COVER PAGE

**Official Study Title**: Cannabidiol (CBD) for the Management of Emergency Dental Pain

**NCT number**: NCT04642404

**IRB Approval Date**: 04/19/2021

**Unique Protocol ID**: HSC20200305H

# Form CT
# UTHSA Clinical Trial Description

This form is not mandatory. Other documents are acceptable if equivalent information is provided.

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|---|---|---|---|
| **UTHSCSA Tracking Number** *(internal use only)* | HSC20200305H | **1. Original Version Date** | 2020-07-07 V1.1 |
| | | **1.1. Revision Date(s)** *add rows as needed* | |

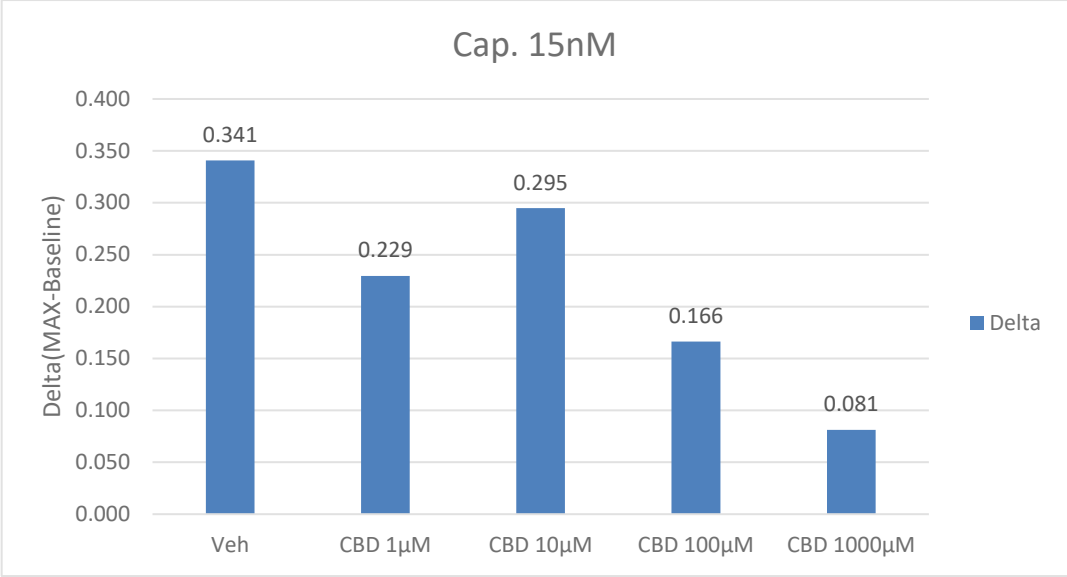
**TITLE: Cannabidiol (CBD) for the management of emergency dental pain**

**2. Background**

*Briefly discuss the important literature relevant to the trial and that provides background for the trial. Include the importance of the trial and any relevant treatment issues or controversies.*

Dental pain can be devastating and often hard to treat effectively and safely. Endodontic pain is being routinely managed with root canal treatment often combined with pharmacologic agents, nonetheless post-operative pain often occurs, especially in cases with pre-operative pain (1, 2). Current analgesic regimens in endodontics mainly include non-steroidal anti-inflammatory drugs (NSAIDS) and acetaminophen often combined with opioids (3-5). These drugs, besides their large variability in effectiveness, are also associated with moderate to severe side-effects that range from gastrointestinal bleeding disorders to liver/kidney damage, cardiovascular effects and even death (6-8). CBD, which is the primary ***non-psychoactive and non-addictive*** compound in cannabis, is currently FDA-approved for the treatment of epileptic seizures, and has already shown potential in treating pain such as arthritis, neuropathic, cancer and chronic pain (9-12). The rational leading to this project is that the use of CBD, a cannabinoid with no psychoactive and addictive effects and mild-to-moderate side effects, may provide a better alternative to these analgesics for dental pain (13, 14). Further, we propose to study in our clinical model the already FDA-approved CBD formulation (Epidiolex, GW Pharmaceuticals) *off-label*, thus ensuring that the drug, if successful, could be more readily available for our dental patients. Notably, the alternative CBD formulation will aim to reduce the rate of opioid prescriptions for dental pain and provide a significant relief to the opioid epidemic. Reported CBD-related AEs after long term use include gastrointestinal effects, sleep disorders and elevated liver transaminases (15, 16). Events after short-term use, which is typically the schedule for dental pain, are not reported (14, 16). Collectively, it is important to note that we do not propose to replace opioids with another drug that can develop psychotic disorders and addiction, nor does our proposed used of CBD present with significant known AEs as often seen with NSAIDS and acetaminophen.

