PHASE 2 EFFICACY EVALUATION OF ADVANTAGE ANTI-CARIES VARNISH

Study Acronym: Kouruhr Masamwahu (Beautiful Smiles and Smiley Teeth and Face)

Advantage Protocol Number: 2016-12-02

IND #128835

IND Sponsor: Advantage Silver Dental Arrest, LLLC
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Redmond, OR 97756

Sponsor Contact: Peter Milgrom, DDS

Principal Investigator: Ohnmar Tut, BDS MPhil

Medical Monitor: John Hedson, MD

Regulatory Monitor: William Cooley, PhD

Version Number: 2.5

Version Date: 01/10/2017

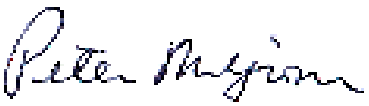
PROTOCOL APPROVAL

Phase 2 Efficacy Evaluation of Advantage Anti-Caries Varnish

STUDY ACRONYM: Kouruhr Masamwahu

1/10/2017

Ohnmar K. Tut, BDS MPhil — Date
Principal Investigator



1/13/2017

Peter Milgrom, DDS — Date
Sub-Investigator

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (May 9, 1997)

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

I have carefully read this protocol, and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and guidelines [21 CFR (Code of Federal Regulations) Parts 11, 50, 54 and 56 and ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) Topic E6 (R1)], and local regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects.

I will provide copies of the protocol and all other information relating to the pre-clinical and prior clinical experience, which were furnished to me, to all physicians and other study personnel responsible to me who participate in this study. I will discuss this information with them to assure that they are adequately informed regarding the study drug and conduct of the study.

I will ensure that the drugs supplied to me for this study will be used only for administration to subjects enrolled in this study protocol and for no other purpose.

I agree to keep records on all subject information (case report forms, informed consent statements, drug accountability records, and all other information collected during the study) in accordance with the current GCP, local and national regulations.

Ohnmar Tut
Printed Principal Investigator Name

Principal Investigator Signature

1/10/2017
Date

SUMMARY OF CHANGES

Protocol Amendment 001

The age range for enrollment was clarified to include subjects 48 – 84 months of age.

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LIST OF ABBREVIATIONS

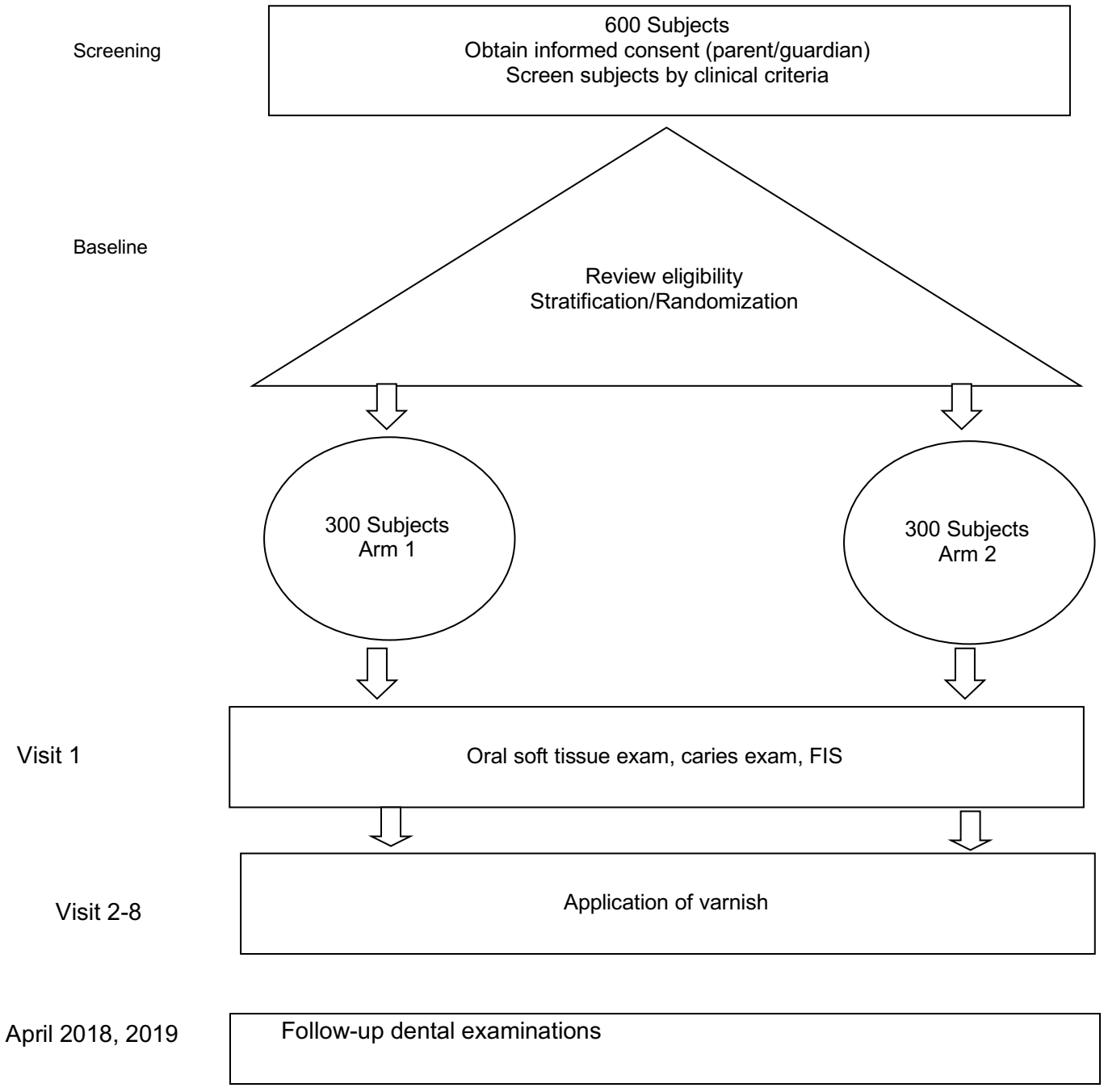
AE	Adverse Event/Adverse Experience
ADA	American Dental Association
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NDA	New Drug Application
OHRP	Office for Human Research Protections
PCP	Primary Care Physician
PHI	Protected Health Information
PI	Principal Investigator
10% PVPI	10% Povidone/1.0% Iodine
SAE	Serious Adverse Event
S-ECC	Severe Early Childhood Caries
SOP	Standard Operating Procedure
WIRB	Western Institutional Review Board

