the study drug administration period and for 1 hour after the removal of the strips.

  Note: Subjects will be under the supervision of study staff to ensure that they do not consume any food or drink anything during and 1-hour post study drug administration.

6.3 Clinic Visit Schedules, Assessments & Procedures

6.3.1 Clinic Visit Schedules

For details on Clinic Visit Schedules refer to Appendix D.

6.3.2 Assessments & Procedures

Clinic Visit 1 (Screening Days -30 to -1)

Subjects will be scheduled for this visit between 6AM and 10AM.

- Informed Consent/Assent & Assign Subject ID
- Inclusion/Exclusion
- Medical/Surgical/Dental History and Concurrent Illnesses
- Salivary Flow Assessment
- Concomitant Medications
- Demographics
- Dental status and comprehensive caries examination including standard radiograph
  Note: If radiographs are deemed appropriate for the study and taken within 6 months prior to the Screening visit, these may be used for determining eligibility and not required to be repeated at Screening
- Screening Laboratory Testing
- Urine Pregnancy Test (females of childbearing potential only)
- Oral Cavity Assessment
- Targeted Physical Exam (general, extraoral, head & neck)
- Vital Signs (blood pressure, heart rate, temperature)
- Microbiology (stimulated saliva ONLY)
  Note: Screening Microbiology sample will be collected on Days -30 to -8 prior to Visit 2
- Discharge

Clinic Visit 2 (Prophylaxis, Day -7 to -2)

Subjects will be scheduled for this visit between 6AM and 10AM.

- Microbiology (Stimulated Saliva and Dental plaque collection)
  Note: Samples need to be obtained prior to oral hygiene training and professional dental prophylaxis
- Professional Dental Prophylaxis (prophylaxis will include removal of bulk plaque and supragingival scaling)
  Note: NO fluoride treatment as part of the procedure, NO subgingival scaling as part of the prophylaxis
- Oral Hygiene Training:
  - Flossing (string): instructions are provided in Appendix E
  - Manual toothbrush technique for routine dental hygiene using a manual toothbrush provided by the sponsor and toothpaste containing fluoride (for instructions refer to Appendix F)
- Oral Hygiene Product Distribution
- Discharge

Clinic Visits 3 & 8-17 (Baseline Day 0, Days 7-11 – Study Drug Administration Days)

AM visits will be scheduled 6AM to 10AM. PM visits will be scheduled 6PM to 10PM

Subjects should not be exposed to study drug if they present with any disruption or loss of integrity in the oral cavity mucosa, gingiva or have lip lesions, (e.g. aphthous stomatitis, active herpetic sores, cheek bites, or severely chapped or cracked lips, etc.).

Pre-Dose

- Confirmation of eligibility (Visit 3 ONLY)
- Medical/Dental History & Concurrent Illness Update (Visit 3 ONLY)
- Study Arm Assignment and Randomization (Visit 3 ONLY)
- Urine Pregnancy Test (females of childbearing potential only) (Visit 3 ONLY)
- Targeted Physical Exam (Visit 3 & 8 ONLY)
- Concomitant Medications Update
- Oral Cavity Assessment: **AM Visits 3, 8, 10, 12, 14, & 16 only**
- Vital Signs (Visits 3, 8 & 17 only)
- Microbiology (Stimulated Saliva & Dental Plaque)
  Note: Microbiology samples will only be collected at Visits 3, 8, 9 and 10
- Brushing and flossing with the dental material provided by the Sponsor

Study Drug Administration:

Instructions for the application of C16G2 Strips or Placebo are provided in the Study Manual and in Appendix G.

- Subjects will have C16G2 Strip (9.2 mg, 18.4 mg, or 36.8 mg in Study Arms 1 through 3, respectively) or Placebo Strip applied to molars and bicuspids and remain on the subject's teeth for up to 90 minutes. Subject will not eat, swish or drink anything during the study drug administration period.

Post-Dose

- C16G2 and Placebo strips will remain on the subject's teeth for 30 minutes (do not manipulate strips during that time)
- Remove strips that have fully self-detached starting 30 minutes after application

- Remove all strips that have not fully self-detached 90 minutes after application
  Note: Dental strips will in most cases fully detach prior to 90 minutes. Only remove strips that fully detach earlier than 90 minutes after application. Subjects will not eat, swish, or drink for one hour after the removal of study drug
- Photographic imaging immediately after study drug application (Visit 3 ONLY)
- Oral Cavity Assessment: AM Visit 3 and PM Visits 9, 11, 13, 15, & 17 only
- Vital Signs (blood pressure, heart rate, temperature) within 20 minutes of removal of the last strip, taken in supine or sitting position (Visits 3, 8 & 17 only)

Prior to Discharge

- Adverse Events
- Oral Hygiene Product Distribution (as needed)
- Discharge

Clinic Visits 4-7 and 18-20

On visits 7, 19 & 20 subjects will be scheduled between 6AM and 10AM. Remaining visits will be scheduled as appropriate, according to clinic visit schedule in Appendix D

- Concomitant Medication Update
- Oral Cavity Assessment
- Targeted Physical Exam (Visits 5, 18 and 20)
- Microbiology (stimulated saliva and dental plaque collection)
- Adverse Events
- Discharge

Clinic Visits 21-22

Subjects will be scheduled for this visit between 6AM and 10AM.

- Microbiology (stimulated saliva and dental plaque collection)
- Discharge
- End of Study (Visit 22 ONLY)

7. ADVERSE EVENTS AND SAFETY MANAGEMENT

7.1 Definition of Adverse Events

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

For the purposes of this definition, “untoward” means unfavorable, negative, or harmful. Note that an AE is any event observed or reported that is associated with the use of the drug, without regard to causality.

Adverse events will be collected and reviewed to evaluate the safety of C16G2 or Placebo Strip. All AEs will be recorded from the first exposure to study drug up to 1 week after the last administration of study drug. After that time point, all ongoing adverse events will be followed in accordance with good medical practice until resolution or the adverse event or condition has stabilized. AEs that occur after exposure to study drug will be classified as treatment-emergent AEs (TEAEs). All AEs whether observed by the Investigator and/or study staff or reported by the subject, will be recorded in the source records and EDC system.

Medical or dental conditions that are present at or before the administration of study drug that manifest with the same intensity or frequency subsequent to administration of study drug will not be recorded as AEs. Similarly, signs or symptoms related to a pre-existing disease will not be recorded as AEs unless there is an increase in the intensity, frequency or duration of the signs or symptoms. These pre-existing events, signs, or symptoms will be entered in the source records and EDC system.

Diagnostic and therapeutic non-invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported, if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

7.2 Assessment of Severity (Intensity) of Adverse Events

The severity or intensity of an AE describes the degree of impact upon the subject and/or the need for, and the extent of medical care required to treat the AE.

Symptoms should be graded as mild, moderate, severe, or life threatening according to the grading scale noted in Table 1. Please refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Table 1: Adverse Events Intensity Description

Grade	Description
Mild (1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate (2)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Severe (3)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Life Threatening (4)	Life-threatening consequences; urgent intervention indicated

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function), but would not be classified as serious unless it met the criteria for an SAE (See Section 7.7).

7.3 Assessment of Causality (Relationship to Study Drug)

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. The Investigator's assessment of causality must be provided for all AEs (serious and non-serious).

Several factors to consider when assessing the relationship of an event to the study drug:

- Alternative etiology - Is the event due to the underlying disorder being studied or to another known disorder?
- Known relationship - Has the event been observed before in patients treated with this study drug or similar products?
- Temporal relationship - Is there a reasonable temporal relationship between the time of onset of the event and the administration of the study drug?
- Concomitant medication - Is the event a known side effect of a concomitant medication?