**Preliminary data.** We isolated TG neurons from C57BL/6 female mice and cultured them for 5 days. This assay takes advantage of a reporter dye (Fura-2) that increases fluorescence by an influx of calcium into the cell, thus providing a measure of neuronal activation. Briefly, TG neurons were incubated with Fura-2AM, then pretreated with CBD (1-1000uM) or vehicle for 5 min. A major subclass of nociceptive ("pain detecting") neurons were then stimulated with capsaicin (15nM for 40s) and intracellular calcium levels $[Ca^{+2}]_I$ were recorded using a FlexStation 3 (Molecular Devices). The net changes in $[Ca^{+2}]_I$ were calculated by subtracting the baseline $[Ca^{+2}]i$ (mean value collected for 60s prior to addition of CBD) from the Max $[Ca^{+2}]i$ value achieved after exposure to the drugs. Preliminary data show that CBD 100uM and 1000uM significantly inhibited capsaicin-induced $[Ca^{+2}]_I$ accumulation. These preliminary data support our central hypothesis that CBD produces analgesia via peripheral inhibition of TG nociceptive neurons.



**3. Objectives and Endpoints** *All data points collected in the study should support an objective or have a regulatory purpose.*
*Complete the table – add rows as needed.*

| 3.1. Objective(s)<br>*Clearly and concisely define the primary and secondary outcomes.* | 3.2. Endpoint<br>*Clearly define the endpoints. (endpoints are the basis for concluding that the objective has been met).* | 3.3. Justification for Endpoint<br>*Briefly explain why the endpoint(s) were chosen.* |
|---|---|---|
| 1. **<u>Primary outcome measure:</u> a.VAS pain intensity differences from baseline among the groups at each time point and maximum pain relief.**<br><br>b.Bite Force measurement using the Bite Fork at baseline, 1.5 h, 3h and 7d. | 1. Patients will report their pain level using a 100mm Visual Analogue Scale (VAS) at 0, 15min, 30min, 45min, 1h, 1.5h, 2 and 3 hour and 1week post-administration visit time of study drug Epidiolex or Placebo.<br><br>2. Patients will report their pain level that is elicited by biting down on the Bite Fork at 0, 1.5h, 3h and 1week post-administration visit time of study drug Epidiolex or Placebo. | 1.The VAS has been shown to be sensitive to changes in a patient's pain experience, is easily understood and easy to use. It has been successfully used in various health fields in children and adults.<br><br>2.The bite force measurement provided additional pain information being able to isolate one particular tooth (the problem tooth) being studies. |
| 2. **<u>Secondary outcome measure:</u> Measure psychoactive effects, mood changes at 0, 1.5h and 3h points, and somnolence at 3h and 1- week time point.** | 2.Patients will report feelings of drug high, alterations in internal perception and alterations in external perception, along with alertness, contentment and calmness by completing the following questionnaires:<br>a. Bowdle questionnaire<br>b. Bond & Lader Mood Scale<br>c. Epworth Sleepiness Scale | 2. The three listed questionnaires are commonly used for psychedelic assessment and safety assessment of cannabinoids use, with a longstanding administration in previous published studies in medical journals such as "Pain", "CNS Drugs", and "Journal of Psychopharmacology". Such effects are not commonly associated with CBD use because of the inherent nature of the absence of THC based on current literature. Nevertheless, patients that report such adverse events at the end of the observation period will be asked to have a family member to accompany them home. |