PROTOCOL SUMMARY

Title	**Phase 2 Efficacy Evaluation of Advantage Anti-Caries Varnish** Acronym Title: Kouruhr Masamwahu
Précis	**The purpose of the study is to determine the efficacy of Advantage Anti-Caries Varnish**
Objectives	Primary ➢ To determine if Advantage Anti-Caries Varnish (test varnish) is superior to a control varnish containing only fluoride in the prevention of new caries lesions. Secondary ➢ To establish that the response of child participants to the test varnish was not inferior to the control varnish
Study Population	Children 60 to 84 months at time of entry
Phase	2
Number of Sites	One, Pohnpei State, Federated States of Micronesia
Study Duration	27 months (includes 3-month enrollment period followed by 24 months of follow up)
Subject Participation Duration	The total duration of subject participation is 24 months.
Description of Agent or Intervention	Single-center, double-blind, controlled Phase 2 study with parallel groups of children. Subjects will be stratified by EEC/school and then randomized to receive either test varnish or control varnish topically to the teeth. Treatment will be administered quarterly for up to 24 months.
Estimated Time to Complete Enrollment	3 months
Number of Subjects	Total number of subjects planned is: up to 600
Inclusion Criteria	1. The subject's parent or legal guardian must provide signed and dated informed consent (parent permission form). 2. The subject's parent or legal guardian of the subject must be willing and able to comply with study requirements. 3. The subject is aged 60-84 months at the time of the screening visit. 4. The subject must be in good general health as evidenced by medical history.
Exclusion Criteria	1. Known allergy to iodine 2. Known allergy to seafood 3. Known hypersensitivity to fluoride varnish 4. Diagnosis of thyroid disease 5. Chronic, prophylactic use of antibiotics

	6. Treatment with another investigational drug or other intervention within 30 days preceding the Baseline Visit.
Route and Dosage Form	Treatment applied to teeth topically (0.2 mL or control)
Primary Outcome Measures	Efficacy: Surface-level primary molar caries increment ($d_2$mfs) at 24- months post baseline
Secondary Outcome Measures	1. Safety: a. Adverse event occurrence 2. Child response (Facial Image Scale 1-5)
	The proposed sample size of 600 subjects will provide >90% power to demonstrate a 30% or greater reduction in caries in the test group as compared to the control varnish group.

Schematic of Study Design:



1. Key Roles

Individuals:	
Principal Investigator:	Dr. Ohnmar Tut Department of Oral Health Sciences University of Washington, Seattle Email: Ohnmar@uw.edu
Sponsor/Investigator:	Peter Milgrom, DDS Professor of Oral Health Sciences University of Washington, Seattle Email: dfrc@uw.edu
Medical Monitor	Johnny Hedson, MD Pohnpei State Hospital Pohnpei, FSM
Regulatory Monitor:	William Cooley, PhD Cooley Consulting, Inc. 531 Chisholm Trail Wyoming OH 45215
Site Director	Marcelle Gallen, BDS Chief of Dental Division Pohnpei State Department of Health Services Pohnpei, FSM
Institution and Locations:	Pohnpei State Department of Health Services Pohnpei, FSM
Biostatistician	Lloyd Mancl, PhD Research Associate Professor of Oral Health Sciences University of Washington Seattle, WA Email: llman@uw.edu
Coordination Center	Regional Clinical Dental Research Center & Research Coordination Center Institute of Translational Health Sciences 1959 NE Pacific St., Box 357480, Seattle, WA 98195 206-685-8132 / FAX: 206-685-9654

2. Introduction: Background Information and Scientific Rationale

2.1 Background Information

Background: Topical fluorides have been the mainstay in the prevention of dental caries for decades. There is abundant data on sodium fluoride's (NaF) ability to foster remineralization of tooth enamel (Gao et al., 2016). Dental NaF varnish preparations are the recommended vehicle for delivering topical NaF for dental caries prevention and arrest in young children under 6 years of age according to guidelines from the American Dental Association (ADA), the American Academy of Pediatric Dentistry and the US Preventive Services Task Force (Weyant et al., 2013; American Academy of Pediatric Dentistry, 2013; Moyer VA 2014). In children, less than 6 years of age, at high risk for dental caries, the recommendation is application of NaF varnish every three months (Weyant et al., 2013). Fluoride varnishes have been shown to be safe in very young children (Milgrom et al., 2014).

However, topical fluoride alone is not enough to thwart tooth decay in high-risk populations. Caries researchers for some time have suggested strategies that combine an antiseptic with topical fluoride to reduce or eliminate the oral cariogenic bacteria reservoir in addition to topical fluoride which primarily remineralizes enamel (Milgrom et al 2009). Povidone iodine is an FDA-approved and widely used bactericidal antiseptic. For the oral flora, iodine has preferential activities against streptococcal species, pathogens implicated in the causation of dental caries (Tam et al., 2006; Furiga et al., 2008). Moreover, iodine's effectiveness may last as long as 6 months (Caufield et al., 1979).

Studies have examined the chemotherapeutic suppression of oral *Streptococcus mutans* (Sm) by povidone iodine (10%) in children with Severe Early Childhood Caries (S-ECC). In one study, the teeth of children two to six years of age were treated topically with povidone iodine (10%) or saline following dental treatment under general anesthesia for S-ECC (Zhan et al, 2006). Levels of Sm were significantly reduced up to three months in the povidone iodine group. A second study demonstrated suppression of Sm up to 90 days in children with S-ECC who received a single application of povidone iodine (10%) followed by a topical application of 1.23% acidulated phosphate fluoride foam after surgical elimination of active caries lesions (Berkowitz et al 2009).

Other studies have assessed the effect of povidone iodine (10%) on dental caries. A clinical study involving babies in Puerto Rico who were at high risk for S-ECC as they were all colonized by Sm and had decay-promoting feeding behaviors, demonstrated that povidone iodine (10%) applied bimonthly was successful in preventing the development of early tooth decay lesions in the maxillary primary incisors (Lopez et al., 2002). In a randomized clinical trial, povidone iodine (10%) applied bi-monthly significantly reduced the rate of recurrent dental decay at six months following treatment of children under general anesthesia for S-ECC (Amin et al., 2004).

Two cohort studies have tested the effect of combining these two anti-caries agents by sequentially applying povidone iodine (10%) followed 5% NaF varnish. The first study assessed the effect of protecting erupting 1st permanent molars from developing dental caries in children five to six years old (Tut & Milgrom, 2010). The second studied the effect in the primary dentition of children 12 to 30 months (Milgrom, Tut & Mancl, 2011). They demonstrated that treatment with povidone iodine reduced the rate of new decay significantly over the standard of care alone. Yet, to date, such combination products have not been brought to the market. Advantage Anti-Caries Varnish was developed to combine the antiseptic povidone iodine and sodium fluoride varnish into a single product for ease of application, particularly in high caries risk, pre-school age children.

