INVESTIGATIONAL PRODUCT:	EDTA Eye Drops (EED)
PROTOCOL DATE AND VERSION:	10 MAR 2023 6
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PROTOCOL SYNOPSIS

Title	A Randomized, Efficacy Assessor-Blinded, Parallel Group, Pilot Study to Assess Preliminary Efficacy and Safety of EDTA Eye Drops (EED) v. an Active Comparator in the Suppression of Herpes Simplex Virus Eruptions in Subjects with a History of Herpes Labialis
Objective	To collect preliminary efficacy and safety data on the use of EED in subjects with a history of herpes labialis, following UV Radiation.
Introduction & Rationale	Herpes simplex virus (HSV) infections are common and can cause significant morbidity both at the time of the original infection and when recurrences occur. There are two types of HSV – HSV-1 and HSV-2. HSV-1, the most common cause of oral "cold sores," is transmitted mainly by oral-to-oral contact. Genital herpes is usually caused by HSV-2, although HSV-1 can also cause genital breakouts. Both HSV-1 and HSV-2 infections are lifelong, with the virus living in the ganglia of nerves that supply the area of the original infection and recurring sporadically in the same area of that nerve's innervation. Most infections and recurrences are asymptomatic, but infectious viral shedding can occur. Patients who are not asymptomatic can develop prodromes of tingling, pain or paresthesia, and eventually blisters and ulcerations with pain. Healing generally occurs within 10 to 19 days after onset in primary infection or within 5 to 10 days in recurrent infection. Lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring. According to WHO, in 2012 an estimated 3.7 billion people under age 50 (67%) had HSV-1 infection globally. Some patients have predictable outbreaks after exposure to noxious stimuli, such as sunlight fever, menstruation, or stress. HSV-1 can cause ocular HSV as well as dermal HSV eruptions. Researchers have found that calcium signaling is involved in the translocation of the virus from the ganglia to the eruption site. It has been found that an increase of calcium levels in the extracellular matrix will precipitate the calcium signaling events that are causal to the migration of the HSV virus from the proximal ganglia to the eruption site. (Hunsperger 2003, Cheshenko 2003) Further, Husperger found in her experiments (in vitro) that the chelation of calcium greatly reduced the reactivation of the HSV virus. EED, which consists of a calcium chelator and a permeation enhancer could be one such intervention. Livionex has had some anecdotal evidence that this intervention could work at preventing an HSV eruption and preventing post prodromal viral shedding. IRB-approved clinical studies of HSV-1 have been performed in normal human volunteers with a history of HSV-1, who develop recurrences with prodromes after exposure to UV light. We will use this technique to induce recurrences in susceptible, HSV-1 infected individuals then treat with EED or a Comparator 5 times daily.

	Abreva® has been chosen as the Comparator product in this study because it is approved by the FDA for treatment of HSV-related cold sores. Dosing 5 times/day has been selected as the dosing regimen because that is the dosing regimen approved for Abreva by FDA. The manufacturers of Abreva recommend that subjects not be treated for greater than 10 days. A maximum of 7 days treatment with study product has been chosen for this study. Thus, treatment in both groups of subjects, will be 5 times daily and will last until healing of the lesion, or up to 7 days following the onset of the prodrome. EED is currently being used at the University of Rochester, NY. Furthermore the 2.6% EDTA eye drops have been used in a Phase I/II study under IND 70,467.
Endpoints	**Primary Efficacy Endpoint** • Proportion of subjects using EED v. those using the Comparator, who do not progress to Stage 3 (vesicle) of a herpes labialis outbreak following UV radiation exposure. **Secondary Efficacy Endpoints** • Pain in the lip and surrounding area • Duration of lesion until healed (loss of hard crust) • Cumulative lesion area (sum of all lesions) • Maximum lesion size (size of the largest lesion) **Safety Endpoint** • Adverse Events
Subjects	**Planned Enrollment** We will enroll until we have 20 subjects that have expressed a lesion from the induction and complete the treatment period of the study. **Study Entry Criteria** ***Inclusion Criteria*** To be eligible for enrollment, a subject must meet the following criteria: 1. Understands the requirements of the study and provides written informed consent prior to undergoing any study-related procedures. 2. Subject is a male or female between the ages of 18-80 years old, inclusive. 3. Fitzpatrick skin type II or III. 4. History of at least one year of herpes labialis induced by UV exposure. 5. Able to recall exact location of most common or most recent outbreak. 6. History of at least 50% of cold sore outbreaks occurring with UV (sun) exposure. 7. At least 1 HSV-1 outbreak within the past 12 months. 8. Experiences prodromal symptoms before HSV-1 outbreaks.