**4. Rationale**
*Briefly state the reason for conducting the clinical trial.*

CBD is currently being tested in ~155 clinical trials for various disorders, with 16 of those trials assessing pain outcomes including one new study assessing analgesic efficacy of CBD after tooth extractions (www.clinicaltrials.gov, accessed March 2020). By an unusual regulatory circumstance, synthetic CBD is a Schedule I drug, whereas hemp-derived CBD is a Schedule V drug. Accordingly, we propose to use the FDA-approved cannabis-derived CBD (Epidiolex, Greenwich Biosciences, CA). Epidiolex is the first, and thus far only, FDA-approved Schedule V CBD oral solution designated for rare forms of epileptic seizures. <u>The objective here</u> is to test Epidiolex *off-label* for the treatment of emergency tooth pain in a human clinical trial. <u>*We hypothesize that Epidiolex will provide substantial pain relief for the patients presenting with emergency odontalgia in our clinical research facility*</u>.

**5. Study Design**

| | | | |
|---|---|---|---|
| **5.1. Number of Groups/Arms** | 3 | **Group name(s)** | 1. CBD 10mg/kg single dose (given one time only )Epidiolex 100mg/ml oral solution<br>2. CBD 20mg/kg single dose (given one time only) Epidiolex 100mg/ml oral solution<br>3. Placebo oral solution single dose (given one time only) |

**5.2. Overall Design**
*Select all applicable*

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ☒ | **Randomization** | | | | ☐ | **Cluster Randomized** | | | | | | | |
| ☐ | **Group-Sequential** | | | | ☐ | **Adaptive Design** | | | | | | | |
| ☐ | **Parallel Design** | | | | ☐ | **Placebo-Controlled** | | | | | | | |
| ☐ | **Superiority** | | | | ☐ | **Equivalence** | | | ☐ | **Non-inferiority** | | | |
| | **Device** | ☐ | Pilot | | ☐ | Pivotal | | | ☐ | Post-Approval | | | |
| | **Drug/Biologic** | ☐ | Phase 1 | ☐ Phase 1/2 | ☒ | Phase 2 | ☐ | Phase 2/3 | ☐ | Phase 3 | ☐ | Phase 4 | |
| ☐ | **Dose escalation** | *If yes, details →* | | | | | | | | | | | |
| ☒ | **Dose ranging** | *If yes, details →* | 10mg/kg single dose (given one time only) Epidiolex 100mg/ml oral solution<br>vs.<br>20mg/kg single dose (given one time only) Epidiolex 100mg/ml oral solution | | | | | | | | | | |
| ☐ | **Sub-studies** | *If yes, details →* | | | | | | | | | | | |

**5.3. Other Design Details**:
Double-arm phase II randomized placebo-controlled trial with quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor)

**6. Study Population**

| **6.1. Study Population(s) Label/Name**<br>*To add more populations – select a row, copy & paste* | **6.2. Identify the criteria for <u>inclusion</u>**<br>*The criteria that <u>every</u> potential participant must satisfy, to qualify for study entry.*<br>All individuals in this study population must meet <u>all</u> of the inclusion criteria in order to be eligible to participate in the study | **6.3. Identify the criteria for <u>exclusion</u>**<br>*The characteristics that make an individual ineligible for study participation.*<br>All individuals in this study population meeting <u>any</u> of the exclusion criteria at baseline will be excluded from study participation. |
|---|---|---|
| Adults 18-75 years old with moderate-severe odontogenic pain | -Healthy adults 18-75 years old, ASA I or II.<br>-Permanent tooth with moderate to severe odontogenic pain, i.e. ≥30 on a 100mm VAS, as reported verbally by the patient.<br>-Clinical pulpal diagnosis of irreversible pulpitis or pulpal necrosis, and periapical diagnosis of symptomatic apical periodontitis.<br>-Test negative for recent cannabis use and/or other drugs of abuse including alcohol (urine tests collected at screening visit. Results will be available on site within 3-5 minutes).<br>-Participant able to understand the forms (English or Spanish) and provide informed written consent | -ASA Class III or IV, patients with hepatic impairment, pregnant or lactating women (pregnancy test is performed at the screening visit).<br>-Patients on drugs metabolized by enzymes that also metabolize CBD (e.g. clobazam, diazepam, topiramate, warfarin), or other drugs known to interact with Epidiolex (as assessed by PI at time of screening).<br>-Self-reported prior experience inhaling cannabis (either via smoking or vaporization).<br>-Use of opioids in the month prior to screening/treatment visit, and/or NSAIDS or acetaminophen 6 hours prior to treatment.<br>-Unwilling to participate |