A phase 1 study of the safety of the new varnish was conducted in 12 healthy children with an average age of 47.6 months (WIRB PRO NUM: 20160539). No child evidenced any intra oral erythema or secondary changes as a consequence of the varnish application either immediately or within 24-48 hours post application. Neither were there any adverse effects. The FDA has reviewed the previous safety work and this protocol and issued IND 128835 for this work. The basic dental varnish formula was previously cleared by the FDA as a medical device and is currently on the market. To our knowledge there have been no adverse event reports on this varnish and it has never been withdrawn from the market. Povidone iodine is widely used in children in medicine. It has been used for intraoral application for many years without problems. Dental NaF varnish and povidone iodine have been applied sequentially at the same patient visit by clinicians for some time and two cohort studies have been published with no reports of harms.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

None of the proposed methods pose any serious risks to the study subjects.

The FDA approves the topical use of 10% PVPI to the skin of children.

Risks from povidone iodine include rash and swelling at the site of application. Iodine can cause thyroid gland problems, but this is rare and is very unlikely at the amount used in this study.

2.2.2 Known Potential Benefits

There are direct benefits to the human subjects participating in this proposal. These include the early detection of caries, its timely management and the possibility of its prevention. All subjects will also receive standard-of-care treatment.

3. Objectives

3.1 Study Objectives

Primary Objective:

To determine if Advantage Anti-Caries Varnish (test varnish) is superior to a control varnish containing only fluoride in the prevention of new caries lesions.

Secondary objectives:

a) To establish that the response of child participants to the test varnish was not inferior to the control varnish
b) To document the safety of the test varnish.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measure

Surface-level primary molar caries increment ($d_2$mfs) at 24 months post baseline

3.2.2 Secondary Outcome Measures

- Adverse event occurrence
- Facial Image Scale score (1-5)

4. Study Design

This is a single center randomized, double-blind, placebo-controlled, parallel-group trial.

4.1 Rationale for Study Design

The hypothesis is that the test varnish will be superior to the control varnish and will not be inferior in patient response than the control varnish. There will be no difference in the frequency of adverse events.

4.2 Rationale for Dosage

The treatment group will be exposed at baseline and once every three to four months after baseline for a maximum period of 24 months. The control group will be exposed to the control varnish in the same manner. The decision for dosing every three to four months with the test varnish was based on earlier work (Berkowitz, Koo et al. 2009) and the AAPD Standard of Care for children at high risk for dental caries.

5. Study Enrollment and Withdrawal

5.1 Subject Numbers

Up to 600 subjects will be enrolled. Half will be randomized to each arm. If a family has more than one eligible child, each will be allowed to enroll.

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

5.2 Subject Inclusion Criteria

1. The subject's parent or legal guardian must provide signed and dated informed consent (parent permission form).
2. The subject's parent or legal guardian of the subject must be willing and able to comply with study requirements.
3. The subject is aged 48-84 months at the time of enrollment.
4. The subject must be in good general health as evidenced by parent report.

5.3 Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from participation in this study:

1. Known allergy to iodine
2. Known allergy to seafood
3. Known hypersensitivity to fluoride varnish
4. Diagnosis of thyroid disease
5. Chronic, prophylactic use of antibiotics
6. Treatment with another investigational drug or other intervention within 30 days preceding the Baseline Visit.

In the event of unique circumstances permitting waiver of any of the above eligibility criteria, documentation of such a waiver must be generated by the Principal Investigator prior to randomization into the study. Enrollment of an otherwise ineligible subject into the study without prior approval of a waiver will be considered a protocol violation.

5.4 Discussion of Subject Characteristics

The study population is high risk for dental caries because of their poverty status and lack of access to fluoridated water. The subject population will largely consist of children who are 60 to 84 months of age at the time of enrollment. The study site is Pohnpei State, Federated States of Micronesia (FSM). Under US law and the Compact of Free Association between the US and FSM, this site is considered to be part of the US. There are no intrinsic (genetic or physiologic) or extrinsic (cultural or environmental) characteristics of the population that would influence the safety, efficacy, dosage or dose regiment of the drug. Children consume a diet largely of processed foods from the US mainland and the main pathogenic organism in the etiology of tooth decay is has been shown to be *Streptococcus mutans,* as it is among children in the US proper. These children also use toothpastes produced in the US and regulated by FDA. In addition, this trial will be supervised by a regulatory monitor based in the US and familiar with US regulations. The consent documents will be in English.

5.5 Strategies for Recruitment and Retention

Children attending Early Childhood Education programs in Pohnpei State will be enrolled. In 2015 there were 9 centers enrolling 597 children. Maximum enrollment will be children. We expect to be able to enroll the entire sample from Nett, Kolonia, Saladak, Awak, ESDM, Pohnpei Catholic, UCCP, Calvary Christian and St. Paul centers but will recruit from other

centers as required. Based on our previous work in Micronesian schools in the US affiliated states we expect nearly every parent to consent and thus for us to enroll the entire sample within two months (Milgrom et al., 2009; Tut et al., 2010; Milgrom et al., 2011).

The parent (or legal guardian) of the potential subject will be approached by a study assistant who will confirm eligibility of the subject. The proposed study will be explained. Written informed consent will be obtained. Up to 600 families will be enrolled.

The Micronesian islands are quite isolated and children do not change schools or move from the islands readily. We will regularly provide healthy snacks at the centers and hold end of year study parties for parents and children at the centers to reduce dropouts. Families whose children complete the first treatment visit will receive a $35 gift card as an incentive. Families whose children complete a year in the study will receive another $35 gift card; families whose children complete two years in the study will receive a third $35 gift card. In addition, the children will receive a study backpack including a set of school supplies. To be more inclusive, all children in the programs will receive a free study t-shirt, irrespective of whether they are enrolled in the study. The incentive levels were determined based on advice from Department of Health. We have conducted two prospective cohort studies with a similar population in the islands. The one-year attrition rate was 1/172 (less than 1%) in one study and no child was lost to follow-up in the other study (Tut & Milgrom, 2010; Milgrom, Tut & Mancl, 2011).