	9. Subject is willing and able to comply with protocol-specified dosing, visits to the clinic and tracking of pain. ***Exclusion Criteria*** Subjects will be excluded from the study if they meet any of the following criteria: 1. Outbreak <2 weeks prior to enrollment. 2. History of herpes simplex vaccine. 3. On antiviral suppression within the past 30 days. 4. Requires more than acetaminophen for pain for recurrent HSV outbreaks. 5. On any systemic or topical steroid, immune suppressant, or chemotherapeutic agent within the past 14 days. 6. Use of tanning beds, history of sunburn, or beach vacation <2 weeks prior to enrollment. 7. History of photosensitivity, lupus erythematosus, or current use of photosensitizing medication. 8. Current immunosuppressed state due to underlying disease (i.e. HIV infection) concomitant treatment (i.e. chemotherapy). 9. Current upper respiratory tract infection or any active illness that could trigger cold sores or affect overall health of the patient or the assessment of the study product. 10. Pregnant or intending to become pregnant during the study. 11. Abnormal skin conditions in the area of the recurrent HSV1 outbreaks. 12. Enrolled in another clinical trial within the past 30 days. 13. Previously treated with EED. 14. On any analgesics or NSAIDs that cannot be stopped during the study. 15. Alcohol or drug abuse.
Design	This will be a randomized, efficacy assessor-blinded, parallel group, pilot study of up to 20 subjects with documented MED induced herpes labialis. Potential subjects will be assessed during a **screening visit** that must take place no greater than 2 weeks prior to the lesion induction visit. During the screening period, subjects that meet all other entry criteria will undergo UV susceptibility testing to determine their individual MED (minimal erythemal dose). UV susceptibility testing takes place over two days with exposure to UV light on specified regions on the subject's back followed by an assessment of the exposed areas 24 hours later to identify the MED. Subjects who have a measurable MED will be allowed to continue to the induction visit. Patients that do not have a measurable MED response will be considered screen failures or they may have repeat MED testing with different levels. At the **Induction Visit**, subjects will undergo UV radiation at a level 3 times their MED. The exposed area of the lip will be marked with indelible ink and a photograph may be taken. Each subject will then be randomly assigned in a 1:1 ratio to receive either EED or Comparator. Subjects will be dispensed

	study medication and instructed how to apply it to the exposed area. When the patient first senses the start of developing a cold sore and applies study medication will be considered Day 1. Dosing of the study product will be done five times daily, beginning at the time that a subject first senses the start of the prodromal phase (Day 1). Subjects will be given a diary card to record their pain levels, progression of lesion development and any unusual symptoms (not normally seen with their outbreaks). Patients will be called daily by the study team after their induction visit to determine the start of prodrome. If after 7 days, the patient does not develop any prodromal senses, the patient will be considered an **induction failure**. When the patient first senses signs or symptoms of a cold sore, they will have the **Day 1** visit conducted within 24 hours. Day 1 visit may be conducted in person or as a MyChart Virtual Visit. Their diary card will be reviewed and if they have experienced a prodrome and/or lesion since the induction visit, their compliance with dosing will be checked. If the subject has noted any unusual symptoms, these will be discussed with medical personnel to determine if the symptoms represent a treatment emergent AE. A photo will be taken of the irradiated area (as marked at the induction visit). The blinded assessor will assess the prodrome and/or lesion and take measurements. On **Days 3, 5, and 7**, the subject will return to the clinic or follow up via virtual video call for assessment of the irradiated area. Study staff will review the subject diary to determine if the subject is correctly noting the lesion stage. Subjects will have a photo taken of the radiated area and asked to continue with dosing as instructed. Any diary card notation of unusual symptoms in subjects will be reviewed by study staff to determine if the symptoms represent a treatment emergent adverse event. The blinded assessor will assess the prodrome and/or lesion and take measurements. More study product may be dispensed as needed. Most subjects' lesions will have resolved by day 7, and they will end study treatment after 7 full days of treatment. If lesion has not resolved by day 7, the maximum number of days the patient may use study drug treatment is 10 days. The **EOS** is the final study visit will take place on Day 10. A photo will be taken of the irradiated area, the diary card will be carefully reviewed and study product (including empty containers) will be collected. If subjects reach EOS without full resolution of their lesion(s), they will be given the option to begin taking a prn medication for the remainder of the outbreak. Measurements will be taken. If an adverse event has occurred but has not resolved by the EOS visit, the subject will be contacted once weekly and status noted until such time as the event has resolved. The blinded assessor will assess the prodrome and/or lesion. A **Safety follow-up phone call** will occur 2 days after the EOS to determine if any new AEs have occurred. Safety will also be evaluated by an independent physician throughout the study. The first independent safety evaluation will be done once 5 subjects