The Investigator will document his/her opinion of AE relationship to study drug using the criteria outlined in Table 2 below.

Table 2: Adverse Event Relationships Description

Relationship	Description
None	The event can be readily explained by the subject's underlying medical condition, a concomitant therapy or other cause and the Investigator believes no relationship exists between the event and study drug. In this case, the Investigator should document the condition, concurrent / underlying illness, medication, study procedure or other cause they believe to be the cause of the adverse event.
Unlikely	The event does not follow a reasonable temporal sequence from administration of study drug nor does the event follow a known or expected response pattern to study drug and may have another cause. In this case, the Investigator should document the condition, concurrent / underlying illness, medication, study procedure or cause they believe may have contributed to the adverse event.
Possible	The subject's condition, concurrent/underlying illness, medication, or study procedures cannot explain the event, and there is a plausible temporal relationship between the event and study drug administration.
Probable	The temporal relationship between the administration of study drug and the adverse event strongly suggests a relationship, and/or the adverse event cannot be reasonably explained by another condition, concurrent / underlying illness, medication, study procedure or other cause, or the adverse event abates with discontinuation of study drug, and recurs with re-administration.

For reporting purposes, AEs assigned a relationship to study drug of "Probable," and "Possible" will be classified as related to study drug. AEs assigned a relationship to study drug of "Unlikely" and "None" will be classified as not related to study drug.

7.4 Suspected Adverse Reaction (SAR) and Adverse Reaction (AR)

Suspected adverse reactions (SARs) are the subset of all AEs for which there is a reasonable possibility to conclude that the study drug caused the event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the study drug and the AE.

An "adverse reaction" (AR) is any AE caused by a drug. ARs are a subset of all SARs for which there is reason to conclude that the study drug caused the event.

An SAR implies a lesser degree of certainty about causality than an AR, which means any AE caused by a drug.

For reporting purposes, AEs assigned a relationship to study drug of "Probable," and "Possible" will be classified as SARs.

AEs assigned a relationship to study drug of "Unlikely" and "None" will not be classified as SARs.

7.5 Unexpected Adverse Events

The Investigator's Brochure (IB) provides Investigators with information (clinical and nonclinical) about the study drug. The IB includes those AEs for which a causal relationship is suspected or confirmed (SARs or ARs), as well as adverse events that may be predicted to occur based on the pharmacological properties of the drug. The IB is used as the basis for the Sponsor's determination of "unexpected" for reporting purposes.

"Unexpected" SARs are AEs not currently listed in the IB. An AE or SAR may also be considered "unexpected" if it is not listed in the IB at the specificity or severity that has been observed.

7.6 Withdrawal Due to Adverse Events

Withdrawal due to an AE should be distinguished from withdrawal due to insufficient response, according to the definition of AE noted earlier, and entered in the source records and EDC system.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

7.7 Serious Adverse Events

7.7.1 Definition of Serious Adverse Events

Serious adverse events (SAEs) are defined as those AEs that meet any of the following criteria:

- Life threatening, that is, any event that, in the opinion of the Investigator, poses an immediate risk of death from that event
- Results in death
- Results in or prolongs hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly/birth defect
- Is an important medical event that may require an intervention to prevent one of the outcomes listed above
- For clarification, an AE or suspected adverse reaction (SAR) is "life-threatening", if, in the view of the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death

The Investigator should exercise medical and scientific judgment when deciding whether SAE reporting is appropriate in other situations not strictly meeting the listed criteria above. Examples of important medical events which may meet the definition of an SAE include: intensive treatment in an emergency room or at home for allergic bronchospasm, certain laboratory abnormalities (e.g., blood dyscrasias), convulsions that do not result in hospitalizations, or development of drug dependency or drug abuse.

Pre-planned hospitalizations and/or elective surgical procedures may not be considered SAEs.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Scheduled or elective same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported, if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

The Investigator should contact the Sponsor's Medical Monitor immediately if there is a question as to whether or not an AE meets the criteria for serious.

7.8 Procedures for Reporting and Recording Serious Adverse Events & Suspected Serious Adverse Reactions

All SAEs, irrespective of relationship to study treatment, must be reported to the Sponsor and the Medical Monitor as soon as possible, but no later than 24 hours from the time of notification. All AE/SAE information and appropriate supporting documentation must be sent electronically to the Medical Monitor & Sponsor.

Medical Monitor:

Marilyn R. Carlson, DMD, MD, RAC

Cell Phone: 858-945-7189

Email: mcarlson@agility-clinical.com

Urgent safety issues should be discussed by telephone with the Medical Monitor as soon as the Investigator or members of the study staff become aware of the issue.

It is very important that the SAEs be reported as soon as possible via the EDC and the information be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality. A brief description of the event must be provided at the time of the initial report. After the initial SAE report has been submitted, relevant follow-up information should be submitted as soon as possible, preferably within one (1) business day of receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be added as follow-up information in the EDC system.

Additional SAE-related supporting documents, such as copies of hospital reports, lab reports, discharge summaries, and autopsy reports, if applicable, may be requested. All subject identifiers, except the subject's initials and unique study identification number, must be removed from documents prior to submission to the Medical Monitor and other Sponsor designees. Subjects' names, personal identification numbers (i.e., medical record numbers), and addresses, etc., should be removed or blocked-out.

Reporting of a suspected serious adverse reaction (SSAR) should not be delayed in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. Any SAE that occurs at any time during the study, whether or not related to study drug, must be reported to the Medical Monitor within 24 hours of first awareness at the site.

The Investigator is responsible for the information recorded on SAE reports. It is the Investigator's responsibility to ensure that the SAE information in the EDC system and source documents are accurate, consistent and in agreement. The Investigator is responsible for continuing SAE follow-up. The results of any additional assessments of the SAE must be reported to the Medical Monitor as an update to the SAE as soon as possible, but no later than 24 hours after first awareness. Details on the SAE reporting procedure are provided in the SAE Reporting Guidelines. Criteria for determining severity and the relationship to study drug for the updated SAE will be the same as those previously described in Sections 7.2 and 7.3.

7.8.1 Reporting Serious Adverse Events to the FDA and IRB

The Investigator will comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB. The completed SAE report will be used by the Sponsor in regulatory filings and may be used by the Investigator to convey SAE information to the IRB.

7.8.2 Following Adverse Events and Serious Adverse Events

All AEs should be followed in accordance with good medical practice until resolution or the adverse event or condition has stabilized. AEs will be followed for one week post last dose in all Study Arms. All SAEs will be followed until the outcome is known or the subject's condition has stabilized.

7.9 Pregnancy

A negative urine pregnancy test result must be confirmed at Screening and Baseline visits.

Female subjects of childbearing potential, defined as not surgically sterile or at least two (2) years postmenopausal, must agree to use one of the following forms of contraception from screening through the last study visit: hormonal (oral, implant, or injection) begun >30 days prior to screening; barrier (condom, diaphragm, or cervical cap with spermicide); intrauterine device (IUD). Acceptable contraceptive options may also include; abstinence, monogamous relationship with same sex partner or partner who has had a vasectomy at least six (6) months prior to the screening visit. In the unlikely event a subject becomes pregnant during the study, the subject will be withdrawn from the study immediately upon confirmation of pregnancy. These subjects will be required to return to the study center to undergo early termination procedures (Sections 9.3.2 and 9.3.3).

In addition, any documented pregnancy will be tracked and followed through outcome. While pregnancy itself is not considered an AE or an SAE, any pregnancy complications or elective termination of a pregnancy for medical reasons will be recorded as an AE and evaluated as a possible SAE.

