Protocol: Pharmacokinetics of Advantage Anti-Caries Varnish

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Purpose of the Study and Background

Objective: The purpose of this study is to characterize basic PK parameters (Cmax, $t_{1/2,}$ Cmin, AUC, and total urinary recovery) to contribute to evidence for the safety of Advantage Anti-Caries Varnish, consistent with Guidance for Industry--Exposure--Response Relationships (April 2003). On a preliminary basis, we will also characterize the microbiome before and immediately after the topical treatment.

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 recommended vehicles for delivering topical NaF for dental caries prevention and arrest according to guidelines from the American Dental Association (ADA) and the US Preventive Services Task Force (Weyant et al., 2013; Moyer VA 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).

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.

The FDA has reviewed this protocol and issued IND 128835 for this work after extensively reviewing the human experience and safety data provided by the Sponsor. The basic dental varnish formula is already cleared by the FDA as a medical device and Elevate Oral Care, LLC currently in marketing the varnish. 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 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.

Assumptions: This is a topical agent where the active ingredients are applied to the teeth and eventually swallowed and absorbed through the GI tract. Minimal amounts are

absorbed through the oral mucosa. Concentrations of iodine and fluoride in the serum will be be directly in proportion to the dose of povidone iodine administered topically to the teeth as part of the varnish. The total urinary recovery of iodine and fluoride, adjusted for baseline levels, will be calculated to estimate the minimum amount absorbed in each patient following application of the varnish.

Criteria for Subject Selection

Number of subjects: There will be 4 up to 20 healthy adult subjects.
Gender of subjects: The subjects will be approximately half male and half female.
Age of subjects: Subjects must be 18 years of age or older.
Racial and Ethnic Origin: In a small study it is not possible to fully represent the racial/ethnic distribution of the region or US. The investigator will attempt to recruit a racial/ethnic diverse population.

Inclusion criteria: Subjects will have at least 20 teeth. Subjects will be healthy and taking no prescription or OTC medications. Healthy status will be determined by history by the attending clinician.

Exclusion criteria: Subjects will be excluded if they have oral mucositis or any ulcerative lesions or hypersensitivity to iodine. Individuals with known hypothyroidism, hyperthyroidism, iodine sensitivity, dermatitis herpetiformis, hypocomplementemic vasculitis, nodular thyroid with heart disease, multinodular goiter, Graves' disease, and autoimmune thyroiditis will be excluded from participation in the study. Subjects who are pregnant or weigh less than 110 pounds will not be eligible to participate.

Methods and Procedures

Design of the Study and Minimization of Bias: Open label exposure--response study.

Randomization: Not applicable

Blinding: Not applicable

Baseline procedures: When informed consent has been obtained, age, race, gender, and ethnicity information will be collected at baseline along with a brief health history. A brief visual examination will be conducted to note any evidence of inflammatory or ulcerative changes to the gums or other oral tissues. It will be confirmed that no seafood or shellfish has been consumed the day prior to or day of the baseline appointment through the 24-hour blood draw period and non-fluoride toothpaste is used on the day of the baseline appointment through the 24-hour blood draw period. An 18 gauge sterile venous cannula will be placed in an upper extremity with a Heparin lock so that the cannula will remain patent. An initial blood sample of 10 mL (one tube) will be withdrawn using a fluoride free tube. Subject will void for a baseline urine sample collection. Subsequent urine will be collected for a 24-hour cumulative sample following application of the study intervention. Using a dental microbrush, dental plaque will be collected

from the buccal surfaces of the upper posterior teeth and the microbrush inserted in a sampling tube and agitated. Subjects will not eat for at least 2 h following application of the varnish.

Study intervention: 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 [Cascade Custom Chemistry, Eugene, OR]. 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.

The specific procedure is a single topical application of 0.4 mL of Advantage Anti-Caries Varnish to the teeth. Teeth will be brushed with a soft toothbrush to remove debris and dried with cotton prior to application. The varnish will be dispensed into a disposable plastic dappen dish premarked to indicate the proper volume and applied with a dental applicator brush. The entire contents of the dappen dish will be applied *following* the baseline procedures.

Blood, urine and plaque sampling following intervention:
Subjects will have blood samples of 10 mL withdrawn at 30 min, 1h, 2h, 3h, 4h, 6h, 8h, 12h and 24 hours. Subjects will continue to collect urine in the original container until 12h and be provided instructions and a container to continue the urine collection to 24 hours. Subjects will remain at the research site for 12 hours and return for the 24-hour timepoint. A 24-hour plaque sample will be obtained in the same manner as the baseline sample.

Blood, urine and plaque sample processing:
Blood samples will be spun in a clinical centrifuge, the plasma withdrawn, and then the plasma will be frozen for later analysis. The total volume of urine at baseline and 24 hours will be recorded and a 10 mL aliquot taken and frozen for later analysis. Plaque samples will be placed in a receiving tube, the tube agitated, and the contents frozen for later analysis.