	have reached EOS. Thereafter, the independent safety evaluation will occur as each subsequent group of 5 subjects reaches EOS and will include data on all subjects having reached EOS.
Enrollment Period	Subjects will be enrolled over a 2 year period.
Treatment Period	Subjects will be treated for up to 7 days from the time they first experience a prodrome and/or a lesion. If lesion has not resolved by day 7, the maximum number of days the patient may use study drug treatment is 10 days. If subjects reach EOS without full resolution of their lesion(s), they will be given the option to begin taking a prn standard of care medication for the remainder of the outbreak. Subjects that do not exhibit a prodrome within 7 days of the induction visit, will be considered induction failures and be discharged from the study. Total time of study participation for any given subject may range from 13 to 25 days.
Location	University of Utah MidValley Clinic, Department of Dermatology
Safety Assessments	Solicited AEs by review of diary cards and discussion with subjects
Efficacy Assessments	Primary: • Number of subjects that experience prodrome (Stage 1) but do not progress to vesicles (Stage 3) by completion of treatment Secondary: • Subject-assessed duration of pain • Clinician-assessed duration of lesion appearance (Stage 3), as reported by subject, to complete healing (Stage 5) • Measurement of cumulative lesion area (all eruptions if more than 1) • Measurement of each lesion (if more than one) from eruption (Stage 3) through healing of hard crust (Stage 4) to identify the largest lesion

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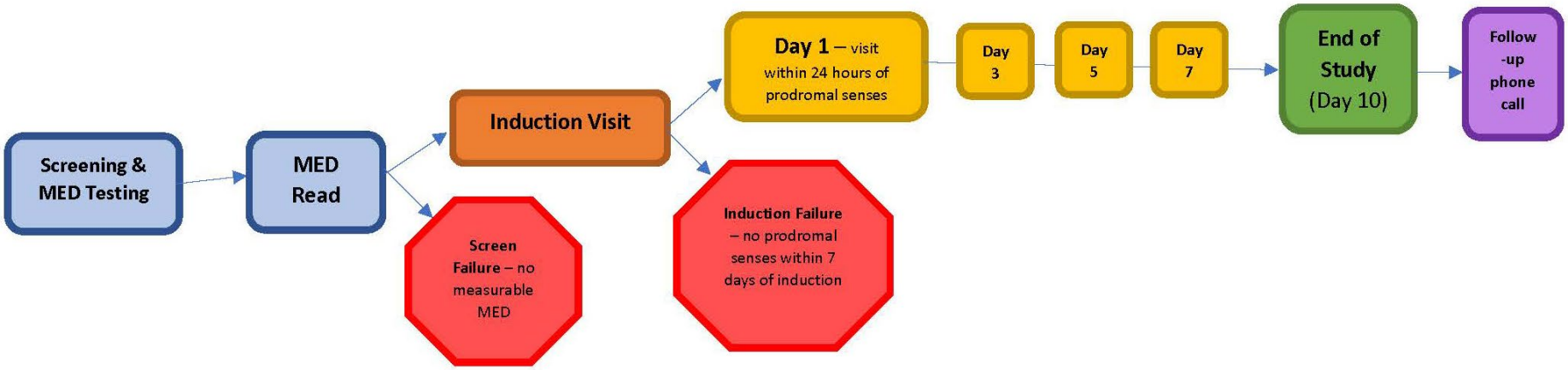
STUDY SCHEMA