All pregnancies are to be reported immediately to the Medical Monitor.

7.10 Management of Medical Emergency (Hypersensitivity)

If a hypersensitivity reaction occurs during the administration of study drug, the Investigator will discontinue the administration of study drug and provide general supportive measures. If an adverse event occurs after administration of study drug, the Investigator will provide general supportive measures.

7.11 Management of Dosing Error

If a dosing error does occur, the Investigator will; 1) monitor the subject, 2) provide general supportive measures, as needed, 3) notify the Medical Monitor and the Sponsor within 24 hours, and, 4) report the dosing error to the IRB, per site’s policy.

8. STATISTICAL CONSIDERATIONS

8.1 General Considerations

Protocol C3J16-S205-00 is a phase 2, single-blind, randomized, placebo controlled study designed to evaluate the safety and microbiological activity of C16G2 Strip applied directly to the tooth surface. Study subjects will receive a single dose of C16G2 Strip or Placebo followed by 5 days of twice-daily dosing 7 days post-first study drug administration. The study will compare 9.2 mg, 18.4 mg and 36.8 mg C16G2 Strip or Placebo administrations in Study Arms 1 through 3, respectively.

The objectives of the study are to assess the targeted antimicrobial activity of C16G2 Strip or Placebo as measured by a reduction in the number of *Streptococcus mutans* in saliva and dental plaque, and assessment of total bacteria in saliva and dental plaque, and to evaluate the safety of multiple C16G2 Strip or Placebo administration in adolescent and adult study subjects,

For the summary table presentations, data will be summarized in tabular format by study arm and treatment group. All statistical analysis will be descriptive in nature. Descriptive summary statistics will include N, mean, standard deviation, median, range (minimum and maximum) for continuous variables, and frequency counts and percent for categorical variables.

8.2 Randomization

Subjects will be sequentially assigned to one of three study arms in the order of enrollment. Each study arm will be fully enrolled (i.e., the last subject in an arm has completed Visit 3) before enrollment is initiated in the next study arm. After confirmation of study eligibility, subjects will be randomized at Visit 3 (Day 0) by authorized and unblinded study staff according to the master randomization schedule from the Sponsor's study statistician. The randomization schedule and associated documentation will be kept in a secure location.

A total of 30 subjects will receive three doses of C16G2 Strip or Placebo. Study subjects will be randomized to receive a single dose of study drug, C16G2 Strip or Placebo, in a 4:1 allocation ratio (eight C16G2 Strip subjects: two Placebo subjects) for each of the three study arms. The three C16G2 Strip doses planned are 9.2 mg, 18.4 mg and 36.8 mg.

8.3 Blinding

The study will be conducted in a single-blind manner. All study subjects will be blinded to the treatment assignment, while the Investigator, study staff/clinicians and the Sponsor's assigned team members (e.g., the Clinical Monitor and the Medical Monitor) will be unblinded as to whether subjects are receiving C16G2 or Placebo.

To ensure blinding, study drug (C16G2 Strip or Placebo) will be prepared in an area outside the purview of study subjects.

8.4 Sample Size Determination

The total number of subjects planned for this study is approximately 24 (n = 8 per arm). There are no data on which to base formal sample size calculations for this study. The data generated in this study will assist with ongoing clinical development of C16G2 Strip. Subjects' data in all three study arms will provide information on the safety and microbiology of a single C16G2 Strip

or Placebo administration. Subjects who do not return for assessments after study drug administration for any reason may be replaced at the Sponsor's discretion.

8.5 Analysis Sets

There will be two analysis sets; the safety analysis set and the microbiology analysis set.

The safety analysis set will be defined as those subjects enrolled and have received any amount of C16G2 Strip or Placebo.

The microbiology analysis set will be comprised of two subsets, the microbiology saliva and microbiology dental plaque subset. These subsets will be based on the subjects who received study drug (C16G2 Strip or Placebo) and have at least a baseline and one post-baseline saliva and dental plaque sample.

8.6 Interim Safety Analysis

There are no interim analyses planned; however, microbiology data will be reviewed by the Sponsor's assigned team in an ongoing manner throughout the course of the study.

8.7 Statistical Analyses

8.7.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics (i.e., age at screening, gender, weight, height, body mass index (BMI), race, ethnicity, medical history, physical examination, prior medications) will be listed for individual subjects and summarized by study arm / treatment group using summary statistics for continuous variables and frequency distributions for discrete variables.

8.7.2 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary and will be summarized for each study arm/treatment group by WHO Anatomical Therapeutic Chemical (WHO ATC) class and medication name. These summaries will present the number and percentage of subjects using each medication.

8.7.3 Completion of the Study and Withdrawals

Withdrawals and the reason for withdrawal (i.e., AE(s), protocol non-compliance, requirement for an unacceptable concomitant medication, lost to follow-up, failed to return, voluntary withdrawal, and other reasons) will be listed. The number and percentage of subjects who complete the study will be summarized. The number and percentage of subjects who withdraw from the study will be tabulated by study arm / treatment group at time of withdrawal.

8.7.4 Protocol Deviations

Protocol deviations will be listed and categorized (i.e., Inclusion/Exclusion Criteria, Randomization, Study Procedures, Missed Study Visit, Visit out of Study Window, Informed Consent, Safety Reporting, Study Drug Administration, Study Drug Accountability, and Other) and summarized based on these categories.

8.7.5 Safety Analysis

8.7.5.1 Adverse Events

Adverse events (AE) will be classified into standard terminology (preferred term and system organ class) using the Medical Dictionary for Regulatory Activities. The severity of each adverse event will be graded as 1) mild, 2) moderate, 3) severe, or 4) life-threatening, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

In addition, all adverse events will be classified as to whether the relationship to study drug was 1) None, 2) Unlikely, 3) Possible, or 4) Probable and followed to resolution or until the adverse event or condition has stabilized.

The incidence and duration of treatment-emergent adverse events (TEAEs) will be summarized by study arm/treatment group according to MedDRA-preferred term and MedDRA system organ class term. An AE will be considered treatment emergent if the onset date and time occur on or after the recorded clock time of study drug administration. Tabulations of adverse events by severity grade and causal relationship to study drug (related, unrelated) will be provided.

For reporting purposes, AEs assigned a relationship to study drug of “Possible” and “Probable” will be classified as related to study drug. AEs assigned a relationship to study drug of “Unlikely” or “None” will be classified as not related to study drug.

The number and percentage of subjects with reported serious adverse experiences (SAEs) and subjects who withdrew due to an AE will be tabulated by study arm/treatment group.

All adverse events will be presented in by-subject listings by reported verbatim term and MedDRA-preferred term, MedDRA system organ class, start and stop date and time, study day, duration, severity, relationship to study drug, seriousness, and outcome. All reported serious adverse events will also be displayed in by-subject listings.

8.7.5.2Oral Cavity Assessment

Oral cavity assessment (hard and soft tissues) findings will be documented at Screening and at each protocol-specified study visit.

Clinically significant examination findings identified at Screening will be added to the subject's Medical History.

After study drug administration clinically significant changes in the oral cavity assessment will be recorded as AEs and these TEAEs will be summarized by study arm / treatment group for each of the protocol specified assessments by calculating the number and proportion of subjects who develop clinically significant findings in the oral cavity after study drug administration.

8.7.5.3 Targeted Physical Examination

Targeted physical examination (general, extraoral, head and neck) findings will be documented at Baseline and at each protocol-specified study visit.

Prior to administration of study drug, clinically significant examination findings will be added to the subject's Medical History.

After study drug administration clinically significant changes in the targeted physical examination will be recorded as AEs.