| **6.4. Will screen failures be allowed to <u>re-screen</u> at a later date?** | ☒ **No** | ☐ **Yes** *If yes, describe criteria below ↓* |
|---|---|---|
| | Since the patients present with emergency pain and their pain will need to be addressed in a timely manner with appropriate treatment, there won't be any re-screening. | |

**7. Study Intervention(s) being tested or evaluated**
*This can include prevention, diagnostic or therapeutic interventions (e.g., drug or device) or educational, health services or basic science interventions (e.g., educational program, health care delivery model, or examining basic physiology)*

This is a therapeutic intervention study where the FDA approved study drug used off-label in two different doses according to randomization will be assessed against a Placebo of similar taste and appearance.
Group 1: CBD 10mg/kg single dose (given one time only )Epidiolex 100mg/ml oral solution
Group 2: CBD 20mg/kg single dose (given one time only) Epidiolex 100mg/ml oral solution
Group 3: Placebo oral solution single dose (given one time only)
The objective here is to test Epidiolex *off-label* for the treatment of emergency tooth pain in a human clinical trial. *We hypothesize that Epidiolex will provide substantial pain relief for the patients presenting with emergency odontalgia in our clinical research facility*.

Patients who present to the UT dental clinics will be provided a standard of care dental exam assessing the oral problem that brought them to the clinic. A non-research, routine oral exam will be provided. If the patient has expressed pain as part of their dental problem, they will be approached by study staff to explain the study and inquire if the patient would be interested in entering the study. If interested, informed consent will be obtained and documented. Medical history, demographics, vitals, pain questionnaire, Bite Force measurement,and study oral exam will be completed. Height & weight of the patient will be obtained for calculation of study medication to be given. Screening labs (urine pregnancy test for women of child-bearing age and urine toxicology) will be completed for research purposes to confirm inclusion/exclusion criteria. Subjects who meet all eligibility criteria will proceed to randomization. Eligible subjects will be randomized in a 1:1 ratio to one of the three study intervention arms: Epidiolex 10mg/kg, Epidiolex 20mg/kg or Placebo. Rescue pain medication of Ibuprofen 600mg or Acetaminophen 500mg will be administered if needed. Pain, Psychoactive and sleep questionnaires will be completed following study intervention administration at the timepoints outlined in the schedule of events. A follow-up research visit will occur one-week post-drug administration where a research sleep questionnaire will be completed and oral exam data collected (pain assessment, reported issues post-treatment, any rescue medication used).

The following coding system will be used to ensure that participant identities remain confidential and to protect against disclosure. Each participant will be assigned a unique Study ID# and all study data collected will be coded with this number. The Study ID# will be linked to participants' names on the Participant Log which will be kept in a secure location separate from the coded study data and will be accessible only to members of the research team. Data collected for this study will be coded with a Study ID# and securely stored in the offices of the research team. Certain personal identifiers required to conduct the study but not for statistical analysis (name and phone numbers) will be kept separate from research data collected and not entered into REDCap. Certain personal identifiers such as date of birth and gender that are needed for statistical analyses will be entered into REDCap. REDCap is password-protected and HIPAA-compliant. Data entered into REDCap is stored on a secure UT Health server. All electronic data will be protected using password-protected computers. Government or university staff may review this study to make sure it is being conducted safely and legally.

The PI will be informed by study staff of any subject who experience an adverse event, whether during the study visits or during the one-week post-procedure time. The PI will proceed with unblinding of the subject's group. Depending on the nature and severity of the adverse event, the patient will be instructed to contact their physician or visit the urgent care clinic.