1. INRODUCTION

1.1 Background and Rationale

Herpes simplex virus (HSV) infections are common and can cause significant morbidity both at the time of the original infection and when recurrences occur. There are two types of HSV – HSV-1 and HSV-2. HSV-1, the most common cause of oral "cold sores," is transmitted mainly by oral-to-oral contact. Genital herpes is usually caused by HSV-2, although HSV-1 can also cause genital breakouts. Both HSV-1 and HSV-2 infections are lifelong, with the virus living in the ganglia of nerves that supply the area of the original infection and recurring sporadically in the same area of that nerve's innervation. Most infections and recurrences are asymptomatic, but infectious viral shedding can occur. Patients who are not asymptomatic can develop prodromes of tingling, pain or paresthesia, and eventually blisters and ulcerations with pain. Healing generally occurs within 10 to 19 days after onset in primary infection or within 5 to 10 days in recurrent infection. Lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring.

According to WHO, in 2012 an estimated 3.7 billion people under age 50 (67%) had HSV-1 infection globally. Some patients have predictable outbreaks after exposure to noxious stimuli, such as sunlight fever, menstruation, or stress.

Researchers have found that calcium signaling is involved in the translocation of the virus from the ganglia to the eruption site. It has been found that an increase of calcium levels in the extracellular matrix will precipitate the calcium signaling events that are causal to the migration of the HSV virus from the proximal ganglia to the eruption site. (Hunsperger 2003, Cheshenko 2003) Further, Husperger found in her experiments (in vitro) that the chelation of calcium greatly reduced the reactivation of the HSV virus.

EDTA Eye Drops (EED), which consists of a calcium chelator and a permeation enhancer, could be one such intervention. Livionex has had some anecdotal evidence that this intervention could work at preventing an HSV eruption and post prodromal viral shedding.

IRB-approved clinical studies of HSV-1 have been performed in normal human volunteers with a history of HSV-1, who develop recurrences with prodromes after exposure to UV light. We will use this technique to induce recurrences in susceptible, HSV-1 infected individuals then treat with EED or Comparator 5 times daily.

Abreva® has been chosen as the Comparator product in this study because it is approved by the FDA for treatment of HSV-related cold sores. Dosing 5 times/day has been selected as the dosing regimen because that is the dosing regimen approved for Abreva by FDA. The manufacturers of Abreva recommend that subjects not be treated for greater than 10 days. A maximum of 7 days treatment with study product has been chosen for this study.

Thus, treatment in both groups of subjects, will be 5 times daily and will last until healing of the lesion, or up to 7 days following the onset of the prodrome.

2. OBJECTIVE

To collect preliminary efficacy and safety data on the use of EED in subjects with a history of herpes labialis, following UV Radiation

2.1 Efficacy Endpoints

2.1.1 Primary:

- Proportion of subjects using EED v. those using the Comparator, who do not progress to Stage 3 (vesicle) of a herpes labialis outbreak following UV radiation exposure

2.1.2 Secondary:

- Pain in the lip and surrounding area
- Duration of lesion until healed (loss of hard crust)
- Cumulative lesion area (sum of all lesions)
- Maximum lesion size (size of the largest lesion)

2.2 Safety Endpoint

Adverse events

3. STUDY DESIGN

This will be a randomized, efficacy assessor-blinded, parallel group, pilot study of up to 20 subjects with documented UV induced herpes labialis. We will enroll until we have 20 subjects that have expressed a lesion from the induction and complete the treatment period of the study. With the possibility of screen failures and induction failures, we may consent up to 35 patients maximum.

Potential subjects will be assessed during a screening visit that must take place no greater than 2 weeks prior to the Induction visit. During the screening period, subjects that meet all other entry criteria will undergo UV susceptibility testing to determine their individual MED (minimal erythemal dose). UV susceptibility testing takes place over two days with exposure to UV light on specified regions on the subject's back followed by an assessment of the exposed areas 24 hours later to identify the MED.

