Title: A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis

NCT Number: NCT04611347

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A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis

Protocol Number: 03

National Clinical Trial (NCT) Identified Number: TBD

IND number: 146012

Principal Investigator: Brent DeGeorge MD, PhD

IND Sponsor: Brent DeGeorge MD, PhD

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Key Roles and Study Governance

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Sponsor-Investigator		
_____	_____	_____
Name (print)	**Signature**	**Date**

ABBREVIATIONS

AE	Adverse Event
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBD	Cannabidiol
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health Related Quality of Life
HSR	Health Science Research
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IP	Interphalangeal
IRB	Institutional Review Board
MP	Metacarpal phalangeal
NCT	National Clinical Trial
NIH	National Institutes of Health
NRS	Numeric Rating Scale
OHRP	Office for Human Research Protections
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
QC	Quality Control
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOC	Standard of Care
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
UVA	University of Virginia
VPR	Vice President for Research

1 PROTOCOL SUMMARY

1.1 Synopsis

Title: A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis.

Study Description: To investigate the therapeutic potential of cannabidiol (CBD) as a topical treatment for thumb basal joint arthritis. ***Rationale***: CBD is commonly being used as an over-the-counter treatment for arthritis-related pain, however no clinical trial has been performed to establish efficacy. ***Hypothesis***: CBD is more effective than placebo for relieving pain and improving patient-reported outcomes for thumb basal joint arthritis.
Study Design: The study design with be a double-blind, randomized controlled trial with crossover. Treatment will be blinded to the subjects and investigators. Patients will be randomly assigned 2 weeks of the CBD or control and then crossover to the other condition for 2 additional weeks. Patients will apply a novel cream containing CBD at the thumb base joint twice daily for 1 hour. Subjects will be advised to observe for physiologic changes, skin changes, or other adverse effects.

Objectives & Endpoints:

Objectives	Endpoints
Primary	
To determine the therapeutic potential of CDB as a topical treatment for thumb basal joint arthritis.	**Hand Functional Assessment**: Change from baseline hand functional assessment including grip, appositional, and oppositional pinch strength (kg); Kapandji score; and metacarpal phalangeal (MP) and interphalangeal (IP) range of motion. **Patient Reported Outcome Measures**: Change from baseline in the PROMIS-29 (Patient-Reported Outcomes Measurement Information System) and PROMIS upper extremity tests. The PROMIS-29 is a free publicly available generic health related quality of life (HRQoL) measure consisting of indices of pain, pain interference, depression, anxiety, global function, and social interactions. The PROMIS upper extremity test utilizes item-response theory and Computer Adaptive Test to efficiently and precisely report patient symptoms and perceived function.
Secondary	