8.7.5.4 Vital Signs

Vital sign results (blood pressure, heart rate and temperature) will be summarized at Visit 1 (Day -30 to Day -7), Visit 3 (Day 0) and Visit 8 (Day 7 /AM) and 17 (Day 11/PM pre- and post-study drug administration for all study arms by calculating the mean, median, standard deviation, and range. Mean change from baseline will also be presented where baseline is defined as prior to study drug administration at Visit 3 (Day 0) for each study visit.

8.7.5.5 Microbiology Analysis

Stimulated saliva and dental plaque samples will be analyzed for the number of *S. mutans* and total number of bacteria present. Samples will be analyzed by MSB and TH agar plating. Samples will be stored for analysis using qRT-PCR and bacterial community analysis. Bacterial community analysis and qRT-PCR data will be analyzed at appropriate time points based on plating assessments. Descriptive statistics utilizing mean, standard deviation, median and range of oral microbes at each time point for each study arm will be determined and compared to Baseline, as applicable.

Further details regarding Microbiology analysis will be presented in the Statistical Analysis Plan (SAP).

9. RESPONSIBILITIES

9.1 Investigator Responsibilities

9.1.1 Compliance with Good Clinical Practice

The Investigator will print name and sign the Investigator Signature Sheet.

The Investigator will ensure adherence to the basic principles of "Good Clinical Practice," as outlined in the Code of Federal Regulations (CFR) 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, part 54, and part 56, as well as the International Conference on Harmonization (ICH) Guideline of Good Clinical Practice (ICH E6) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" in Appendix I, ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the subject.

9.1.2 Institutional Review Board (IRB)

The Investigator will submit this protocol and any materials (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to the IRB. Approval from the IRB must be obtained before starting the study and documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the IRB granted the approval.

The Investigator will submit all SAE reports to the IRB within the locally specified time requirement. The Investigator will submit any safety report from the Sponsor to the IRB within the locally specified time requirement. The Investigator is responsible for submitting all protocol amendments to the appropriate IRB prior to implementation.

9.1.3 Informed Consent

Informed Consent and Assent:

The Investigator will obtain verbal or written assent, as appropriate, and written informed consent from one parent or legal guardian of each participant, if consistent with IRB policy and state law, for each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The Investigator will utilize IRB-approved assent and consent forms.

Each informed consent form (ICF) will be signed and dated by the parent or legal guardian of the subject, and the person obtaining the informed consent. By signing the informed consent form or giving oral or written assent, the parent or legal guardian and the subject agree that the subject will complete all evaluations unless the parent, legal guardian or subject withdraws consent or the subject is withdrawn from the study for any reason.

As part of the informed consent, the Investigator will obtain HIPAA compliant authorization from subjects to use and disclose relevant protected health information (PHI) and permission for

authorized representatives of C3 Jian, LLC, or regulatory authorities including the FDA, to review in confidence any records identifying subjects in the clinical study.

Recruitment efforts may precede obtaining informed consent; however, informed consent must be obtained prior to any protocol specific procedures being performed.

The Investigator will communicate any new information on safety to subjects who consent to participate in this study in accordance with IRB requirements. The ICF and assent will be updated, if necessary.

9.1.4 Confidentiality

The Investigator will assure that subjects' anonymity will be strictly maintained and that their identities will be protected from unauthorized parties. Only subject initials and an identification code (i.e., not names) will be recorded and submitted to the Sponsor or IRB.

The Investigator agrees that all information received from C3 Jian, LLC, including but not limited to the Investigator's Brochure, this protocol, EDC data, the study drug, and any other study information, are the sole and exclusive property of C3 Jian, LLC. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from C3 Jian, LLC.

The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

9.1.5 Study Files and Retention of Records

The Investigator will maintain adequate and accurate records that fully document the conduct of the study and enable study data to be verified. These documents should be classified into separate categories: 1) Investigator's study file and 2) subject clinical source documents.

- The Investigator's study file includes the original protocol, protocol amendments, EDC data, and query forms, IRB approval with correspondence, approved informed consent forms, drug records, staff curriculum vitae (CV) and authorization forms, and other appropriate documents and correspondence.

- Subject clinical source documents include, but are not limited to, the subject's medical/dental records, ECGs, pathology and special assessment reports, consultant letters, screening and enrollment log, as applicable.

The Investigator will make the source documents for this study available to C3 Jian, LLC. or its representatives, or to regulatory or health authority inspectors. The Investigator will retain all study documents for at least two years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region (i.e., United States, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least two years after the investigation is discontinued and regulatory authorities have been notified. The Investigator may retain documents longer if required by applicable regulatory requirements or by agreement with C3 Jian, LLC.

The Investigator will notify C3 Jian, LLC prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Investigator must notify C3 Jian, LLC in writing in advance. If the Investigator cannot guarantee this archiving requirement at the study center for any or all of the documents, special arrangements will be made between the Investigator and C3 Jian, LLC for storage. If source documents are required for continued care of the subject, appropriate copies for storage off site will be made.

9.1.6 Study Data - Electronic Data Capture

The Investigator is responsible for the completeness and accuracy of information entered in the source records and EDC system for each individual enrolled. The Investigator will review and approve all EDC entries; document the reason that a subject withdraws from the study in the source records and EDC system and attempt to obtain termination assessments; and continue follow-up to document the outcome of any adverse event.

9.1.7 Drug Accountability

The Investigator is responsible for ensuring adequate accountability of all used and unused study drug, including acknowledgment of receipt of each shipment of study products (quantity and condition) and subject dispensing records. Dispensing records will document quantities received and quantities dispensed, kit or lot number (if applicable), date dispensed, Subject identifier number, and initials of the person dispensing study drug.

The Investigator will make these study drug accountability records available to the study monitor. At the end of the study and after the Study Monitor has completed study drug accountability, drug supplies will be returned for destruction, unless an alternative disposition is arranged and approved by the Sponsor.

Unused study drug such as partially used strip pouches and boxes must not be discarded or destroyed by the Investigator until requested in writing by the Sponsor and only after the Clinical Monitor has conducted the final investigational product accountability. At this point, the Sponsor may request in writing that study drug inventory be destroyed in compliance with their institutional requirements.

9.1.8 Inspections

The Investigator will make the source documents (paper and/or electronic) for this study available to C3 Jian, LLC or its authorized designee, or to the regulatory or health authority inspectors.

9.1.9 Protocol and IRB Compliance

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will submit all amendments to the protocol to the IRB in accordance with local requirements. Approval by the IRB will be obtained before amendments are implemented.

9.2 Sponsor Responsibilities

C3 Jian, LLC is the Sponsor of this study. C3 Jian, LLC or its designee is responsible for selecting qualified Investigators, providing them with information needed to conduct the study properly, monitoring the study to ensure it is conducted in compliance with the Code of Federal Regulations (CFR), local/regional requirements, GCP guidelines, and the protocol, and reporting the new adverse events or risks to the Investigators, FDA and local regulatory authorities in a timely manner.

9.2.1 Protocol, Protocol Amendments, and Safety Updates

C3 Jian, LLC is responsible for the protocol and protocol amendments, except those intended to reduce immediate risk to subjects. C3 Jian, LLC is responsible for submitting the protocol and protocol amendments to the appropriate regulatory authorities.

C3 Jian, LLC is responsible for providing written safety updates to the Investigator. Safety updates include any information that significantly bears on the subject's risk to receive the study drug.

9.2.2 Monitoring of Study

Prior to the initiation of the study, C3 Jian, LLC or its designee will ensure the Investigator and study staff understands the investigational status of the product, all requirements of the protocol, and regulatory responsibilities as an Investigator. The Clinical Monitor will visit each clinical site at appropriate intervals to ensure compliance with the protocol and to verify accuracy and completeness of data reported, and accountability of supplies of investigational product.