Subjects who have a measurable MED will be allowed to enroll in the study. Each subject will be randomly assigned in a 1:1 ratio to receive either EED or Comparator.

Subjects that do not have a measurable MED will be considered screen failures or may have repeat MED testing with new values.

At the Induction Visit, subjects will undergo UV radiation at a level 3 times their MED. The exposed area of the lip will be marked with indelible ink and a baseline photograph may be taken.

Each subject will then be randomly assigned in a 1:1 ratio to receive either EED or Comparator. Subjects will be dispensed study medication and instructed how to apply it to the exposed area. Dosing of the study product will be done 5 times daily, beginning at the time that a subject first senses the start of the prodromal phase (Day 1). The EED is a clear viscous eye drop, and the Comparator is a white cream substance. Therefore, the subject and principal investigator will be unblinded, and only efficacy assessments will be done by a qualified trained blinded assessor.

Subjects will be given a diary card to record their pain levels (starting at Day 1), progression of lesion development and any unusual symptoms (not normally seen with their outbreaks).

Patients will be called daily by the study team after their induction visit to determine the start of prodrome. When the patient first senses the prodromal phase, they need to be seen within 24 hours for the Day 1 visit. Patients that do not have prodromal senses within 7 days of the induction will be considered induction failures. Induction failure patients will be asked to return their study drug to the study team.

On Days 1, 3, 5, and 7 the subject will follow up in person or via virtual MyChart visit with blinded assessor during which the subject's diary card will be reviewed and compliance with dosing checked. If the subject has noted any unusual symptoms, these will be discussed with medical personnel to determine if a treatment emergent adverse event has occurred or, if the subject has not started treatment, whether their medical history should be updated. If possible, the lesion will be measured. A photo will be taken of the irradiated area (as marked at the induction visit). More study drug may be dispensed as needed. Most subjects' lesions will have resolved by day 7, and they will end study treatment after 7 full days of

treatment. If lesion has not resolved by day 7, the maximum number of days the patient may use study drug treatment is 10 days. An end of study (EOS) visit will occur as soon as their lesion is healed or Day 10, whichever comes first.

The EOS visit (Day 10) is expected to be the final study visit. EOS will occur when a subject's lesion is fully healed or Day 10 (whichever comes first). A photo will be taken of the irradiated area, the diary card will be carefully reviewed and study product (including empty containers) will be collected. Subjects who developed a lesion that has not yet healed will be given the option to begin taking a prn medication that has been previously prescribed to treat an outbreak.

If an adverse event has occurred but has not resolved by the EOS visit, the subject will be contacted once weekly, and status of the AE noted until such time as the event has resolved.

4. STUDY TREATMENT

4.1 EDTA Eye Drops

Livionex Inc. has agreed to supply EED. It consists of 2.6% EDTA plus a permeation enhancer (MSM). EED will be packaged in standard dropper bottles and labeled as containing 2.6% EDTA plus MSM as a surfactant.

4.2 Comparator: Abreva®

Abreva, manufactured by Avinir Pharmaceuticals, is an antiviral agent approved by the FDA for treatment of cold sores. It is packaged in tubes of 2g each.

4.3 Randomization Codes

A simple randomization code will be generated by the Investigator so that subjects are randomly assigned in a 1:1 ratio to either EED or Abreva.

5. SUBJECT POPULATION

We will enroll until we have 20 subjects that have expressed a lesion from the induction and complete the treatment period of the study. With the possibility of screen failures and induction failures, we may consent up to 35 patients maximum.

5.1 Inclusion Criteria

To be eligible for enrollment, a subject must meet the following criteria:

1. Understands the requirements of the study and provides written informed consent prior to undergoing any study-related procedures.

2. Subject is a male or female between the ages of 18-80 years old, inclusive.
3. Fitzpatrick skin type II or III.
4. History of at least one year of herpes labialis induced by UV exposure.
5. Able to recall exact location of most common or most recent outbreak.
6. History of at least 50% of cold sore outbreaks occurring with UV (sun) exposure.
7. At least 1 HSV-1 outbreak within the past 12 months.
8. Experiences prodromal symptoms before HSV-1 outbreaks.
9. Subject is willing and able to comply with protocol-specified dosing, visits to the clinic and tracking of pain.