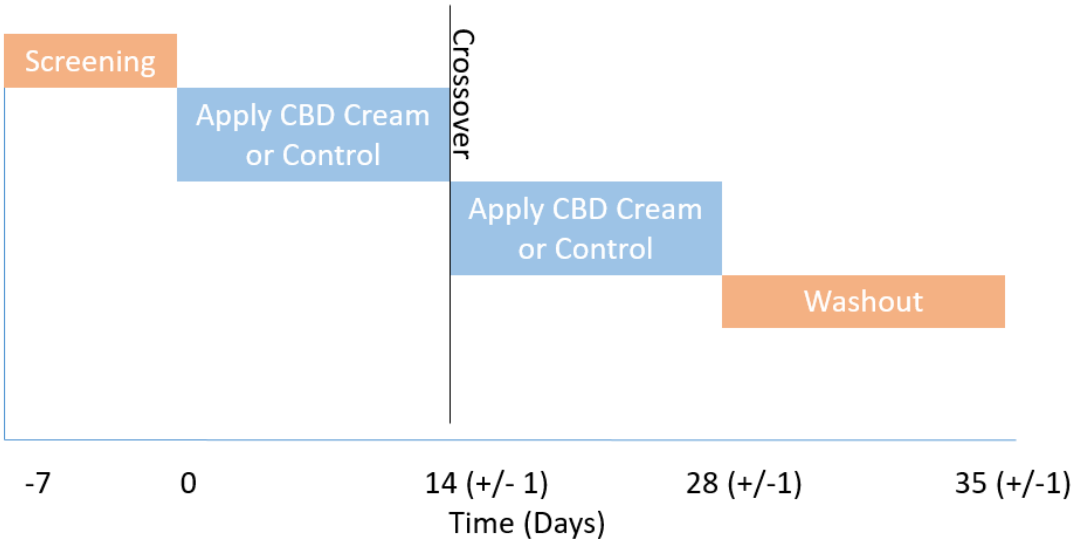
To determine the safety of treatment CBD.	Safety will be determined by evaluating: • The frequency and severity of adverse events from the beginning of treatment through the end of study participation. • Changes in skin appearance from baseline using standardized skin assessment tool. (patient will be removed from study with a score >/= 2) • Clinically significant change in CBC (baseline and follow-up) • Clinically significant change in basic metabolic panel (i.e., BUN, creatinine, CO2, Cl, K, Na, and glucose) (baseline and weekly follow-up) • Clinically significant change in hepatic function testing (i.e., serum transaminases [ALT/AST], total bilirubin, and alkaline phosphatase) (baseline and weekly follow-up) • Clinically significant change in vital sign assessments (i.e., heart rate and blood pressure) (baseline and weekly follow-up) • Suicidal behavior and thoughts as a specific question using the Columbia-Suicide Severity Rating Scale (C-SSRS) (baseline and weekly follow-up)

Study Population: 40 subjects with presenting with thumb basal joint arthritis over the age of 18 will be recruited from the UVA Hand Center.

Description of Sites/Facilities This will be a single-site study conducted at the UVA Hand Center at the University of Virginia.

Enrolling Participants:	
Description of Study Intervention:	The study design will be a double-blind randomized control trial with crossover. Treatment will be blinded to the subjects and investigators. Patients will be randomly assigned two (2) weeks of the case (CBD) or control cream and then crossover to the other cream for two (2) additional weeks. Patients will apply the topical cream at their thumb basal joint twice daily for 1 hour. The subjects will be advised to observe for physiologic changes, skin changes, or other adverse effects. If mild to serious adverse events are noticed, the creams will be removed immediately and appropriate care and observation will be taken. Each condition will last for 2 weeks and then subjects will be contacted by the study coordinator to facilitate crossover into the other condition. To capture any delayed-onset adverse events, including those related to skin changes that might develop after the drug is discontinued, subjects will attend a follow-up visit seven (7) days following the last dose of investigational cream.
Study Duration:	This study will last one year from the beginning of subject recruitment to data analysis.
Participant Duration:	Subjects will be enrolled in this study for approximately six (6) weeks from Screening until the final Study Visit.

1.2 Schema



2 INTRODUCTION

2.1 Study Rationale

Arthritis of the thumb basal joint is common, leading to debilitating pain, weakness, and instability that severely limits function (1). Cannabidiol (CBD) is a non-psychoactive hemp derivative with demonstrated efficacy for reducing cancer-related pain; however, its role in the treatment of arthritis-related pain has yet to be established.

2.2 Background

Numerous studies have shown the safety and efficacy of topical CBD for the treatment of osteoarthritis in dogs (2) and rats (3). Topical administration has been shown to have increased regional bioavailability and attenuates inflammation and pain without significant side-effects. The dose of maximum absorption and efficacy seen in rats was shown to be 6.2 mg/day (3). To date, no studies have been performed to evaluate the safety and efficacy of topical CBD for the treatment of basal thumb arthritis in human subjects.