The Clinical Monitor(s) will be available for consultation with the Investigator and serve as a liaison between the site and the Sponsor. The Clinical Monitor or authorized representatives of the Sponsor may inspect all data, documents, and records required to be maintained by the Investigator including but not limited to, medical/dental records and pharmacy records for subjects participating in this study. The study center will permit access to such records.

9.2.3 Data Handling and Recording

C3 Jian, LLC. or its authorized designee is responsible for data processing. The Investigator is responsible for the accurate and timely completion of EDC entries. These entries will be reviewed for accuracy and completeness by the Clinical Monitor remotely on an ongoing basis and during study center visits. If necessary, the study center will be contacted for corrections and/or clarifications. All data will be entered into a study database for analysis and reporting. Upon completion of data entry, the database will receive a quality assurance check to ensure acceptable accuracy and completeness.

9.2.4 Study Report and Publication

C3 Jian, LLC is responsible for submitting the study report to the appropriate regulatory authorities and for publishing the results of this study. No results will be published without prior review and approval by C3 Jian, LLC.

Within one year of the final clinical study report, the results of the entire study will be submitted for public disclosure in abstract, manuscript, or presentation form, under the guidance of the

Publication Committee. Following that disclosure, Investigators in this study may communicate, orally present, or publish site specific results in scientific journals or other scholarly media in accordance with the conditions set forth in the Clinical Study Agreement. No such communication, presentation, or publication will include C3 Jian's confidential information.

Investigator(s) will submit any proposed publication or presentation to C3 Jian, LLC at least 45 days prior to submission of the publication or presentation. Investigator(s) will withhold publication or presentation for an additional 90 days in order to enable C3 Jian, LLC to obtain patent protection, if deemed necessary. These terms will hold except to the extent different period(s) may be provided for in the Clinical Study Agreement between the parties, in which case such different time period shall control.

9.3 Joint Investigator / Sponsor Responsibilities

9.3.1 Access to Information, Quality Control and Assurance

In accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, the Clinical Monitor will have direct access to the Investigator's source documentation at regular intervals throughout the study, in order to document compliance with the protocol and verify the completeness and accuracy of the data recorded in the source records and EDC system. The Investigator will cooperate with the Clinical Monitor to ensure that any problems detected in the course of these monitoring visits are resolved in a reasonable period of time.

Clinical Monitors will periodically audit, at mutually convenient times during and after the study, all EDC entries and corresponding source documents, for each subject. In addition to remote monitoring via the EDC system, monitoring on-site visits provide C3 Jian, LLC with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of EDC entries, to resolve any inconsistencies in the study records, and to assure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

9.3.2 Withdrawal of Subjects

Any subject may choose to withdraw from the study for any reason and at any time. The Investigator will withdraw any subject if it is not in the subject's best interest to continue or the subject is not compliant with study assessments. When a subject is withdrawn from the study (regardless of the reason), the date and reason will be recorded. In addition, all evaluations specified for the End of Study Visit 22 will be performed, if feasible.

In addition, subjects may choose to withdraw authorization to use and disclose their protected health information (PHI) as defined by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator or Sponsor prior to the date of such withdrawal will continue to be used and disclosed.

Subjects may be removed from the study if one or more of the following events occur:

- Significant protocol violation on the part of the Investigator;
- Failure of subject to meet the study entrance criteria;
- Significant noncompliance on the part of the subject with study procedures;

- Withdrawal of consent (refusal of the subject to continue treatment or assessments);
- Develops medical condition, taking a medication which could affect study outcome (e.g., antibiotic);
- Due to adverse event or unacceptable toxicity;
- Decision by the Investigator that termination is in the subject's best medical interest;
- Unrelated medical illness or complication;
- Lost to follow up.

9.3.3 Study Discontinuation

Both the Investigator and C3 Jian, LLC reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, both the Investigator and C3 Jian, LLC will assure that adequate consideration is given to the protection of the subjects' interests. All subjects will undergo all evaluations specified for the end of study (Study Visit 22), in an "exit" examination, if the study is terminated prematurely.

Subject's medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subjects will receive written copies of all laboratory data to bring to their health care provider. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, C3 Jian's Medical Monitor (or designee), and the Institutional Review Board (IRB).

The information developed in this clinical study will be used by C3 Jian, LLC in the clinical development of the study drug. C3 Jian, LLC may disclose information to clinical Investigators, to other pharmaceutical companies, to the FDA and to other government agencies as required.

10. ETHICS

10.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the Seoul, Korea revision (2008), as provided in Appendix I.

10.2 Institutional Review Board

The protocol, informed consent, and any materials (e.g., advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB.

The IRB is responsible for reviewing the protocol, informed consent, Investigator's Brochure, all amendments, and periodic safety reports in accordance with current institutional, local, and national regulations. A letter documenting the IRB's approval of the protocol will be provided to the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator will submit all periodic reports and updates that the IRB may require, including any final close out reports. The Investigator will inform the IRB of any reportable adverse events and protocol deviations.

11. REFERENCES

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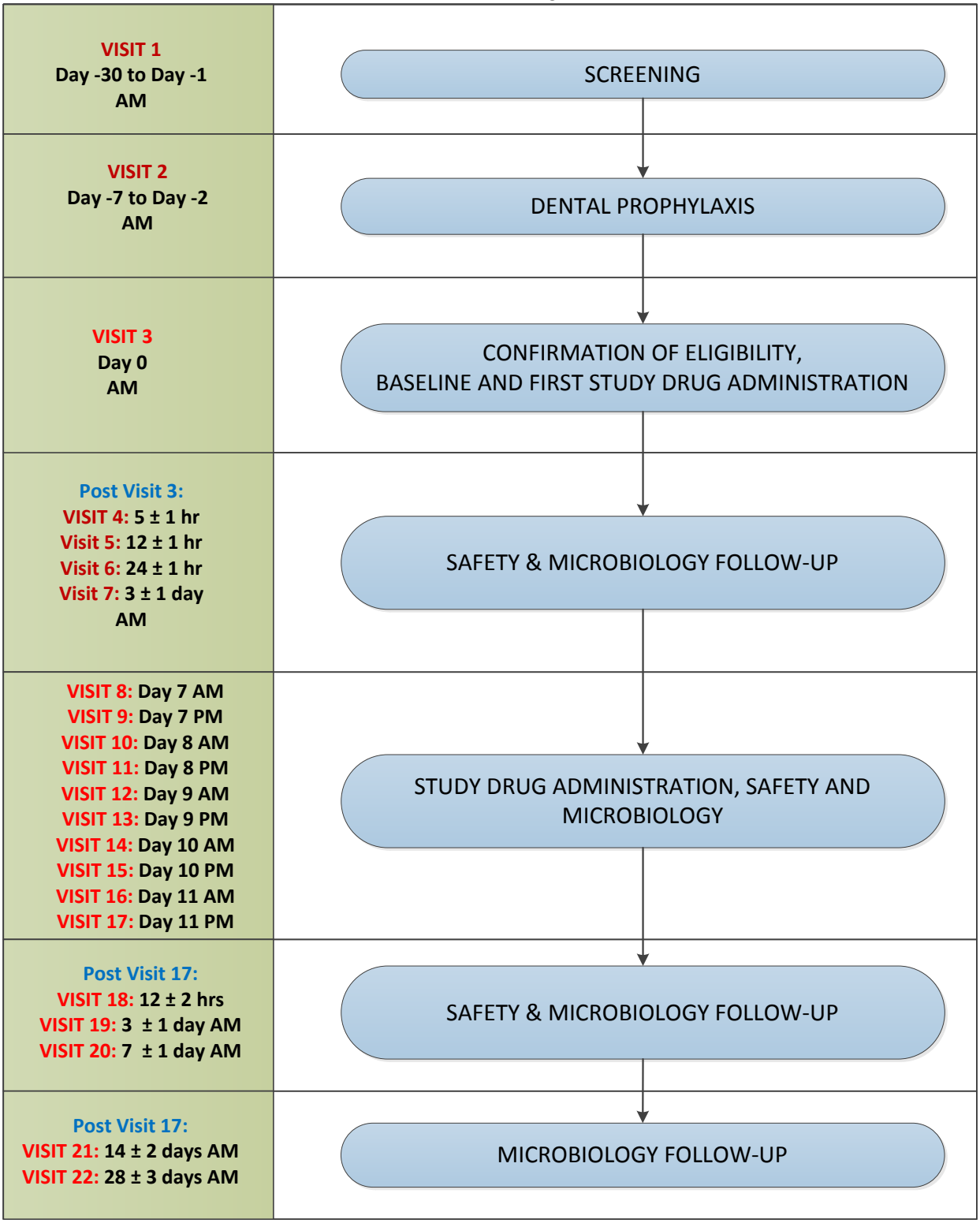
APPENDIX A: C3J16-S205-00 STUDY SCHEMATIC