**8. Protocol-Directed procedures, items, services or tests**
*List all procedures directed by the study plan - including items or services provided as part of routine or conventional care and those needed to diagnosis or treat research related complications.*

Important Note – The protocol directed procedures listed must match those in the Schedule of Activities (attachment)

**8.1. Drugs** *(trade and generic, dosage, route of administration)*

1. Epidiolex (cannabidiol) 100mg/ml oral solution given in a one time only single dose of either Group 1:10mg/kg OR Group 2: 20mg/kg (Research)
2. Placebo oral solution developed in a similar taste and appearance as the Epidiolex (Research)
3. Rescue Medication (Ibuprofen 600mg or acetaminophen/codeine 650/60mg if contraindication to Ibuprofen); as needed post-study intervention per provider discretion (Research)

**8.2. Devices**

**8.3. Biologics**

**8.4. Laboratory Tests**

Urine pregnancy test (Research)
Urine toxicology (drug screen; Research)

**8.5. Imaging Procedures**

**8.6. Other Research Procedures** *(e.g., other safety and efficacy assessments.)*

Medical History and Demographics (Routine care)
Oral Examination w/ vitals (Routine care)
Pain, Psychoactive and Sleep scale Questionnaires (Research)
Randomization to one of three study groups: Group 1) Epidiolex 10mg/kg; Group 2) Epidiolex 20mg/kg; Group 3) Placebo (Research)
Planned dental treatment (Routine care)

| **8.7 Attach a Schedule of Activities (SOA) Excel File** [Download the Template here: *Schedule of Activities*] | *Check to indicate that the SOA Excel File is attached →* | ☒ |
|---|---|---|

| **9.** | **Preparation/Handling/ Storage/Accountability of Investigational Drug, Biologic, or Device** |
|---|---|
| ☐ | *N/A - This study does not include any investigational products (e.g. drugs, devices or biologics)* |
| ☐ | *N/A - An Investigator Brochure is attached* |
| ☐ | *N/A - A Drug/Device Manual is attached* |

**9.1. Acquisition and accountability**

*State how the study intervention and control product will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product.*

Local Walgreens Pharmacy will provide the drug and placebo at requested intervals during the study to study team who will oversee drug accountability, storage and administration. The study medication in both concentrations and the placebo will be provided by the pharmacy in a multi-use vials, ready to be drawn from according to the patient height/weight once a patient is randomized. Approved study staff will safely discard any remaining medication in the bottle when expired in accordance with the university drug disposal policy. When study recruitment has been completed, all remaining study drug will be discarded in the same manner.

**9.2. Formulation, Appearance, Packaging, and Labeling**

*Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.*

Epidiolex is manufactured by GW Pharmaceuticals. EPIDIOLEX is a strawberry flavored clear, colorless to yellow solution supplied in a 105 mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution (NDC 70127-100-01). Each mL contains 100 mg of cannabidiol. EPIDIOLEX is packaged in a carton with two 5 mL calibrated oral dosing syringes and a bottle adapter (NDC 70127-100-10). The pharmacy will provide the Epidiolex in a multi-dose vial to be drawn upon when the patient is randomized. Placebo will appear in a similar form.

**9.3. Product Storage and Stability**

*Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).*

Store EPIDIOLEX in an upright position at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F). *[See USP Controlled Room Temperature]*. Do not freeze. Keep the cap tightly closed. Use within 12 weeks of first opening the bottle, then discard any remainder.

**9.4. Preparation**

*Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section. For devices, include any relevant assembly or use instructions.*

Following randomization, study staff will retrieve the study drug or placebo bottle and prepare the amount based on patient's randomization group and weight/height. Study staff will prepare the dose in a 10ml calibrated syringe and wrap it with non-transparent tape so patient and clinician are blinded to the amount/type of medication used. Placebo will be prepared in the same manner, thus blinding the clinician study staff to study product used.

## 10. Study Intervention Additional Details

### 10.1. Measures to Minimize Bias: Randomization and Blinding

*This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised. Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.*

REDCap will be utilized to create the randomization for treatment arm for all participants. Limited data will be entered into the REDCap software which will create a unique Study ID# for each participant. Randomization will also occur in REDCap per individual unique Study ID# created by the software.