5.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following criteria:

1. Outbreak <2 weeks prior to enrollment.
2. History of herpes simplex vaccine.
3. On antiviral suppression within the past 30 days.
4. Requires more than acetaminophen for pain from recurrent HSV outbreaks.
5. On any systemic or topical steroid, immune suppressant or chemotherapeutic agent within the past 14 days.
6. Use of tanning beds, history of sunburn, or beach vacation <2 weeks prior to enrollment.
7. History of photosensitivity, lupus erythematosus, or current use of photosensitizing medication.
8. Current immunosuppressed state due to underlying disease (i.e. HIV infection) concomitant treatment (i.e. chemotherapy).
9. Current upper respiratory tract infection or any active illness that could trigger cold sores or affect overall health of the patient or the assessment of the study agent.
10. Pregnant or intending to become pregnant during the study.
11. Abnormal skin conditions in the area of the recurrent HSV1 outbreaks.
12. Enrolled in another clinical trial within the past 30 days.
13. Previously treated with EED.
14. On any analgesics or NSAIDs that cannot be stopped during the study.
15. Alcohol or drug abuse.

6. STUDY PROCEDURES

6.1 Study Visits

6.1.1 Screening Visit (Days -14 to 0)

No more than 14 days prior to their planned start of study, subjects will report to the dermatology clinic for the following screening procedures:

- Presentation, review and signing of the informed consent.
- Review of their medical history.
- Review of HSV history.
- Assist with setting up MyChart account.
- Review of Inclusion and Exclusion criteria.
- Limited Physical Exam – to ensure that there are no co-morbidities that may interfere with study compliance or results.
- Notation of any concomitant medications the subject is currently taking (and that do not conflict with entry criteria).

ONLY IF the subject meets all entry criteria and is considered by the Investigator to be able to comply with and complete all study procedures, may they proceed to the final screening procedure of UV Susceptibility and Calculation of MED (refer to Study Manual for detailed instructions) consisting of:

  - Exposure to UV Radiation.
  - Assessment of Exposed Area – no more than 24 hours after exposure.

6.1.2 Induction Visit

Upon reporting to the clinic for their induction visit, the subject will be randomized to receive either EED or Abreva. The following assessments will then be performed to establish baseline values prior to dosing:

- Review of Medical History and Concomitant Medications for any changes between Screening and Day 1 (Treatment emergent AEs are collected in this study beginning with first instance of dosing. Any unusual symptoms prior to the start of dosing will be recorded, if appropriate, as an update to the subject's medical history).

- Limited Physical Exam to check for any changes between Screening and Day 1(changes in PE after start of dosing will be assessed as possible treatment emergent AEs)

If the subject remains qualified for the study:

- They will be dispensed study product (EED or Abreva) and instructed to use it 5 times daily beginning when they first sense a prodrome or see a lesion (they will be asked to note the day and time of their first dose on their diary card).
- They will be given a diary card and instructed how to complete it. A practice diary completion may be done to ensure that subjects know how to complete the diary.

Subjects will then be discharged from the clinic with an appointment to return on Day 3 via virtual video call. They will be instructed to bring their Diary Card and the tube/bottle of study product that they have received.

6.1.3 Day 1 Visit

Day 1 visit will occur within 24 hours of experiencing signs or symptoms of a cold sore. The patient will start applying study drug as soon as they notice signs or symptoms of a cold sore. The subject will present for a follow up appointment in clinic or via virtual video call consisting of:

- Review of the subject's diary card to identify possible treatment emergent adverse events.
- Assessment of the subject's pain on a visual analog scale.
- Measurement of the lesion will be taken (if lesion is present).
- Photographs of area exposed to UV radiation may be asked to be taken by subjects and uploaded into their MyChart account. If patients are present in clinic, photographs will be taken by study staff.
- If the subject has experienced a prodrome or lesion they should have started dosing. The study staff will review their dosing compliance and examine the study product tube/bottle. If the subject is not complying with the dosing regimen, the study staff will determine whether non-compliance is serious enough to warrant terminating the subject's participation. Otherwise, minor non-compliance should be noted, and the subject should be retrained on how to dose themselves.