5.6 Treatment Assignment Procedures

5.6.1 Subject Identification Numbers

Participants will be randomly assigned to one of the two inventions with a 1:1 allocation as per a computer-generated randomization schedule with stratification on school and with randomly permuted blocks of sizes 2 and 4. Stratification and blocking will ensure the two interventions are equally balanced within school and randomly permuted blocks sizes will ensure concealment. The study biostatistician will create the randomization lists using the “sample” function of the R statistical software (Version 3.3.0; The R Foundation for Statistical Computing, 2016).

5.6.2 Randomization Procedures

The study biostatistician will create the randomization lists using the “sample” function of the R statistical software (Version 3.3.0; The R Foundation for Statistical Computing, 2016).

The biostatistician will generate an assignment list. Individual envelopes will be prepared and the clinician will open the envelope to reveal the instruction for which coded drug (A or B) to apply. The envelopes and the drug containers

will be color coded to minimize error. In each case a second staff member will verify on site that the child received the correct coded treatment.

5.7 Masking Procedures

All study personnel except for designated personnel in the data center will be blinded to the participant treatment assignment. In order to maintain blinding, the caries scoring examinations will precede the application of test varnishes at baseline. The staff member applying these varnishes will not perform the caries scoring exams in order to eliminate examiner bias and ensure blinding to treatment assignment.

5.8 Reasons for Withdrawal

Subjects' parents or legal guardians will be advised in the written consent that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Principal Investigator's discretion at any time.

A subject may be withdrawn from the study for the following reasons:

Examples of non-adverse-event related reasons for withdrawal

1. Withdrawal of consent by parent/guardian
2. Principal Investigator-initiated withdrawal
3. Request of primary care physician
4. Failure to meet entry criteria (either newly developed or not previously recognized)
5. Lost to follow-up/failure to return
6. Early termination of study

Examples of adverse event-related reasons for withdrawal

1. New illness that in the opinion of the Principal Investigator warrants withdrawal
2. Death
3. Other adverse event

5.8.1 Handling of Withdrawals

In the event of voluntary withdrawal from the study, a Premature Withdrawal (PW) Visit will be conducted to obtain a final caries exam and ensure that appropriate care under medical supervision is provided until the symptoms of any AE resolve or the subject's condition becomes stable or deemed chronic.

Reasonable effort should be made to contact any subject lost to follow up during the course of the study in order to complete study-related assessments and collect safety data.

Subjects who are withdrawn from the study will not be replaced.

5.9 Termination of Study

The study may be discontinued at the discretion of the Sponsor or the Principal Investigator if there is sufficient reasonable cause.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient rate of subject accrual.
- Insufficient adherence to protocol requirements.
- Data which are not sufficiently complete and/or evaluable.

Written notification, documenting the reason for study termination, will be provided to the Principal Investigator and regulatory authorities. In the event of early termination of the study, all subjects will be seen for a final visit for safety purposes. The study site will notify the Western IRB and the Pohnpei State Department of Health Services of the study termination and provide the reason(s).

6. Investigational Product

6.1 Investigational Product Description

6.1.1 Acquisition

Test and control varnishes will be obtained from Cascade Custom Chemistry, Eugene, OR

6.1.2 Formulation, Packaging, and Labeling

Advantage Anti-Caries Varnish. The active ingredients are 10% (w/v) Povidone Iodine CAS RN 25655-41-8 and 5% (w/v) Sodium Fluoride CAS RN 7681-49-4 in Ethanol 200 Proof. The formulation of the dosage form includes 10% Nt-2 Premium Shellac, 1% sodium phosphate, dibasic anhydrous, 0.5% ammonium phosphate, monobasic, and 1% caramel cream flavor (Bell 29.26303) as inactive ingredients. One and two-year shelf life of the varnish has been established according to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products (Revision 2, November 2003).

The active control varnish will be the same fluoride varnish without iodine with an appropriate FDA approved food dye added to match the color of the test agent. There will be no difference in the treatment and control varnishes except for the povidone iodine.

The varnishes will be packaged in 12 mL multi use bottles with the following labeling.

Advantage Anti Cavity Varnish or Control Varnish

- Apply as per protocol
- For Investigational Use Only
- Drug Code A or B
- Contact: Dr. Peter Milgrom, +1206-251-6831 (24 hours)

6.1.3 Product Storage and Stability

All investigational products will be kept in a secure, safe area under recommended storage conditions with access limited in the study office. Expiration or use-by dates, as applicable, for all products will be documented by staff.

6.2 Dosage, Preparation and Administration of Study Investigational Products

Advantage Anti-Cavity Varnish and Control Varnish

A maximum of 0.2 mL will be applied to the teeth with a dental brush.
Test or control varnish will be applied topically following baseline examination and at each 3 to 4-month intervals.

6.3 Accountability Procedures for the Investigational Product(s)

The Principal Investigator (Tut) and Site Director (Gallen) must maintain accurate records (including dates) of all supplies received from Advantage. All treatment applications (A or B) will be recorded on a Drug Accountability Log completed by the Study Director. All remaining drug will be returned to the sponsor and documented on the Drug Disposal Log.

6.4 Assessment of Subject Compliance with Investigational Product

As test drug and control drug will be administered by the study personnel, is not anticipated that subject compliance with treatment will be an issue. In the event a dose is missed; the missed dose will be captured as a protocol deviation and documented in the source documents.

6.5 Coding/Emergency Treatment Disclosure

The Principal Investigator will be given a sealed envelope containing the randomized treatment assignment code for each subject to be opened only in the event of a medical emergency.

Neither premature withdrawal from the study nor most clinical emergencies necessitate disclosure of treatment assignment. Most emergency situations can be handled by withdrawing study treatment without disclosure of treatment assignment. However, in rare circumstances under which knowledge of the drug assignment is necessary for the treatment of a serious adverse event, the Principal Investigator (Tut) must discuss the situation with the Site Director (Gallen) and Dr. Milgrom, if circumstances permit, before deciding whether or not to disclose treatment assignment. If disclosure of individual treatment assignment is undertaken, it must be made by the Principal Investigator responsible for the care of the involved subject in consultation with the Medical Monitor (Hedson). The subject will be withdrawn from further exposure to study drug.

Emergency treatment disclosure is a reportable event, requiring notification to the Principal Investigator within 24 hours of the disclosure. The assigned treatment must not be revealed to other study staff or to individuals who are not involved directly in the clinical care of the subject, unless disclosure to the individual is critical to the care of the subject.

6.6 Concomitant Medications/Treatments

Subjects may not be receiving treatment with another investigational drug within 30 days preceding the baseline visit and throughout participation in this study.

Chronic prophylactic use of antibiotics at enrollment is an exclusion criterion; however, if during the course of the study, the subject's PCP prescribes antibiotics (e.g., for treatment of otitis media), the Study Coordinator will record the medication on the Concomitant Medications Log. The study subject will receive the study drug application regardless of prescribed antibiotics by subject's PCP.