Unblinding of a subject who has experienced an adverse event will be conducted by the PI by review of the online system of that particular subject's study e-chart and will occur within 24 hours of the AE notification. The PI will document and assess the unblinded information and appropriately report the AE, additionally make the appropriate treatment recommendations for the patient to ensure safety. In the case of serial adverse events of a similar type, or with a serious adverse event, the PI will unblind all participants and report to the IRB as required.

We will collect subject names and phone numbers to be recorded in the Participant Log in order to track when patients are scheduled for their regular clinic visits as research data collection will be linked to these regularly scheduled visits.

### 10.2. Study Intervention Compliance

*Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries).*

Participants will be monitored continuously throughout the 3 hours study intervention timeline by either a licensed dentist or licensed registered nurse. Administration of the Epidiolex study drug or Placebo will be achieved by a licensed dentist. All study personnel will be fully calibrated as to the study requirements/standards prior to initiation of the study. Each participant will be assigned a pre-numbered study packet containing all study required case report forms, including the questionnaires with assigned administration times clearly noted at the top of the document. A study 'Time Out' will occur to review that all study documentation has been completed and the appropriate randomization has occurred prior to escorting the participant to the operatory for the dental procedure.

### 10.3. Permitted Concomitant Therapy

*This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints).*

Ibuprofen 600mg and acetaminophen/codeine 650/60mg if a contraindication for 600mg ibuprofen exists, will be allowed in the trial.
These medications will be given at patient's request as a rescue medication during the observation period. We do not expect any drug-to drug interaction with these medications.

These analgesics will reduce the pain levels. To that end we will perform a time-to-rescue analysis. The subjects will complete the study.

### 10.4. Rescue Medicine

*List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions.*

☐ *N/A, no rescue medicine*

Ibuprofen 600mg (or acetaminophen/codeine 650/60mg, if 600mg contraindication for ibuprofen exists) will be provided in the 3-hour observation period as a rescue medication, if needed.

## 11. Study Intervention Discontinuation

### 11.1. Discontinuation of Study Intervention

*Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or re-challenging with study intervention.*

Participant safety monitoring, source documentation review and decision to discontinue study intervention will be under the oversight of the PI. Subjects will be monitored at each study visit/study follow up for any potential AE's or SAE's. To further

minimize risk to subjects and subsequent study discontinuation, the following medications will be screened for and restricted during the study intervention:

Patients on drugs metabolized by enzymes that also metabolize CBD (e.g. clobazam, diazepam, topiramate, warfarin). Epidiolex is metabolized by CYP3A4 and CYP2C19 and has the potential to inhibit CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations, therefore we chose to avoid potential drug interactions.

Info copied from drug prescription: **Effect of Other Drugs on EPIDIOLEX**
Moderate or Strong Inhibitors of CYP3A4 or CYP2C19
EPIDIOLEX is metabolized by CYP3A4 and CYP2C19. Therefore, coadministration with a moderate or strong inhibitor of CYP3A4 or CYP2C19 will increase cannabidiol plasma concentrations, which may result in a greater risk of adverse reactions.
Strong CYP3A4 or CYP2C19 Inducers
Coadministration with a strong CYP3A4 or CYP2C19 inducer will decrease cannabidiol plasma concentrations, which may lower the efficacy of EPIDIOLEX.

**Effect of EPIDIOLEX on Other Drugs**
UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 Substrates
1. In vitro data predict drug-drug interactions with CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5' diphospho-glucuronosyltransferase 1A9 (UGT1A9) (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when coadministered with EPIDIOLEX. Coadministration of EPIDIOLEX is also predicted to cause clinically significant interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates.

2. Self-reported prior experience inhaling cannabis (either via smoking or vaporization). Cannabis trials often present with high placebo effect. Cannabis naïve subjects are thus proposed to minimize this effect as well the possibility of tachyphylaxis.

3. Use of opioids in the month prior to screening/treatment visit, and/or NSAIDS or acetaminophen 6 hours prior to treatment. Any analgesic can potentially mask the effects of the study drug and increase placebo effect.