Nitecka-Buchta et al. performed a double-blind randomized controlled trial of topical CBD for 60 total patients with myofascial pain. Topical application of 67 mg CBD – including other minor cannabinoids – was applied to masseter muscles twice daily for 14 days in the case group. Visual Analog Scores (VAS) were reduced from 5.6 on Day 0 to 1.7 on Day 14 (70.2% reduction) in the case group, versus 5.1 on Day 0 and 4.6 on Day 14 (9.8% reduction) in the control group (p = 0.00). (4)

Xu et al. performed a randomized controlled trial with cross-over for topical CBD treatment of 29 patients with symptomatic lower extremity neuropathy. Topical application of 250 mg of pure CBD (case arm) was applied up to four (4) times daily for four (4) weeks, and then patients switched to emu oil (control arm) with the same application for 4 weeks followed by cross-over. They showed a statistically significant reduction in Neuropathic Pain Scale scores for intense (5.11 to 4.02) (p=0.009) and sharp (4.01 to 3.09) (p<0.001) pain between case and control arms. (5)

No side effects or adverse events were noted in either clinical trial.

We have designed a randomized, controlled crossover design clinical trial to assess the safety and efficacy of topical CBD versus placebo for the treatment of thumb basal joint arthritis.

3 RISK/BENEFIT ASSESSMENT

3.1.1 Known Potential Risks

No major side effects were noted from previous topical studies. Minor side effects from topical and oral CBD studies include nausea, diarrhea, fatigue, change in appetite, and weight gain/loss (3). Exogenous CBD may affect the metabolism of Coumadin and other drugs based on the P450 metabolism. Another theoretical risk is contact dermatitis.

3.1.2 Assessment of Potential Risks and Benefits

A potential benefit of this treatment is the potential pain relief and gain of hand function if the CBD is effective at improving symptoms.

In addition – if the study shows that the administration of CBD cream will alleviate arthritic symptoms, this would be a cheap and easy treatment that could be used for many patients by delaying or potentially avoiding surgical intervention and improving their quality of life.

There has yet to be a randomized controlled trial demonstrating benefit of topical CBD products in this patients with osteoarthritis. The risks involved as detailed above are mitigated by safety monitoring and are outweighed by the ability to add to the current research in Cannabidiol products, which are currently understudied.

4 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To determine therapeutic potential of CDB as a topical	**Hand Functional Assessment**: Change from baseline in hand functional assessment including grip, appositional,

treatment for thumb basal joint arthritis.	and oppositional pinch strength (kg); Kapandji score; and MP and IP range of motion. **Patient Reported Outcome Measures**: Change from baseline in the PROMIS-29 (Patient-Reported Outcomes Measurement Information System) and PROMIS upper extremity tests. The PROMIS-29 is a free publicly available generic health related quality of life (HRQoL) measure consisting of indices of pain, pain interference, depression, anxiety, global function, and social interactions. The PROMIS upper extremity test utilizes item-response theory and Computer Adaptive Test to efficiently and precisely report patient symptoms and perceived function.
Secondary	
To determine the safety of treatment CBD.	Safety will be determined by evaluating: • The frequency and severity of adverse events from the beginning of treatment through the end of study participation. • Changes in skin appearance from baseline using standardized skin assessment tool (patient will be removed from study with a score >/= 2) • Clinically significant change in CBC (baseline and weekly follow-up) • Clinically significant change in basic metabolic panel (i.e., BUN, creatinine, CO2, Cl, K, Na, and glucose) (baseline and weekly follow-up) • Clinically significant change in hepatic function testing (i.e., serum transaminases [ALT/AST], total bilirubin, and alkaline phosphatase) (baseline and weekly follow-up) • Clinically significant change in vital sign assessments (i.e., heart rate and blood pressure) • Suicidal behavior and thoughts as a specific question using the Columbia-Suicide Severity Rating Scale (C-SSRS) at baseline and follow-up.

5 STUDY DESIGN

5.1 Overall Design

The study design will be a double-blind randomized controlled trial with crossover. Treatment will be blinded to the subjects and investigators. Patients will be randomly

assigned two (2) weeks of the case or control topical cream and then crossover to the other cream for two (2) more weeks. Patients will apply the cream at their thumb basal joint twice daily for one (1) hour. The subjects will be advised to observe for physiologic changes, skin changes, or other adverse effects. If mild to severe drug-related adverse events are noticed, the creams will be removed immediately and appropriate care and observation will be taken. Each condition will last for two (2) weeks and then subjects will be contacted by the study coordinator to facilitate crossover into the other condition. This study will last one year from the beginning of subject recruitment to data analysis. Subjects will be enrolled in this study for approximately six (6) weeks from Screening until the final Study Visit.