Concomitant medication use, including all prescription, over-the-counter medications, vitamins, and nutritional supplementation, will be recorded commencing with the screening visit and at each visit through completion of the study. All concomitant medications must be used according to the prescriber's instructions.

Fluoridated toothpaste will be provided under this protocol to all subjects.

7. Study Schedule/Procedures and Evaluations

Subject recruitment procedures:

- The study assistant or supervisor will make contact with the parent/caregiver through the Early Childhood Education Center (ECE) or at home. This individual will explain the study and obtain informed consent.
- The assistant will record the subject's age and sex and medical history based on parent/guardian report.
- The assistant will record concomitant medication use over the past 90 days.
- The informed consent packet will carry a pre-assigned subject number. If a parent does not consent, the reason will be recorded and the study number will not be used. If the family has a second child who is eligible, the study number shall be the same as the first child in the family enrolled, followed by the notation –2.

7.1 Baseline Visit

- The visit will be at the Center
- The examiner will conduct the baseline dental and oral examination.
- After the baseline visit, the study staff will record on lists of the subjects, the treatment code assigned by the statistician.

7.2 First Treatment Visit

- A study assistant will consult the student list and apply the assigned treatment.
- The study assistant will administer the Facial Images Scale, immediately following the varnish treatment.

7.3 Visits 2-8

- The visit will be at the Center
- The examiner will conduct the dental and oral examination at visits 4 and 8.
- A study assistant will retrieve the drug assignment and will apply the assigned agent
- The assistant will review and record concomitant medications
- The assistant will review and record adverse events

7.4 Follow-Up Contacts

The subject's teacher will be contacted 48 hours following treatment. If the child is not attending or the teacher knows of a problem, the parent will be contacted to determine if there is a reportable AE. The medical monitor will assign causality. No treatments will be done on Fridays to avoid having to make home visits in order to obtain the basic AE information on the weekend.

7.5 Premature Withdrawal

In the event of premature withdrawal from the study, the Premature Withdrawal (PW) visit procedures and evaluations should be completed whether or not the decision to withdraw is determined at a routine or unscheduled visit. If it is determined via telephone contact that a premature withdrawal will occur, the parent/guardian should be asked to bring the child in for a PW visit.

Activities to be completed include:

- The Examiner will conduct the Oral Soft Tissue exam
- The Examiner will conduct the caries exam
- The assistant will record concomitant medication use.
- The assistant will review and record on the AE Follow-Up Log the status of adverse events that are unresolved at the time of the premature withdrawal visit.

Premature withdrawal (including reports of subjects who are lost to follow up) should be reported to the Site Director within 24 hours of the site's knowledge of the event.

7.6 Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Principal Investigator. The date and reason for the unscheduled visit will be recorded in the subject's source documentation.

Activities to be completed include:

- The Examiner will conduct the Oral Soft Tissue exam
- The Examiner will conduct the caries exam
- The assistant will record concomitant medication use.
- The assistant will review and record on the AE Follow-Up Log the status of adverse events that are unresolved at the time of the unscheduled visit.

8. Assessments

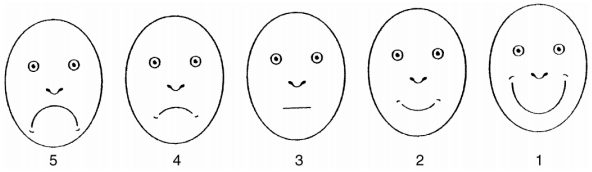
8.1 Primary and Secondary Outcome Variables

Primary Outcome Variable

The primary outcome will be the surface-level primary molar caries increment ($d_{2\text{-}3}$mfs/DMFS) at two years post baseline, but the incremental dental caries at one year will also be compared between the two interventions. Only the statistician and sponsor will know of the one-year finding.

Secondary Outcome Variable:

Child response on the depicted Facial Image Scale (Buchanan & Niven, 2002) to the treatment will be recorded immediately after the initial treatment visit and after the fourth treatment visit.



8.2 Efficacy Assessments

8.2.1 Caries Examination

Two examiners will be trained and calibrated according to National Institute of Dental and Craniofacial Research Early Childhood Caries Collaborative criteria, which are based on the World Health Organization caries classification system. The children will be visually examined using a mouth mirror and artificial light. No explorers will be used. The outcome will be assessed by visual examination by two trained and calibrated examiners.

8.3 Safety Assessments

Adverse events, including frequency and severity, and perceived relationship to the investigational product, will be compared between the treatment groups.

8.3.1. General Health (Medical History and Physical Examination)

The subject's general health status at enrollment will be assessed by medical history using the parent or legal guardian as the informant.

The Study Site Coordinator will rule out a history of thyroid disease and iodine allergy (e.g., allergy to seafood).

All concomitant medications taken by the subject will be recorded at the time of consent and updated at each follow-up study visit (including all prescription and over-the-counter medications, vitamins, and nutritional supplements taken within the past three months).

9. Assessment of Safety

9.1 Specification of Safety Parameters

- Adverse events

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Adverse events will be recorded at each contact with the teacher or parent.

Adverse events will be reviewed on a monthly basis by the Medical Monitor (Hedson); serious adverse events and other protocol-specified reportable events will be assessed in real time by the Principal Investigator (Tut) and Site Director (Gallen).

9.3 Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with any use of a drug, whether or not related to the drug. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose. This excludes minor fluctuations in signs or symptoms of the disease under study, but includes significant worsening of the disease. It also includes any apparently unrelated illness and any accident that occurs during participation in the study.

Some examples of adverse events are:

- Development of an illness during the study.
- Development of symptoms which may or may not be related to the use of a concomitant medication or investigational product.

All adverse events, whether observed by the Principal Investigator, elicited from or volunteered by the subject, subject's teacher or parent/guardian, should be recorded on the Adverse Event Log. This reporting will include a brief description of the event, the date of onset, the date of resolution, the duration and type of event, the severity, contributing factors, and any action taken with respect to the investigational product.

AEs occurring after informed consent is obtained but prior to randomization will be recorded as medical history, unless possibly related to a study procedure, in which case they will be recorded as adverse events in the case report form. New adverse events will be captured and reported on the AE log until 30 days following the last treatment or premature withdrawal, whichever comes first.

9.4 Expected Adverse Reactions

Risks from povidone iodine include rash and swelling at the site of application. Iodine can cause thyroid gland problems.