6.1.4 Study Days 3, 5, and 7 Visits

On Days 3, 5, and 7, the subject will present for a follow up appointment in clinic or via virtual video call consisting of:

- Review of the subject's diary card to identify possible treatment emergent adverse events.
- Assessment of the subject's pain on a visual analog scale.
- Measurement of the lesion will be taken (if lesion is present).
- Photographs of area exposed to UV radiation may be asked to be taken by subjects and uploaded into their MyChart account. If patients are present in clinic, photographs will be taken by study staff.
- If the subject has experienced a prodrome or lesion they should have started dosing. The study staff will review their dosing compliance and examine the study product tube/bottle. If the subject is not complying with the dosing regimen, the study staff will determine whether non-compliance is serious enough to warrant terminating the subject's participation. Otherwise, minor non-compliance should be noted, and the subject should be retrained on how to dose themselves.

Once patients reach the Stage 2/3 lesion their lesion may be swabbed for viral culture (HSV PCR). If the patient reaches Stage 2/3 over the weekend, the lesion will not be swabbed. We will reserve this for the first five patients but may continue to do all patients to ensure lesion is in fact a cold sore and not a reaction to the UV radiation.

6.1.5 EOS – End of Study Visit (Day 10 – or after subject's lesion has fully healed)

An EOS visit will occur after the subject's lesion has fully healed or Day 10 (whichever comes first), the subject will present to the clinic for a follow up appointment in clinic or via virtual video call consisting of:

- Review of the subject's diary card to identify possible treatment emergent adverse events. If the subject has an AE that has not resolved by this time, the site staff will explain to the subject that they will be called every week to check on the status of the AE, until it is resolved.
- Assessment of the subject's pain on a visual analog scale.

- Photographs of area exposed to UV radiation may be asked to be taken by subjects and uploaded into their MyChart account. If patients are present in clinic, photographs will be taken by study staff.

The subject's diary card and all tubes//bottles of study product (empty, partially used or unused) will be collected and the subject will be released from the study.

6.2 Early Discontinuation Visit

If at any time during the study, a subject wants to stop participating or the Investigator believes it is in the subject's best interest to stop treatment, every effort should be made to complete the final assessments noted in the EOS visit.

6.3 Follow-up Phone Call Visits

Two days and seven days after the patient's final study visit, the study team will contact them to ask if they have had any unusual symptoms since their last visit. If patients answer yes, they may be asked to return to the clinic for an exam to determine if the symptoms are due to the study treatment.

7. EFFICACY EVALUATIONS

7.1 Number of subjects that experience prodrome (Stage 1) but do not progress to vesicles (Stage 3) by completion of treatment

The Principal Investigator or his designee will review all photographs taken from Day 1 through the EOS visit against the onset of prodrome date and the date of healing or 7 full days of treatment noted on the subject's diary card. They will then determine the duration of the HSV outbreak (prodrome to healed). This may or may not agree with the subject's assessment of "healed" but should be based on the collective information gathered during the subject's time on study. The blinded assessor will assess the prodrome and/or lesion at every clinic visit starting at day 3. The blinded assessor will only be responsible for the rating of the prodrome and or/lesions. The blinded assessor will not be performing safety evaluations. The unblinded staff will instruct the subject to not talk with the blinded assessor about which treatment they have been using.

7.2 Subject-assessed duration of pain

Each subject will evaluate their pain daily on a visual analog scale contained in their diary card. They will begin their pain rating on Day 1 and end at their EOS visit.

8. SAFETY EVALUATIONS

8.1 Adverse Events

8.1.1 Treatment Emergent Adverse Events

An adverse event (AE) or adverse experience is any untoward medical occurrence in a in an individual who is using the study product and that does not necessarily have a causal relationship with the study product but that occurs after the start of dosing and up to 2 days after the EOS visit. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study product, whether or not considered related to it. Pre-existing conditions, which increase in frequency or severity or worsen in nature during or as a consequence of use of a drug in human clinical studies, will also be considered as adverse experiences.