The schematic below is applicable for each of the three study arms, which will be enrolled in an ascending dose escalation manner



APPENDIX B: SCHEDULE OF STUDY ASSESSMENTS & PROCEDURES

STUDY ASSESSMENTS & PROCEDURES	SCREENING DAY -30 TO -1	PROPHY DAY -7 TO -2	BASELINE DAY 0	FOLLOW-UP 5, 12, 24 ± 1 HR AND 3 ± 1 DAY POST V3	DOSING DAYS 7-11	FOLLOW-UP 12 ± 2 HRS AND 3, 7 ± 1 DAYS POST V17	FOLLOW-UP 14 ± 2 DAYS AND 28 ± 3 DAYS POST V17
	VISIT 1	VISIT 2	VISIT 3	VISITS 4-7	VISITS 8-17	VISITS 18-20	VISITS 21 & 22
Informed Consent/Assent & Subject ID	X						
Inclusion/Exclusion	X						
Medical/Surgical/Dental History & Concurrent Illness	X		X				
Salivary Flow Assessment	X						
Concomitant Medications	X		X	X	X	X	
Demographics (incl. height & weight)	X						
Dental Status & Caries Examination [a]	X						
Screening Laboratory Testing	X						
Urine pregnancy test (females only)	X		X				
Oral Cavity Assessment	X		X[m]	X	X[m]	X	
Targeted Physical Exam	X		X	X (Visit 5 only)	X (Visit 8 only)	X (Visits 18 & 20 only)	
Vital Signs [b]	X		X		X (Visit 8 and 17 only)		
Microbiology [c]	X[d]	X[e]	X[f]	X	X (Visits 8, 9 & 10 only)	X	X
Professional Dental Prophylaxis [g]		X					
Randomization			X				
Training on flossing & brushing [h]		X					
Study Drug Administration [i]			X		X		
Photographic imaging [j]			X				
Adverse Events [k]			X	X	X	X	
Oral Hygiene Product Distribution [l]		X					
End of Study							X (Visit 22 only)

Legend:

[a] Dental status and comprehensive caries examination including standard radiographs

Note: If radiographs deemed appropriate for the study and taken within 6 months prior to the screening visit are available, these may be used for determining eligibility and will not be repeated at screening.

[b] Vital Signs: Blood pressure, heart rate and temperature taken in sitting or supine position at Screening Visit 1, Dosing Visits 3, 8 and 17 pre- and post study drug administration.

[c] Microbiology: For details on stimulated saliva and dental plaque sample collection schedules and microbiology assessments refer to Appendix C. Subjects will not perform oral hygiene at home prior to attending the study center at Visits 1 through 22 for stimulated saliva and dental plaque samples collection. For details see Section 6.2 - Subject Instructions

[d] Microbiology Screening Assessment: Subjects will be screened, including *S. mutans* assessment, within 30 days of planned dosing with the study drug. The stimulated saliva will be collected in a sterile fashion to confirm baseline *S. mutans* ≥ 1 X 10^5 CFUs/mL

[e] Microbiology Samples at Visit 2: Stimulated saliva and dental plaque will be taken prior to performing professional dental prophylaxis and oral hygiene training.

[f] Microbiology Samples at Visits 3 and 8-10: Stimulated saliva and dental plaque will be taken prior to oral hygiene and study drug administration.

[g] Professional Dental Prophylaxis: Will include removal of bulk plaque and supragingival scaling; Note: NO fluoride treatment as part of the procedure, NO subgingival scaling as part of the prophylaxis.

[h] Subject training on flossing and tooth brushing: Visit 2/Prophy: includes the appropriate use of dental floss per Appendix E, routine brushing with a manual toothbrush and a regular toothpaste containing fluoride per Appendix F. Retraining will be conducted as needed during the study.

[i] Study Drug Administration: Subjects will receive C16G2 or Placebo Strips at the clinic (for details refer to Appendix A and Section 6). Subjects will brush and floss their teeth prior to study drug administration **after** microbiology samples were taken

[j] Photographic imaging: Oral photographs of strip application will be taken immediately after strip application at Visit 3

[k] Adverse Events: Subjects will be reminded to immediately notify the Investigator of any untoward effects up until 7 days post the last administration of study drug. All ongoing adverse events will be followed in accordance with good medical practice until resolution or the adverse event or condition has stabilized.

[l] Oral Hygiene Product Distribution: After dental prophylaxis at Visit 2, subjects will receive a manual toothbrush, a regular toothpaste containing fluoride and dental floss to take home and will be instructed to exclusively use these dental products during the study. In addition, subjects will be resupplied with these dental products as needed.

[m] Oral Cavity Assessments: On Screening Visit 1, Dosing Visits 3, 8 – 17 OCA will be performed. On the first study drug administration day at Visit 3, OCAs will be performed prior to study drug administration and post study drug administration. At AM Visits 8, 10, 12, 14, and 16, OCA will be performed prior to study drug administration, at PM Visits 9, 11, 13, 15, and 17, OCAs will be performed post-study drug administration.

APPENDIX C: SCHEDULE OF MICROBIOLOGY ASSESSMENTS

MICROBIOLOGY ASSESSMENT [a]	SCREENING DAY -30 TO -7[B]	PROPHY DAY -7 TO -2	BASELINE DAY 0	DAYS 0, 1 & 3	DAYS 7 & 8	DAYS 12, 14, 18, 25, 39
	VISIT 1	VISIT 2	VISIT 3 PRE-DOSE	VISIT 4-7	VISITS 8, 9, 10 PRE-DOSE	VISITS 18-22
S. mutans by MSB agar plating	X[b]	X	X	X	X	X
Total bacteria by TH agar plating			X	X	X	X (Visits 18-20 & 22 only)

[a] Samples will be stored for testing by qRT-PCR and bacterial community analysis at appropriate time points based on plating assessments.
[b] Screening microbiology sample must be collected prior to dental prophylaxis at Visit 2. Stimulated saliva ONLY at Screening