5.2 Justification for Dose

Nitecka-Buchta *et al*. performed a double-blind randomized controlled trial of topical CBD for 60 total patients with myofascial pain. Topical application of 67 mg CBD – including other minor cannabinoids – was applied to masseter muscles twice daily for 14 days in the case group. Visual Analog Scores (VAS) were reduced from 5.6 on Day 0 to 1.7 on Day 14 (70.2% reduction) in the case group, versus 5.1 on Day 0 and 4.6 on Day 14 (9.8% reduction) in the control group (p = 0.00). (4)

Xu *et al.* performed a randomized controlled trial with cross-over for topical CBD treatment of 29 patients with symptomatic lower extremity neuropathy. Topical application of 250 mg of pure CBD (case arm) was applied up to four (4) times daily for four (4) weeks, and then patients switched to emu oil (control arm) with the same application for 4 weeks followed by cross-over. They showed a statistically significant reduction in Neuropathic Pain Scale scores for intense (5.11 to 4.02) (p=0.009) and sharp (4.01 to 3.09) (p<0.001) pain between case and control arms. (5)

No side effects or adverse events were noted in either clinical trial.

5.3 End of Study Definition

Primary completion date is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes defined as the final date for the collection of data for the primary endpoint.

Study completion date is the date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.

6 STUDY POPULATION

6.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 18 years or older.
4. Females of childbearing potential must have a negative urine and blood pregnancy test at Screening and a negative urine pregnancy test before study drug is administered. Females must abstain from sex or use a highly effective method of contraception during the period from Screening to administration of study drug and for 30 days after the last dose of study medication. Standard acceptable methods include abstinence or the use of a highly effective method of contraception, including; hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom with spermicide, vasectomy, intrauterine device. If females are of non-child bearing potential, they must be post-menopausal defined as: age > 55 with no menses within the past 12 months, or history of hysterectomy, or history of bilateral oophorectomy, or bilateral tubal ligation.
5. Males must consent to use a medically acceptable method of contraception throughout the entire study period and for 90 days after their last study drug application. They must agree to not donate sperm for 90 days after their last study drug application.
6. Presence of radiographically confirmed diagnosis of thumb basal joint arthritis.

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Subject does not speak English.
2. Subject is blind.
3. Severe cardiac, pulmonary, liver and /or renal disease.
4. Coumadin use at time of screening.
5. History of mental illness.
6. Subjects who are incarcerated.
7. History of drug or substance abuse.
8. Pre-existing CBD or hemp based product usage.
9. Subject has had a corticosteroid injection ≤ 3 months prior.
10. Subject has had prior surgery for osteoarthritis treatment.
11. Females who are pregnant, nursing or planning a pregnancy; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from Screening to the first dose of study medication and for 30 days after the last dose of study medication. Standard acceptable methods include abstinence or the use of a highly effective method of contraception, including; hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom with spermicide, vasectomy, intrauterine device.
12. Any skin disease or condition, including eczema, psoriasis, melanoma, acne or contact dermatitis, scarring, imperfections, lesions, tattoos or discoloration that may affect treatment application, application site assessments, or affect absorption of the study drug.
13. Subjects with ALT/AST >3 times the upper limit of normal at screening.
14. Subjects with history of or active depression or suicide ideation based on Columbia-Suicide Severity Rating Scale (C-SSRS).

15. Subjects taking prescription or non-prescription medication which are substrates of CYP3A4 (Itraconazole, Ketoconazole, Azamulin, Troleandomycin, Verapamil, John's wart, Phenobarbital), CYP2C19 (Nootkatone, Ticlopidine, Rifampin, Omeprazole), CYP2C8 (Montelukast, Quercetin, Phenelzine, Rifampin, Clopidogrel) , CYP2C9 (Sulfaphenazole, Tienilic acid, Carbamazepine, Apalutamide, Fluconazole, Celecoxib), CYP1A2 (alpha-Naphthoflavone, Furafylline, Phenytoin, Rifampin, Ritonavir, smoking, Teriflunomide, Ciproflaoxacin, oral contraceptives, Alloprinol) and CYP2B6 (Sertraline, Phencyclidine, Thiotepa, Ticlopidine, Carbamazepine, Efavirenez, Rifampin, Bupropion) within 14 days of the study procedure.