An AE **does not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Worsening of symptoms associated with expected progression of periodontal disease are not considered an adverse event in this study

8.1.2 Evaluation and Reporting of Adverse Events

All AEs (i.e. a new event or an exacerbation of a pre-existing condition) that occur after the start of dosing and up to 2 after the EOS visit, will be recorded as an AE or SAE (if applicable). (Any event occurring prior to start of treatment on Day 1 will be recorded as part of the subject's medical history.) All subjects who have used the study product at least once will be evaluated for safety.

8.1.3 Serious Adverse Events

An SAE is an AE from this study that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study dentifrice
- Considered significant by the investigator for any other reason

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.4 Serious Adverse Event Reporting Requirements

- Within 24 hours of the Investigator's knowledge of an SAE, the site should contact the manufacturer (Livionex) and report the circumstances of the SAE.
- This initial reporting should contain as much information as is available to the Investigator.
- The Investigator should also notify the IRB of Serious Adverse Events occurring at the site in accordance with local procedures.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF.

The blind may not be broken unless it is determined necessary in order to provide appropriate treatment to the subject. Upon breaking of the blind or the final unblinding of study data, if the event is related to Abreva, the Investigator will notify Avinir Pharmaceuticals of the SAE.

8.2 Independent Safety Review

An independent clinician will be assigned to review all available safety assessments on subjects as soon as 5 subjects reach EOS. This reviewer will be blinded to study treatment unless a safety concern is raised that requires identification of the subject's treatment group. Each subsequent safety evaluation will be conducted as 5 more subjects reach EOS and will include all available information from all subjects that have that have reached at least EOS. In other words, with each group of 5 subjects, the total reviewed will increase by 10 until all 20 subjects are included in the final independent safety evaluation.

The independent clinician will advise the Principal Investigator of any safety concerns or trends that could be a reason to terminate a specific subject's participation or to stop the study until it is deemed safe to continue.

9. STATISTICAL METHODS

9.1 Analysis Populations

Analysis populations are defined as follows:

- The Safety population will include all subjects who use EED or Abreva for at least one day.
- The Per Protocol population will include all subjects (that were not induction failures) who complete the study, defined as attending all study visits.

9.2 Efficacy Analysis

The proportion of patients with nonulcerative recurrences which do not progress to vesicles (Phase 3) will be compared between treatment groups using a x2 test. The episode duration and lesion size parameters will be compared between the treatment groups with a two-sample Student t-test. The time to lesion healing will be assessed using Kaplan-Meier methods. To illustrate the total clinical benefit of EED, an analysis of time to lesion healing and lesion area for all recurrences (i.e., including both ulcerative lesions and nonulcerative recurrences) will be performed as ‘‘all lesions.’’ In this analysis, the impact of prevention of ulcerative lesions will be introduced by assigning zero values to nonulcerative recurrences.

9.3 Safety Analysis

The safety analysis will be conducted on the Safety population.

Collection of AEs will begin on the first day of treatment and will be reported in simple per-subject listings.

10. SCHEDULE OF ASSESSMENTS

ASSESSMENT	SCREENING	Induction Visit	Daily after induction visit to Day 1	DAY 1	DAY 5	DAY 7	DAY 10/ EOS	Follow-up phone call (EOS +2 days)
Informed Consent	X							
Medical/HSV History	X	X (med hx only)						
Urine Pregnancy Test (for woman of child bearing potential only)	X							
Limited Physical Exam	X	X						
Concomitant Medications	X	X						X
UV susceptibility test / MED testing	X (exposure)							
MED Reading		X						
Randomization		X						
UV exposure at 3 x MED (cold sore inducing)		X						
Study Product Dispensed		X						
Dosing Begins				X				
Dosing Ends						X		
Collect Study Product (including empty tubes//bottles)							X	
Photograph of irradiated area and lesion may be taken		X		X	X	X	X	X
Measurement of lesion (if possible)				X	X	X	X	X
Dispensing of Diary Card		X						
Review of Diary Card/Dosing compliance				X	X	X	X	
Solicitation of Adverse Events			X	X	X	X	X	X
Rating of lesion by blinded assessor				X	X	X	X	
Phone call to check for prodromal senses			X					