9.5 Serious Adverse Events

A serious adverse drug event is defined as any adverse event that results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity; or substantial disruption of the ability to conduct normal life functions
- [a congenital anomaly/birth defect – noted as not applicable in this population]

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include (but are not limited to) allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or convulsions that do not result in inpatient hospitalization.

This category also includes any event the Principal Investigator judges to be serious or that would suggest a significant hazard, contraindication, side effect or precaution. Any adverse event or suspected adverse reaction is considered "life threatening" if, in the view of either the Principal Investigator or sponsor, its occurrence places the patient or subject at

immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Reports of serious adverse events require immediate notification (within 24 hours of the site's awareness) to the Principal Investigator and Sponsor whether or not the Study Site Coordinator believes that the event is related to investigational product or is expected.

9.5.1 Unanticipated Problems

The Principal Investigator must conform to the adverse event reporting timelines, formats and requirements of the various entities to which he is responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

9.5.2 Procedures to be Followed in the Event of Abnormal Clinical Findings

At each parent or teacher contact the site study staff will assess adverse events by recording all reports by the subject's parent/guardian or teacher and by assessment of clinical features.

An unscheduled visit may be performed at any time during the study as deemed necessary by the Principal Investigator. The Site Director will inform the subject's parent/guardian when medical care is needed for adverse events of which the Principal Investigator becomes aware (e.g., illness) and may refer the subject back to the PCP for further work-up. The Principal Investigator may determine that the subject should be withdrawn from the study treatment.

9.6 Reporting Procedures

9.6.1 Reportable Events

The following incidents will be considered reportable events and will be reported to the Principal Investigator within 24 hours of the site's awareness of the event.

- Serious Adverse Event
- Emergency Treatment Disclosure
- Post-Treatment Adverse Events*, including
  - Nausea
  - Not eating
  - Vomiting
  - Difficulty swallowing or breathing
  - Swelling around the lips or skin on the face
  - Itchiness around the lips or skin of the face
  - Hives or rash

9.6.2 Serious Adverse Events

Within 24 hours of the site's awareness of the serious adverse event (SAE), the site will report the SAE to the Principal Investigator and provide subject identification and a brief description of the event, including the Medical Monitor's assessment of causality (unrelated, unlikely related, possibly related, probably related, or definitely related to the study drug).

Within 24 hours of the telephone report, the site will update the AE log to ensure that the concomitant medication log is current, and enter the SAE report. This report will include: documentation that serious adverse event criteria have been met; a detailed description of the event and other relevant information; the current status of the experience; if the subject has died, the date of death and autopsy report, if available; and the Medical Monitor's current opinion of the relationship between the event and the investigational treatment.

9.6.3 Adverse Event Causality Definitions

For each adverse event, the relationship to the study drug (Medical Monitor's attribution of causality) must be recorded as one of the following on the Adverse Event Log:

TERM	DEFINITION	CLARIFICATION
Unrelated	No possible relationship	The temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible.
	Not reasonably related, although a causal relationship cannot be ruled out	While the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug.
Possible	Causal relationship is uncertain	The temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, dechallenge or rechallenge information is either unknown or equivocal, and while other potential causes may not exist, a causal relationship to the study drug does not appear probable.
Probable	High degree of certainty for causal relationship	The temporal relationship between drug exposure and the adverse event onset/course is reasonable. There is a clinically compatible response to dechallenge (rechallenge is not required), and other causes have been eliminated or are unlikely.
Definite	Causal relationship is certain	The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to dechallenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

9.6.4 Adverse Event Severity Definitions

The severity of each adverse event must be recorded as one of the following on the Adverse Event Log:

MILD	No limitation of usual activities
MODERATE	Some limitation of usual activities
SEVERE	Inability to carry out usual activities

9.7 Responsibilities of Investigator/Sponsor/ for Reporting Serious Adverse Events

Serious adverse events occurring after informed consent is obtained but prior to randomization will be recorded as medical history, unless possibly related to a study procedure, in which case they will be reported as SAEs to the Medical Monitor within 24 hours of the site's awareness.

9.7.1 Regulatory Reporting for Studies Conducted Under an IND

The Principal Investigator will comply with the Western IRB regulations regarding the reporting of adverse events.

The Sponsor will report events that are serious, unexpected and that are associated with the study drug (SUSAR) to the Food and Drug Administration (FDA) within the required timelines as specified in 21 CFR Part 312.32; fatal and life-threatening events within 7 calendar days (by phone or fax) and all other SAEs in writing within 15 calendar days. All serious events designated as "not associated" with study product(s) will be reported to the FDA at least annually in a summary format.

9.7.2 Other Unanticipated Problems

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

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the WIRB-approved research protocol; and (b) the characteristics of the subject population being studied;

- Related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets any of the three criteria above generally will warrant consideration of substantive changes or corrective actions in order to protect the safety, welfare, or rights of subjects or others.

Unanticipated problems noted by the site will be recorded and reported to the Principal Investigator within 24 hours of the site's awareness and to the WIRB per local reporting requirements.

9.8 Type and Duration of Follow-up of Subjects after Adverse Events

All adverse events will be followed until resolution or an appropriate endpoint is reached (e.g., the Medical Monitor attributes the adverse event to a cause other than the study drug or assesses it to be chronic or stable).

9.9 Halting Rules

Adverse events, particularly serious adverse events such as deaths and hospitalizations, will be carefully considered by the Sponsor. If necessary, the Sponsor will halt the study.

10. Site Monitoring

10.1 Clinical Site Monitoring

To ensure compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements, the Regulatory Monitor (Cooley) is responsible for monitoring to ensure the site is conducting the study according to the protocol, Standard Operating Procedures (SOPs), and other written instructions and regulatory guidelines. Monitoring visits by a Regulatory Monitor will be arranged in advance, at a mutually-acceptable time, with site personnel.

The site personnel must allow sufficient time for the Regulatory Monitor to review CRFs and relevant source documents, including access to electronic medical records, and address data queries.

The Investigators should be available to answer questions or resolve data clarifications. The monitoring plan will include written procedures for periodic and closeout monitoring visit activities, documentation and communication of visit findings, and maintenance of the record of on-site visits. The monitoring plan will serve as a guide to ensure standardization of study-specific procedures for the Regulatory Monitor who is responsible for ongoing quality review.

10.2 Regulatory Inspections

During the course of the study and after it has been completed, it is possible that one or more study site visits will be undertaken by authorized representatives of the Sponsor, WIRB, or regulatory agencies, such as the Food and Drug Administration (FDA). These audits may take place at any time during or after the study and are based on the local regulations, as well as ICH guidelines.