APPENDIX D: CLINIC VISIT SCHEDULE

STUDY PERIODS	VISIT #	SCHEDULE	
Screening Visit 1	Visit 1	Day -30 to -1 AM*	
Dental Prophylaxis Visit 2	Visit 2	Day -7 to -2 AM*	
Baseline & Study Drug Administration Visit 3	Visit 3	Day 0 AM*	
Safety and Microbiology Follow-up Visits 4-7	Visit 4	5 ± 1 hour	Post Visit 3
	Visit 5	12 ± 1 hour	
	Visit 6	24 ± 1 hour	
	Visit 7	3 ± 1 day AM*	
Study Drug Administration Visits 8-17	Visit 8	Day 7 / AM*	
	Visit 9	Day 7 / PM**	
	Visit 10	Day 8 / AM*	
	Visit 11	Day 8 / PM**	
	Visit 12	Day 9 / AM*	
	Visit 13	Day 9 / PM**	
	Visit 14	Day 10 / AM*	
	Visit 15	Day 10 / PM**	
	Visit 16	Day 11 / AM*	
	Visit 17	Day 11 / PM**	
Safety and Microbiology Follow-up Visits 18-20	Visit 18	12 ± 2 hours	Post Visit 17
	Visit 19	3 ± 1 day AM*	
	Visit 20	7 ± 1 day AM*	
Microbiology Follow-up Visits 21-22	Visit 21	14 ± 2 days AM*	
	Visit 22	28 ± 3 day AM*	

*AM visits will be scheduled between 6AM and 10AM
** PM visits will be scheduled between 6PM and 10PM

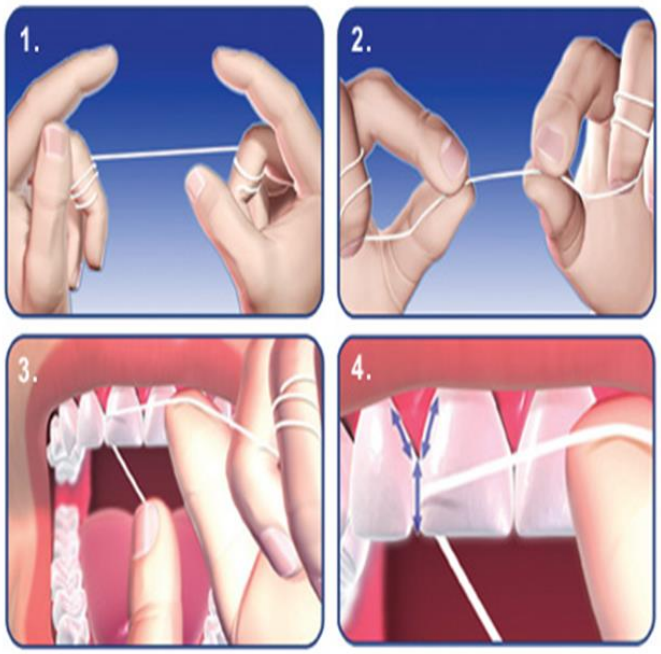
APPENDIX E: FLOSSING INSTRUCTIONS

Flossing with string will remove food particles and debris from between teeth to allow study drug to reach all tooth surfaces. Study staff will train the study subject using the instructions below. Depending on the flossing habits of the subject or preference, either rolled or pre-strung floss may be used.

Rolled Floss Instructions:

1. You will floss between all your teeth using the supplied dental floss
2. Dispense approximately 2 feet of dental floss and wrap both ends of the dental floss around your index or middle finger
3. Using your index or middle finger and thumb to hold the floss tight insert the floss between your teeth
4. Press the floss against the side of one tooth and move the floss up and down 3 times. Repeat for the adjacent tooth surface
5. Gently pull the floss from between the teeth and floss between all remaining teeth in the same manner

Figure 1: Flossing



Pre-strung Floss Instructions:

1. You will floss between all your teeth using the supplied dental pre-strung floss
2. Insert the floss between your teeth, press the floss against the side of one tooth and move the floss up and down 3 times. Repeat for the adjacent tooth surface
3. Gently pull the floss from between the teeth and floss between all remaining teeth in the same manner

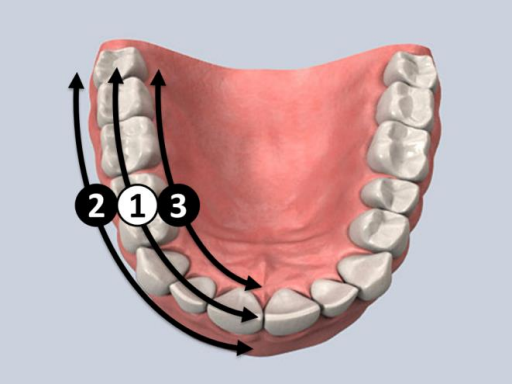
APPENDIX F: ROUTINE MANUAL BRUSH INSTRUCTIONS

Subjects will brush their teeth at home with a manual toothbrush and a regular toothpaste containing fluoride (e.g., Crest Regular™) provided by the study center (see Section 6.2 - Subject Instructions). Subjects will dispense a routine (~ 1 mL) amount of toothpaste onto the toothbrush head and brush 30 seconds per quadrant, for a total of 2 minutes.

Instruct the subject as follows:

1. Hold the toothbrush handle lightly when brushing
2. Study staff will observe you during brushing to ensure correct tooth brushing
3. To start brushing, place the brush head on the top surface (occlusal) of the back molar
4. Brush the occlusal surface of the first quadrant of the lower teeth for a total of approximately 10 seconds. Each brush stroke should move the brush head back and forth across the occlusal surface of several teeth. The brush should advance forward in the mouth with each successive brush stroke as illustrated in Figure 2, Line 1. When reaching the end of the quadrant continue brushing while advancing the toothbrush rearward to the back molars with each successive brush stroke
5. Continue brushing the outer surface of the first quadrant of the lower teeth closest to the cheek as illustrated in Figure 2, Line 2 by brushing forward and backward across several teeth for 10 seconds
6. Repeat for the inner surface of the first quadrant of the lower teeth closest to the tongue as illustrated in Figure 2, Line 3. Brush forward and backward for 10 seconds
7. Repeat the brushing steps above for each of the remaining 3 quadrants of the mouth.
8. If any teeth are not adequately brushed in the allotted time revisit those teeth prior to proceeding to other tooth surfaces

Figure 2: Routine Manual Toothbrush Use



APPENDIX G: STUDY DRUG APPLICATION INSTRUCTIONS

The tooth strip is designed with dimensions sufficient to cover the occlusal surface of the molars and 1 or 2 bicuspids along with the majority of the lateral tooth surfaces of these teeth. The anterior teeth will not be covered by the tooth strip during treatment. To achieve effective dosing the tooth strip is formulated with an adhesive polymer that adheres to the tooth surface on contact and prevents shifting during treatment. Because of the adhesive nature of the adhesive polymer it will be difficult to realign the tooth strip after a significant portion of the tooth strip has been adhered to the tooth surface. Once fully adhered to the tooth surface, tooth strip realignment should not be attempted.

The tooth strip formulation requires hydration to achieve effective drug release. To achieve effective tooth strip application that results in effective release of drug the tooth strips should be applied to teeth covered with saliva. DO NOT dry the teeth prior to strip application.