6.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (for NIH studies) and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6.4 Lifestyle Considerations

Females must abstain from sex or use a highly effective method of contraception during the period from Screening to administration of study drug and for 30 days after the last dose of study medication. Standard acceptable methods include abstinence or the use of a highly effective method of contraception, including; hormonal contraception, diaphragm, cervical cap, vaginal sponge, condom with spermicide, vasectomy, intrauterine device. If females are of non-child bearing potential, they must be post-menopausal defined as: age > 55 with no menses within the past 12 months, or history of hysterectomy, or history of bilateral oophorectomy, or bilateral tubal ligation.

Males must consent to use a medically acceptable method of contraception throughout the entire study period and for 90 days after their last study drug application. They must agree to not donate sperm for 90 days after their last study drug application.

Subjects will be advised not to drive or operate machinery until they have gained sufficient experience on study drug.

7 STUDY INTERVENTION

7.1 Description of Study Intervention(s)

Product with description, all names, dosage form	Potency	Investigational or Standard of Care (SOC)	Packaging/Appearance	Manufacturer	Storage Conditions
Case – 99.99% pure cannabidiol (CBD) with 100% Pure USDA Organic Shea Butter	6.2 mg/mL	Investigational	Placed within 10mL syringe labeled with approved institutional labeling for research use only.	Eco-X, Inc, Grand Junction, CO (CBD) Mary Taylor Naturals, LLC, Fort Myers, FL (Shea Butter)	Room Temperature
Control – 100% Pure USDA Organic Shea Butter	N/A	Investigational	Placed within 10mL syringe labeled with approved institutional labeling for research use only.	Mary Taylor Naturals, LLC, Fort Myers, FL	Room Temperature

7.2 Dosing and Administration

Subjects will be randomized to receive a total of 28mL of either 6.2 mg/mL of CBD with Shae butter or Shae butter alone placed within three (3) 10mL syringes. Subjects will be advised to apply 1 mL of the cream overlying their thumb basal joint dorsally twice daily, approximately every 12 hours. In the CBD condition, the cream will be formulated to deliver approximately 12.4 mg of purified CBD per day, whereas in the control condition the Shea butter will be utilized alone. The purified CBD is colorless and odorless to facilitate blinding.

The CBD with Shae Butter or Shae butter alone will be provided to subjects in 10 mL syringes without a needle, with a rubber topper. Subjects will be instructed to store the cream at room temperature. Subjects may dispense the cream from the syringe into a gloved hand. Gloves will be provided to the subject along with the investigational product. The cream will need to be applied to the base of the thumb until completely absorbed. Subjects should avoid water to the area for at least one hour.

7.3 Preparation/Handling/Storage/Accountability

7.3.1 Acquisition and Accountability

The investigational drugs (CBD with Shea butter and Shea butter control) will be stored in a secure area within the UVA Hand Center. Study drug accountability will be maintained by the research team. The investigational drugs will be distributed to the subjects by the study team and are returned to the study team at the next visit. Any remaining investigational drugs will be destroyed in accord with institutional policies.

7.3.2 Formulation, Appearance, Packaging, and Labeling

Hemp Isolate (CBD) will be used from Eco-X, Inc. (2536 Rimrock Avenue, Suite 400 Box 324, Grand Junction, CO 81505). The product is rated for personal care products formulations and the product was tested by Desert Valley Testing.

In the Michael Timko, PhD Laboratory at the University of Virginia, the CBD will be mixed to the final desired concentration with USDA Organic Shae butter (Mary Taylor Naturals, LLC, 2126 Alicia Street, Fort Myers, FL 33901). The control group will receive USDA Organic Shae butter only.