The purpose of the audit is to determine whether or not the study is being, or has been, conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent regulatory authority inspection.

If such audits are to occur, they will be arranged for a reasonable and agreed-upon time.

11. Statistical Considerations

11.1 Study Hypotheses

The hypothesis is that the test varnish will be superior to the control varnish and will not be inferior in patient response to the control varnish. Also, there will be no difference in the frequency of adverse events.

11.2 Sample Size Considerations

The primary outcome will be the surface-level primary molar caries increment ($d_{2\text{-}3}$mfs/DMFS) at two years post baseline, but the incremental dental caries at one year will also be compared between the two interventions. Based on the caries levels reported by Tut et al. (2010) and Chi et al. (2016) a conservative estimate for the coefficient of variation (100 x standard deviation/mean) is 75%. Using a two-sided 0.025 significance level to control the type I error for testing at 1 and 2

years post baseline, 120 participants per intervention are required to demonstrate a 30% or greater reduction in caries in the test group as compared to the NaF varnish group with 90% power (van Belle and Martin, 1993; Champley, 2015). A 30% reduction by PVP-I + F^- versus NaF varnish alone was reported by Milgrom et al (2011) for any new caries (%), and a greater reduction would be expected in the amount of new caries in a high-risk caries population. To accommodate for attrition (up to 15%), although it is expected to be very low in the study population, a total of 280 participants will be enrolled.

11.3 Statistical Analysis Plan

11.3.1 Primary Statistical Analysis.

The primary analysis will be conducted in accordance with the intention-to-treat principle, and multiple imputation procedures will be used to account for missing caries information (Schafer, 1997). For the primary outcome, incremental dental caries based on $d_{2\text{-}3}$mfs/DMFS, the unit of analysis will be the child and the mean dental caries increment will be compared between the two interventions separately at 1 and 2 years post baseline using a two-sample t test assuming unequal variances. This approach assumes the distribution of dental caries increment is approximately symmetrical, which is often true in high-risk caries populations. In this case, non-symmetry, log-linear regression using robust standard errors, which can accommodate count outcomes with skewed distribution, will be used to compare the caries rates between the two interventions (Hardin & Hilbe, 2003). Covariate-adjusted linear (or log-linear) regression models using robust standard errors will be used to compare dental caries increment, adjusting for baseline dental caries, stratification variables (education center and school), gender and age of the participant (Hardin and Hilbe, 2003). Analyses will be performed using R (The R Foundation for Statistical Computing, 2016; Version 3.3.0) and SAS (SAS Institute, Cary, NC, Version 9.4).

11.3.2 Analysis of Safety Data.

Adverse events (AEs) will be tabulated by treatment group, severity, and perceived relationship to investigational product. For each AE, treatment group comparisons regarding the occurrence of at least one event will be made using Fisher's exact tests. The comparisons will be repeated excluding all mild symptoms. Similar analyses will be performed after grouping AEs by body system using standard Medical Dictionary for Regulatory Activities (MedDRA) coding. Individual AEs will be listed, with particular attention paid to serious AEs.

11.3.3 Participant Disposition.

The frequency and reasons for withdrawal will be summarized by treatment group, as will the number of missed visits and missed treatment applications (compliance).

12. Source Documents and Access to Source Data/Documents

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

12.1 Primary Source Documents

The Principal Investigator must maintain primary source documents supporting significant data for each subject in the subject's notes. During monitoring visits, the clinical site monitor will validate data in the CRF against these source data.

12.2 CRF Worksheets

The site will be supplied with a set of forms-based schedule of activities and corresponding source document worksheets (SDW) that correspond to the case report form (CRF) for this study. The worksheets will serve as source documents for study observations. Additional source documentation for information not specifically included on the source document may be recorded on a separate document.

Access to the source documents should be limited to those working on the study. Access to the database will be restricted.

13. Ethics/Protection of Human Subjects

13.1 Ethical Standard

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA), and any applicable national and local regulations including FDA regulations under 21 CFR Parts 11, 50, 54, 56, 312 and 314.

The Principal Investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

13.2 Institutional Review Board

The Western IRB will review and approve the submission activities for the conduct of this protocol. The trial will not begin until the study has been approved by the WIRB, all required regulatory documentation is on file at both the site and the Principal Investigator and staff are trained on the protocol and data capture procedures.

13.3 Amendments

The Principal Investigator will discuss any proposed protocol changes with the Sponsor and no modifications will be made without prior written approval and WIRB approval of the amended protocol, except where clinical judgment requires an immediate change for reasons of subject welfare. The WIRB will be informed of any amendments to the protocol or consent form, and approval (where and when appropriate) will be obtained before implementation.

13.4 Informed Consent Process

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50.

In accordance with relevant regulations, a parent informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read and/or explained to each parent/guardian. Each subject's parent or legal guardian will sign such an informed consent form. The subject's parent/guardian must be assured of the freedom to withdraw from participation in the study at any time.

It is the Principal Investigator's responsibility to make sure that the subject's parent/guardian understands what he or she is agreeing to and that written informed consent is obtained before the subject is involved in any protocol-defined procedures, including screening procedures. It is also the Principal Investigator's responsibility to retain the original signed consent forms and provide each subject's parent/guardian with a copy of the signed consent form.

As children will be enrolled in this study, the informed consent process will be documented in the form of permission from the parent or legal guardian in the parent permission form; child assent (affirmative agreement by a child to participate in research) will not be employed in this study.

13.5 Exclusion of Women, Minorities, and Children (Special Populations)

This study will enroll children aged 60 to 84 months. There will be no exclusion due to gender, race or ethnicity.

13.6 Subject Confidentiality

The Principal Investigator must assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times. Personal medical information will always be treated as confidential. The parent/guardian's Authorization allows the Sponsor-Investigator to receive and review the subjects' protected health information that may be re-disclosed to any authorized representative of the Sponsor for review of subject medical records in the context of the study.

13.7 Study Discontinuation

At the completion of the study, study closeout procedures will be implemented.

14. Data Handling and Record Keeping

The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

14.1 Data Management Responsibilities

The Biostatistician will be responsible for all data collection procedures. The Data Management Plan includes, but is not limited to:

- Overview of data management processes utilized for study
- Universal data handling conventions
- Study-specific data handling conventions
- Coding dictionaries and practices
- Specifications for logic and edit checks
- External data handling practices
- Final study closeout activities
- Audit plans
- Sample CRF annotation
- Biostatistician contact information
- Section for tracking revisions to the plan
- Administrative report specifications

The Data Management Plan serves to document the practices and procedures deployed to promote consistent, efficient, and effective data management practices leading to the creation of a high-quality database ready for analysis. The plan serves as the authoritative source, documenting data management practices, and decisions that are agreed to with the Principal Investigator at the start of the study and as necessary updates are made during the conduct of the study.

