Protocol: Pharmacokinetics of Advantage Arrest

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Purpose of the Study and Background

Objective: The purpose of this study is to characterize basic PK parameters (Cmax, $t_{1/2,}$ AUC, and total urinary recovery) to contribute to evidence for the safety of Advantage Arrest, consistent with Guidance for Industry--Exposure--Response Relationships (April 2003). On a preliminary basis, we will also characterize the microbiome before and 24-hours after the topical treatment.

Background: The Sponsor/Investigator conducted a preliminary PK study in six adults (Vasquez et al., 2012) in which 38% diammine silver fluoride (silver diamine fluoride) was applied topically to three teeth in each subject and maximum serum concentration and time to maximum serum concentration were studied over four hours. Mean amount of the agent applied was 7.57 mg. Over the four-hour observation period the mean maximum serum concentrations were 1.86 umol/L for fluoride and 206 nmol/L for silver. These maximums were reached at 3 h and 2.5 h for fluoride and silver, respectively. Fluoride exposure was below the EPA oral reference dose. Silver exposure exceeded the EPA oral reference dose for cumulative daily exposure over a lifetime, but for occasional use was well below concentrations associated with toxicity. Nevertheless, the number of subjects was limited and the follow-up period too short to calculate the AUC. Although diammine silver fluoride is available in many countries, there are no other published PK studies to our knowledge.

Assumptions: This is a topical agent where the active ingredients are applied to the teeth and eventually swallowed and may be absorbed through the GI tract or excreted. Minimal amounts are absorbed through the oral mucosa. Serum concentrations of silver and fluoride will be be proportional to the dose of silver and fluoride administered topically to the teeth as part of Advantage Arrest. The total urinary recovery of fluoride, adjusted for baseline levels, will be calculated to estimate the minimum amount absorbed in each patient following application of the varnish. As biliary excretion is the principle route of elimination of silver (Lansdown et al., 2010), it is unlikely that significant amounts of silver will be recovered in the urine.

Criteria for Subject Selection

Number of subjects: There will be up to 20 healthy adult subjects enrolled in the study with the goal of at least 16 subjects to complete the study.
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, including topical fluoride gels or rinses. Healthy status will be determined by self-reported medical history by the attending clinician.

Exclusion criteria: Subjects will be excluded if they have oral mucositis or any ulcerative lesions or hypersensitivity to silver or fluoride. Subjects who are pregnant, breastfeeding, 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. Non-fluoride toothpaste will be 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. An initial blood sample of 6 mL (one tube for serum collection) will be withdrawn using a fluoride free tube (BD Vacutainer with Clot Activator Plus Royal Blue Stopper). Subject will void for a baseline urine sample collection. 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.

Study intervention: Advantage Arrest, Aqueous Diamine Silver Fluoride $[Ag(NH_3)]_2F$, CAS RN 33040-28-7, 38.3% to 43.2% in purified water 5.0 - 5.9% (w/v) fluoride; 24.4 - 28.8% (w/v) silver, Silver Diamine Fluoride

Teeth will be brushed with a soft toothbrush to remove debris and dried with cotton prior to application. The specific procedure is that 5 mg (1 drop) of Advantage Arrest will be dispensed into a plastic dappen dish and all of the material will be applied to the facial cervical surfaces of 5 posterior teeth with an applicator. To calculate the amount of Advantage Arrest applied: the dappen dish with the initial amount of Advantage Arrest dispensed and applicator will be weighed before application and after application. The amount applied will be calculated as the difference in weights before and after application. The amount applied will be recorded. The teeth will remain isolated with cotton rolls for 3 minutes and then rinsed with water and high volume evacuation. Subjects will not eat for at least 2 h following application of the test agent.

Blood, urine and plaque sampling following intervention:
Subjects will have blood samples of 6 mL withdrawn at 30 min, 1h, 2h, 3h, 4h, 6h, 8h, 12h and 24 hours. Urine will be collected for a 24-hour cumulative sample following application of the study intervention. 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 through the 12 hour blood and urine collection 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 serum withdrawn, and then the serum will be frozen for later analysis. The total volume of urine at baseline, 12 and 24 hours will be recorded and a 10 mL aliquot will be taken of each sample 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: Serum and urine samples will be analyzed for F- by ion chromatography and Ag+ by ICPMS (Inductively coupled plasma mass spectrometry). Cmax, Tmax, Cmin (last measurable time point), $t_{1/2}$, and the AUC will be calculated from serum samples. Total amount recovered will be calculated from urine samples. 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 and sub-investigators 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 silver or fluoride, changes to intraoral tissues: erythema, gingival inflammation, or soft tissue changes. Advantage Arrest has been used extensively since clearance as a medical device in 2014 and the Sponsor knows of no adverse effects. The same agent is approved in Japan and there have no harms reported. There 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 University of Washington Medical Center and the Regional Clinical Dental Research Center at University of Washington School of Dentistry 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 timepoint to defray the costs of parking, transportation and any inconvenience from study participation.

References:

Lansdown AB. A pharmacological and toxicological profile of silver as an antimicrobial agent in medical devices. Adv Pharmacol Sci. 2010;2010:910686.

Vasquez E, Zegarra G, Chirinos E, Castillo JL, Taves DR, Watson GE, Dills R, Mancl LL, Milgrom P. Short term serum pharmacokinetics of diammine silver fluoride after oral application. BMC Oral Health 2012;12:60.