1. Prior to study drug administration subjects will be instructed to have their mouth closed and teeth well covered by saliva
2. Immediately prior to application of a tooth strip, remove the release liner from the single strip to be applied (do not remove the release liner from other tooth strips at this time)
   Note: The side of the strip in contact with the release liner is the side containing study drug that will be attached to the tooth surface
3. Subject will be instructed to swallow any excess saliva in their mouth and open their mouth
4. Using cheek retractors pull back the subject's cheeks one at a time
5. Instruct the subject to set their tongue away from the teeth where the strips will be applied, or alternatively, use a tongue depressor to ensure the tongue does not come in contact with the strip during application
6. Align the rear of the tooth strip to the rearmost molar and lay it down on the teeth starting from the rearmost molar and ending with the most proximal tooth the tooth strip covers (this will usually be first or second bicuspid). The side of the strip that is in contact with the release liner contains the active drug and should be applied to the tooth surface. The strip should cover the entire occlusal surface of all molars
7. Adhere the tooth strip to the occlusal surface of the tooth using a finger tip
8. Adhere the tooth strip to the buccal and lingual surfaces of the tooth using a finger tip
9. The subject will be instructed to close their mouth after application of the tooth strip and instructed not to grind their teeth
10. Repeat steps 1 through 7 for the remaining 3 tooth strip applications

APPENDIX H: C16G2 AND PLACEBO STRIP APPLICATION PHOTOGRAPHIC IMAGING

Adapted with modifications from www.dentistrytoday.com

Study staff will image the subject's teeth as follows using the camera provided by the sponsor

a. Immediately after study drug application (maxillary and mandibular occlusal view at Visit 3 only)

NOTE: When using retractors and mirrors for imaging it is important not to disrupt the strip application.

Shot No. 1: Maxillary Occlusal View
For many practitioners the maxillary and mandibular occlusal shots present the most difficulty (Figures 1a and 1b). This photographic image is always taken with both retractors and an occlusal mirror. Camera settings are identical to the anterior retracted shot, although patient and operator positioning are different and ultimately critical to success. The patient should be reclined to approximately 45° and asked to raise his or her chin. The operator should be in front of the patient. Cheek retractors should be placed so that the lips can be pulled upward and outward; in some cases the medial corners of the cheek retractors will touch at the middle of the upper lip. If properly used, the cheek retractors will keep the buccal soft tissue and lips away from the teeth, allowing for proper visualization of not only the posterior teeth but the anterior teeth as well. Standard cheek retractors or "fork" retractors may be used.

The mirror should be inserted so that the edge extends behind the most posterior tooth. It may sometimes rest on the tuberosity as a means of stabilization. Rotate the mirror downward so that the back side is touching the lower incisor teeth. In doing so, the operator can help the patient "open wide" but also attain the 45° angle needed to properly capture the image. Fogging of the mirror can again be a challenge with preventive strategies including warming the mirror, gentle bursts of air, or asking the patient to breathe in and hold his or her breath.

The image captured should ideally include all maxillary teeth and allow visualization of incisal edges and embrasures. The vertical midline should be the anatomic midline of the patient, and the point of focus should be the premolars. In some cases the operator must allow the camera to focus on the premolars (e.g. hold the camera shutter button half-way, locking the focus), and then recompose the image to achieve better framing. If the center of the palate is used as the point of focus, the teeth may appear out of focus because of limited depth of field.

Shot No. 2: Mandibular Occlusal View
The mandibular occlusal shot is accomplished with the same camera settings, and similar positioning of the patient and operator as the maxillary occlusal (Figures 1c to 1e). The patient should be reclined at a minimum of 45°, and should raise the chin as far as possible (neck extended maximally). Standard retractors (or a fork retractor) should always be used to keep soft tissue and lips away from the teeth. If standard cheek retractors are used, they should be positioned to pull the lips downward and outward. Insert the mirror so that the end rests on soft tissue behind the most posterior teeth, making sure that it is not touching the teeth. Rotate the mirror upward so that the back of the mirror is resting against the maxillary incisor teeth; the image should be taken at approximately 45° to the mirror.

Figure 1a. Positioning of the patient and the operator to capture the maxillary occlusal image. Note the position of the cheek retractors upward and outward. Optimally, the angle to the mirror should be 45º to fully capture the teeth in the photograph.

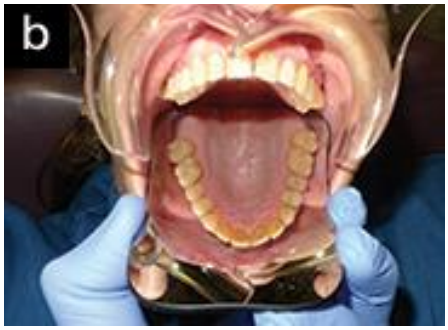


Figure 1b. Wide view of positioning to capture the maxillary occlusal image. Note the position of the cheek retractors upward and outward to pull the lips and soft tissue away from the teeth. The back of the mirror is behind the most posterior maxillary teeth.

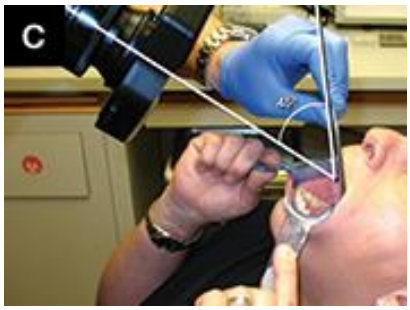


Figure 1c. Positioning of the patient and the operator to capture the mandibular occlusal image. Note the position of the cheek retractors pulled downward and outward. Optimally the angle to the mirror should be 45º to fully capture the teeth in the photograph.

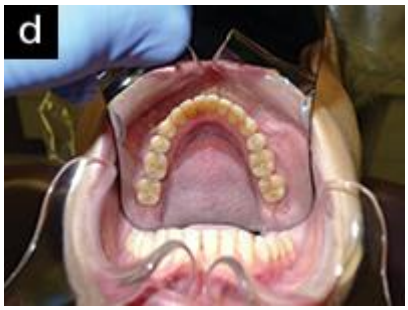


Figure 1d. Wide view of positioning to capture the mandibular occlusal image. Note the position of the cheek retractors downward and outward to pull the lips and soft tissue away from the teeth. The back of the mirror is behind the teeth and resting on soft tissue.

Figure 1e. Close-up showing the back of the mirror touching the maxillary teeth when preparing to capture the mandibular occlusal photograph.

Too often, the patient's tongue may prevent visualizing all of the mandibular teeth. It is sometimes helpful to ask the patient to "lower their tongue" having the patient practice doing so in a facial mirror. Other times it may be possible for the patient to move their tongue to the posterior, or the mirror could be used to hold the tongue out of the way.

The image should be framed so that the vertical midline is the anatomic midline of the patient. Like the maxillary occlusal image, ideally all mandibular teeth are visible and the anterior incisal edges and embrasures are discernable. The point of focus for the mandibular occlusal shot are the premolars. Recomposition may be necessary after focusing as described for the maxillary photographic image.

Common errors for the occlusal images include: allowing the end of the mirror to rest on the teeth, potentially producing a double image or viewing unreflected teeth; capturing the image at less than 45°, which results in unreflected teeth being seen in the image; fogging of the mirror; inadequate framing; and obscuring of the teeth by the tongue.

Labelling and Uploading Images

Image Labeling

Label each of the two images taken with the subject identifier followed by the photograph's number and the time point as follows in the examples below:

For subject #V102-01-001, Photo 1
S205-01-001 P1

For subject #V102-01-001, Photo 2
S205-01-001 P2

Image Uploading

Within the main clinical site folder (e.g. C3J16-S205-00 Site 01) there is a sub folder for "Strip Images". Create a new folder for each subject within the "Strip Images" folder using the subject identifier (e.g. S205-01-001). Upload one image for each required photo to this folder. There will be a total of 2 photographic images for each subject on the first day of dosing (Visit 3).

APPENDIX I: DECLARATION OF HELSINKI

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

Corresponding Author: World Medical Association, 13, ch. du Levant, CIB - Bâtiment A, 01210 Ferney-Voltaire, France; wma@wma.net.

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