Protocol: Pharmacokinetics of Advantage Arrest in Children

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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) in healthy children to contribute to evidence for the safety of Advantage Arrest, consistent with Guidance for Industry--Exposure--Response Relationships (April 2003).

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.

The Sponsor/Investigator conducted an additional PK study to further characterize the kinetics of silver and fluoride with sixteen healthy adults (Lin et al., 2019) in which 38% silver diamine fluoride was applied topically to five teeth in each subject (estimated 4-11milligrams per subject), and maximum serum concentration and time to maximum serum concentration were studied via serum and urine samples over 24 hours. Over the 24-hour observation period, the silver serum peak was .67ng/mL. This maximum was reached at 3 h, and the elimination half-life of silver was estimated to be 46 hours. Baseline fluoride serum levels were between less than 10 through 50ng/mL. The estimated urinary fluoride was 1.29mg, and no silver was recovered in the urine. The study duration was too short to fully capture the pharmacokinetics of silver and return of serum silver to baseline levels. A study duration of 4-7days with 48, 72, 120, and 168-hour sampling time points is needed.

In both studies, the dose and time to peak serum silver was comparable. Peak serum silver concentrations were higher in the Vasquez et al study which could be due to lack of rinsing post-application. In both studies, there was a 400-fold safety margin in the amount applied compared to the US EPA's lowest allowable effect level for silver exposure at 1g.

There are no published PK studies with children. The investigative team at the University of Washington developed a physiologically-based pharmacokinetic (PBPK) model to predict silver disposition in children, as there are data establishing the safety of fluoride exposure in children in both the anesthesia and dental literature. The predictive performance of the model was assessed by comparing the predicted PK profiles and parameters with the observed data from published rat and human data following intravenous or oral silver administration. The PBPK model was applied to the pediatric population by accounting for developmental physiological changes. From this model, the predicted silver concentrations were within 2-fold of observed blood and tissue silver concentrations in rats and within the 95% confidence interval of observed plasma silver concentrations in healthy human adults. For a given SDF dose, the simulated peak plasma silver concentrations were 5.2-, 4.3-, 2.7-, 1.3-fold higher in children aged 1-2

years, 2-4 years, 5-10 years and 12-17 years, respectively, compared to adults. The half-life of silver was comparable in all ages and plasma and tissue silver concentrations were predicted to return to baseline levels within 10 days after SDF application. Based on the predictions, younger children will have transiently higher silver plasma concentrations than adults, though smaller increases are expected if less SDF is applied.

Assumptions for Proposed Study: 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.

Criteria for Subject Selection

Number of subjects: There will be up to 50 healthy children subjects enrolled in the study with the goal of at least 21 subjects to complete the study.
Gender of subjects: The subjects will be approximately half male and half female.
Age of subjects: Subjects will be 5-12 years of age.
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 be healthy. Healthy status will be determined by self-reported medical history evaluated by the attending clinician. Subjects will have at least one carious lesion.
Exclusion criteria: Subjects will be excluded if they have oral mucositis, any ulcerative lesions, or hypersensitivity to silver or fluoride. Subjects with a history of SDF treatment within 3 months will be excluded.

Methods and Procedures

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

Randomization: Not applicable.

Blinding: Not applicable.

Baseline procedures: Once informed consent and assent have 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 blood draw period. A blood sample of 6 mL (one tube for serum collection) will be withdrawn at an assigned time point using a fluoride free tube.

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 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 carious lesion/s 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 1 minute and then rinsed with water and high volume evacuation. Subjects will not eat for at least 2 h following application of Advantage Arrest.

Blood sampling following intervention: Subjects will have one blood sample of 6 mL withdrawn at an assigned time point: 3 subjects per timepoint at 2, 4, 6, 24, 48, 96 and 168 hrs.

Blood processing: Blood samples will be spun in a clinical centrifuge, the serum withdrawn, and then the serum will be frozen for later analysis.

Sample Analysis: Serum 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.

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 UCSF Pediatric Dental Clinic in a password protected room. Only investigative personnel will have access. The data will be available for inspection by regulatory monitors and FDA.

Risk-Benefit Assessment

Risk Category: 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 Canada and 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 at UCSF Benioff Children's Hospital in the University of California, San Francisco in Pediatric Dental Clinic and the Clinical and Translational Science Institute by licensed personnel under the Clinical and Translational Science Institute**.**

Potential Benefits: The Advantage Arrest will help slow or arrest their existing carious lesion/s and aid in the prevention of new lesions.

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 among patients at the University of California, San Francisco Pediatric Dental Clinic. Flyers will also be posted in at the University of California, San Francisco Pediatric Dental Clinic to notify potential subjects of the opportunity to participate. They will call or email Hellene Ellenikiotis, DDS 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 PI and enrolled.

Process of Consent: Potential subjects 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 their child to take part in the study. They will be reminded that whether or not they decide to participate will not affect their care at University of California, San Francisco Pediatric Dental Clinic and they can ask questions about participation or discontinue participation at any time.

Process of Assent: Potential subjects will have the opportunity to ask questions and will be informed that participation is voluntary. All communication will be had at an age-appropriate level. They will have the opportunity to take the assent 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 University of California, San Francisco Pediatric Dental Clinic and they can ask questions about participation or discontinue participation at any time.

Minimize Pressure to Participate: Pressure to participate will be minimized by ensuring all subjects are aware that their decision to participate or not will have no consequences. They can say yes or no, and nothing will be different. Everyone will be just as happy with them.

Parent/Subject Capacity: Parents must have the capacity to give informed consent and subjects must have the capacity to give assent. Subjects must be English speaking and able to read and understand English.

Parent/Subject Comprehension: Potential parents and subjects 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 and Assent: Once potential parents and subjects have had a chance to read the approved consent and assent forms, and had their questions answered following the consent/assent discussion, they will be asked to sign the forms. The study staff will sign the form and provide the participant a fully signed and dated copy. The original signed consent and assent forms will be stored in a locked cabinet at the University of California, San Francisco Pediatric Dental Clinic at Benioff Children's Hospital.

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

Payment for Participation: A $100 volunteer compensation will be provided.

Reimbursement for Participation: Reimbursement will be provided to defray the costs of parking and transportation for 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.

Lin YS, Rothen ML, Milgrom P. Pharmacokinetics of 38% topical silver diamine fluoride in healthy adult volunteers. J Am Den Ass 2019;150(3):186-192.