Data will be transferred periodically from the study site to the University of Washington to prepare reports. At the close of the study, the locked database will be transferred to the Biostatistician for analysis.

The Biostatistician will be responsible for design of the randomization scheme, creation of analytical databases, and the statistical analysis plan.

14.2 Data Capture Methods

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into the study database by the Data Manager. This system is protected by 128-bit server certificates and utilizes authenticated, password-protected accounts for each site. The system is compliant with relevant FDA regulatory requirements per 21 CFR Part 11.

14.3 Types of Data

Data for this study will include clinical assessments, safety, and outcome measures (e.g., expected adverse reactions). Safety data are contained in the clinical data set.

14.4 Timing/Reports

Enrollments and ***study activity*** (***protocol-specified reportable events,*** as described in Section 9.6.1) reports will be generated as they occur to a pre-determined distribution list that includes the Principal Investigator and team.

Clinical monitoring reports will be generated periodically with electronic distribution to the PI and team. Per the Clinical Monitoring Plan, the clinical monitor reports include routine reports of aggregate, blinded adverse event data for ongoing review by for potential trends, and adverse event and concomitant medication reports for the PI to review for standardization of coding.

Safety monitoring reports will be provided by the Biostatistician per the safety monitoring plan.

Missing data, missing electronic signatures of the Principal Investigator, and requests for ***data clarification*** reports will be generated to the site on a regular basis.

Monitoring Visit Reports will be generated after each clinical site monitoring visit, per the monitoring plan.

At the completion of the study, data will be securely transferred to the Biostatistician. Once the Biostatistician and the PI agree that all queries have been adequately resolved and the database has been deemed “clean”, the database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) the database are removed at this time.

All site personnel, Sponsor and staff will remain blinded as to treatment assignments until the conclusion of the entire study. A designated unblinded biostatistician will have access to the treatment assignments, and this individual will not communicate about study-related matters to any other staff involved in the study. The study code will be broken by the study-responsible statistician after all outstanding substantive data queries have been resolved.

14.5 Study Records

14.5.1 Study File and Site Documents

The Principal Investigator should have the following study documents accessible to the Clinical Site Monitor during the study. These records are kept in the study office in Pohnpei.

1. Signed Form FDA 1572
   This study will be conducted under the supervision and direction of the Principal Investigator listed in Section 1 of the Form FDA 1572. Sub-Investigators are listed in Section 6 of the Form FDA 1572. The study will be conducted at the address(es) listed in Section 3 of the Form FDA 1572.
2. Curriculum vitae for the Principal Investigator and all personnel listed on Form FDA 1572
   The Principal Investigator is responsible for providing copies of the protocol and all other information relating to the preclinical and prior clinical experience, which were furnished to him/her, to all other study personnel who participate in this study. The Principal Investigator will discuss this information with them to assure that they are adequately informed regarding the investigational product and conduct of the study. The Principal Investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities.
3. The signed IRB form/letter stating IRB approval of protocol, consent forms, and any other study materials (e.g., patient instruction materials, advertisement notices), documentation of the IRB composition, and all IRB correspondence including notification/approval of protocol amendments, notification of serious, unexpected, suspect adverse drug reactions to the IRB, and IRB notification of study termination
4. Training records
   Records of protocol-specific training will be maintained.
5. IRB-approved consent form
6. Signed protocol (and amendments, where applicable)
7. Signed parent/guardian permission forms
8. Copies of the completed source document worksheets
9. Delegation Log with names, signatures, initials, and functional role of all persons completing protocol assessments and providing back-up to the Principal Investigator.
10. Accountability of investigational product
11. Record of all monitoring visits by Clinical Site Monitor(s)
12. Copies of correspondence
13. Certificate for Human Subject Protection Program (HSPP) for each individual named on the Delegation Log who has direct subject contact
14. Copy of professional licensure/registration, as applicable, for each individual named on the Delegation Log, who has direct subject contact, ensuring licensure is in the locality in which the study will be conducted
15. The Principal Investigator must also retain adequate documentation, together with the subject's hospital/medical records, as the subject's source data for the study.

14.5.2 Maintenance and Retention of Records

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. The Principal Investigator will be instructed to retain all study records required by federal regulations in a secure and safe facility with limited access for one of the following time periods based on notification from the Monitor.

The Principal Investigator will be instructed to consult with and provide advance written notice to the Monitor before disposal of any study records and to notify the Monitor of any change in the location, disposition, or custody of the study files. No study document or image should be destroyed without prior written agreement between the Sponsor and the Principal Investigator.

Regulations require retention for:

- A period of at least two years after notification from the Sponsor that a U.S. NDA (New Drug Application) has been approved for the indication that was investigated or 15 years according to International Conference on Harmonization (ICH) guidelines.

- Or, if no NDA is filed or approved for such indication, a period of at least two years after the investigation is completed or discontinued, and the FDA (Food and Drug Administration) has been notified by the Sponsor.

14.6 Protocol Deviations

A protocol deviation is accidental or unintentional changes to, or non-compliance with the research protocol that do not increase risk or decrease benefit or; do not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher, or research staff.

A deviation may be due to the research subject’s non-adherence, or an unintentional change to or non-compliance with the research protocol on the part of a researcher. Examples of a deviation include: A rescheduled study visit; Failure to collect an ancillary self-report questionnaire; or Subject’s refusal to complete scheduled research activities.

Protocol deviations will be recorded in the subject’s file and log.

14.7 Protocol Violations

A protocol violation is any accidental or unintentional noncompliance with the WIRB approved protocol without prior approval requirements that may increase risk or decrease benefit, affects subjects' rights, safety, or welfare, or the integrity of the study data. The noncompliance may be either on the part of the subject, the Principal Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the Principal Investigator. The Study will maintain a database of violations that are not already documented in the clinical database. Corrective and preventive action plans will be documented to minimize recurrence of protocol violations, where applicable.

Protocol violations must be sent to the WIRB per WIRB guidelines. The Principal Investigator and staff are responsible for knowing and adhering to the WIRB requirements.

15. Publication Policy

Following completion of the study, the Principal Investigator may submit for publication the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Thus, the Sponsor will register this trial in the public trials registry, *ClinicalTrials.gov*.

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17. Addendum

Addendum is protocol amendment 001. The age range for enrollment was clarified to include subjects 48 – 84 months of age.