**Continued Study Monitoring and Halting Rules:**

Study drug is administered one time only at study hour zero with monitoring for the next three hours. Once the assigned study drug is given, the subject will continue in the 3-hour study observation period, even if they request the rescue medication. Only if they specifically request to formally withdraw from the study will they proceed to the dental treatment early, however subjects will be asked to complete the 3rd hour pain and Psychoactive Assessment Questionnaires at the time of consuming the rescue medication. Each patient is different in regards to their pain endurance level, so subjects will be instructed to request rescue medication when their pain becomes uncomfortable. Subjects will be encouraged to wait at least 60 minutes after the one time administration of the study drug before consuming any rescue medication. Subjects will additionally be asked to attend the one-week follow-up visit and complete the VAS and Sleepiness Scale Assessment.

In the case that a serious event appears within the same arm more than three times, we will discontinue the arm of the study. The PI will unblind the cases for close monitoring of the adverse event.

### 11.2. Continued Follow-up Discontinuation of Study Intervention

*Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems involving risks to subjects or others (UPIRSOs).*

We will have a follow-up study visit 1 week after intervention to assess safety and ask them to complete a survey in redcap to report adverse events or unanticipated problems. The PI will proceed with unblinding of the subject's group depending on the nature and severity of the adverse event. The patient will be instructed to contact their physician or visit the urgent care clinic to address any medical event.

## 12. Statistical Considerations

### 12.1. Statistical Hypotheses

*State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.*

We hypothesize that Epidiolex will provide substantial pain relief for the patients presenting with emergency odontalgia in our clinical research facility.

**12.2. Sample Size Determination**

*Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.*

This is a pilot clinical trial to determine the necessary effect size for an appropriately powered definitive clinical trial that will be pursued in a subsequent R01 (or UG3/UH3) application submitted to the NIH. We plan to enroll a convenience sample of N=22/group. We note that prior definitive studies in this pain model have detected NSAIDs such as ibuprofen with a similar sample size (17, 18).

**12.3. Populations for Analyses**

*Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).*

All participants in all three groups will be included in the analyses. The 3 groups will be compared to each other. While we expect that randomization will lead to balanced groups, we will specifically assess for age and sex balance and perform sensitivity analyses, if indicated. Further, we will employ generalized estimating equation models accounting for correlation between pain measures at various timepoints to assess the timepoint when maximum analgesia is observed.

**12.4. Statistical Analyses**

*Include analysis of primary efficacy endpoints, secondary endpoints, safety analyses, and any planned interim analyses*

This analysis will provide critical information for subsequent sample size calculations and endpoint determination in the subsequent main study. Mixed model analyses will be used for both primary and secondary outcomes. AEs among the groups will be analyzed with $X^2$ tests. The time-to-rescue medication will be summarized using Kaplan-Meier curves and compared between groups using stratified log-rank tests. Level of significance will be set at a=0.05. JMP software and GraphPad will be used for the analyses and the graphs.


1. Nixdorf DR, Moana-Filho EJ, Law AS, McGuire LA, Hodges JS, John MT. Frequency of nonodontogenic pain after endodontic therapy: a systematic review and meta-analysis. J Endod 2010;36(9):1494-1498.
2. Smith EA, Marshall JG, Selph SS, Barker DR, Sedgley CM. Nonsteroidal Anti-inflammatory Drugs for Managing Postoperative Endodontic Pain in Patients Who Present with Preoperative Pain: A Systematic Review and Meta-analysis. J Endod 2017;43(1):7-15.
3. Wong YJ, Keenan J, Hudson K, Bryan H, Naftolin F, Thompson VP, et al. Opioid, NSAID, and OTC Analgesic Medications for Dental Procedures: PEARL Network Findings. Compend Contin Educ Dent 2016;37(10):710-718.
4. Alghofaily M, Romberg E, Aldahmash S, Tordik PA. Opioid-prescribing Habits of Practitioner and Educator Members of the American Association of Endodontists: Report of a National Survey. J Endod 2019.
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