Sample Analysis: Blood and urine samples will be analyzed by ion chromatography using EPA standard methods. Cmax, Cmin (last measurable time point), $t_{1/2}$, and the AUC will be calculated. Plaque will be analyzed by 16S ribosomal RNA profiling

Data Analysis and Monitoring:
Subject disposition: The frequency and reason for subject withdrawal will be summarized.

Data Analysis and reporting: The PI will be responsible for performing all analyses, creating the output for the analyses and disseminating results to the study team. The Principal Investigator and the rest of the study team will then review the results. The Principal Investigator will be responsible for drafting and preparing a final report of the study.

Data Storage and Confidentiality
The data will be stored on password protected computers in the Clinical Research Center at the UWMC and in a locked cabinet and on password protected computers at the Regional Clinical Dental Research Center at the University of Washington School of Dentistry. Only investigative personnel will have access. The data will be available for inspection by regulatory monitors and FDA.

Risk-Benefit Assessment

Risk Category: Greater than Minimal Risk

Potential Risk: Hypersensitivity to the varnish components, changes to intraoral tissues: erythema, gingival inflammation, or soft tissue changes. Both the sodium fluoride varnish and povidone iodine are already cleared by the FDA and have been used for many years intraorally. Fluoride varnishes are recommended by the US Preventive Services Task Force and professional organizations. There also may be bruising at the site of the blood collection.

Protection Against Risks: The study will be carried out in the Clinical Research Center at the UWMC by licensed personnel under the Institute of Translational Health Sciences.

Potential Benefits: There is no direct benefit to the participant.

Alternatives to Participation: The alternative is to decline participation.

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment:
Subjects will be recruited from among University of Washington (UW) employees, patients, or visitors. Flyers will be posted in the UW Health Sciences to notify potential subjects of the opportunity to participate. They will call or email staff at the School of Dentistry Regional Clinical Dental Research Center (RCDRC) for more information or to schedule an appointment. Subjects who meet the study's criteria for entry will be recruited into the study by the dental staff and enrolled.

Process of Consent: Potential participants will have the opportunity to ask questions and will be informed that participation is voluntary. They will have the opportunity to take the consent home to consider whether or not they want to take part in the study. They will be reminded that whether or not they decide to participate will not affect their care at the UWMC or the School of Dentistry and they can ask questions about participation or discontinue participation at any time.

Subject Capacity: Participants must have the capacity to give informed consent, be English speaking and able to read and understand English.

Subject / Representative Comprehension: Potential participants will be asked to clarify their understanding of the objectives of the study. They will also be asked to clarify their understanding of the risks and benefits of participation.

Documentation of Consent: Once potential participants have had a chance to read the approved consent form and had their questions answered following the consent discussion, they will be asked to sign the form. The study staff will sign the form and provide the participant a fully signed and dated copy. The original signed consent form will be stored in a locked cabinet at the Regional Clinical Dental Research Center at the University of Washington School of Dentistry.

Costs to the Subject: The participants will not incur any costs associated with the study.

Payment for Participation: A $400 volunteer compensation will be provided following the 24 hour blood draw to defray the costs of parking, transportation and any inconvenience from study participation.

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Analysis Plan

For the pharmacokinetic analysis, baseline serum iodine and fluoride concentrations will be subtracted from other timed serum concentrations to adjust for baseline endogenous levels of iodine and fluoride. Baseline-corrected concentrations that have a negative value (i.e., measured concentration was lower than baseline concentration) or result in concentrations at the limit of detection for multiple time points (i.e., 10 ng/mL for fluoride) will be excluded.

Pharmacokinetic analysis will be performed using Phoenix WinNonlin (Certara).

- The elimination rate constant (k_{elim}) will be determined by nonlinear regression of the terminal slope.
- Area under the curve (AUC): The $AUC_{0-\infty}$ will be calculated using a log-linear trapezoidal rule of baseline-corrected serum concentrations and extrapolated to infinite time by C_{last}/k_{elim}, where C_{last} is the last concentration used in the estimation of k_{elim}. The 24-hour AUC ($AUC_{0-24\ h}$) will be calculated using a log-linear trapezoidal rule of total iodine or fluoride serum concentrations from time = 0 to 24 h.
- The total urinary recovery of iodine and fluoride will be determined by multiplying the concentration measured in the urine collected over 24 hours by the total volume of urine collected over 24 hours.
- The renal clearance of iodine and fluoride will be calculated as the total urinary recovery/$AUC_{0-24\ h}$.
- The time to peak concentration (T_{max}), observed and baseline-corrected peak concentrations (C_{max}), and observed 24-h concentration ($C_{24\ h}$) will be reported.

Statistical analysis will be performed using Excel to calculate the mean ± standard deviation for the pharmacokinetic parameters. No statistical comparisons will be made as it is a single arm study.