Instructions on how to apply and remove the creams will be provided and explained to subjects. Investigational product will be labeled appropriately for the product to be administered for home use. Minimum labeling requirements include space for subject identification (name or other ID), product name/strength/beyond use date, basic instructions for use, emergency contact information and protocol number. The subjects will be instructed to store the cream at room temperature, and to keep the product out of reach of children.

Notes: This study is using a plant derived cannabinoid (phytocannabinoid) preparations containing CBD. Phytocannabinoid preparations unlike chemically-synthesized cannabinoids, also contain low levels of non-cannabinoid constituents of the Cannabis plant that belong to miscellaneous groups of natural products (primarily terpenoids and flavonoids). The low levels of these adjuvants in the purified material may contribute to the analgesic, as well as the anti-inflammatory effects of Cannabis extracts, but for all intents and purpose are below levels that would be considered therapeutically relevant. Plant derived CBD is identical chemically to endocannabinoids (present endogenously in human or animal tissues) and synthetic CBD. The majority of all CBD containing products on the commercial market are prepared with phytocannabinoid preparations of varied purity.

7.3.3 Product Storage and Stability

The case and control creams are stored by the research team at the UVA Hand Center at room temperature and protected from light. The creams will be used in the study within six (6) months from formulation. After formulation and packaging in the Timko Laboratory, no further preparation such as thawing, diluting, mixing, and/or reconstitution will be required.

7.4 Study Intervention Compliance

Subjects will be instructed to return all tubes containing the control or CBD Cream to the study team at each visit.

7.5 Registration, Randomization and Blinding

Registration will occur following verification of eligibility by the treating physician.

Participants who are consented and accrued to the study should be registered in OnCore in accordance with the Clinical Trial Management System Policy via the UVa OnCore Resources link in Oncore. General guidelines are available in the OnCore User Manual and Data Entry Guide.

Treatment allocation will be discussed with participants during the process of informed consent, and informed consent must be documented prior to randomization. The study participants will be randomized to either the treatment group or placebo group (1:1 ratio) once consent is signed and inclusion/exclusion criteria are satisfied. All investigators and subjects will be blinded. The study coordinator will have the master randomization list.

7.5.1 Emergency Unblinding Procedures

Randomization codes and corresponding treatment assignment will be made available to the Primary Investigator (PI) for emergency use when applicable. If it is not reasonable to inform the PI in advance of unblinding, the study staff must promptly document in the subject's source record and should subsequently contact the PI to explain any premature unblinding of treatment assignment [such as accidental unblinding or unblinding due to a serious adverse event (SAE)]. The PI will document within study correspondence the rationale, circumstances, and the person or persons being informed about the unblinding.

7.6 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

8 STUDY CLOSURE, STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

8.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that would warrant termination or suspension include, but are not limited to

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Change in funding status

Study may resume once concerns about safety, protocol compliance, and data quality are addressed by the IRB, and Food and Drug Administration (FDA).

Participants receiving study treatment at the time of study discontinuation should complete procedures described in section 8.3.

8.2 Participant Discontinuation/Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

A participant's study treatment would be discontinued for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant decision to withdraw from study treatment and/or the study.

The reason for participant discontinuation or withdrawal from study treatment will be recorded. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced. Participants that withdraw from the study (not only from study treatment, but all study follow-up) will not be contacted for any further study visits.

8.3 Procedures for Discontinuation of Study Intervention

Discontinuation from study treatment means that the subject is withdrawn from the study. In the event of study discontinuation, the participant will not be contacted for any further study visits.

8.4 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for one scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 24 hours and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant.
- These contact attempts should be documented in the study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Clinical Assessments

Hand Functional Assessment: Hand functional assessment will include grip, appositional, and oppositional pinch strength (kg); Kapandji score; and MP and IP range of motion. Assessments will be performed at Baseline and study Days 7, 14, 21, and 28.

Patient Reported Outcome Measures: The PROMIS-29 and PROMIS upper extremity tests will be collected. The PROMIS-29 is a free publicly available generic HRQoL measure consisting of indices of pain, pain interference, depression, anxiety, global function, and social interactions (Attachment 1, Appendix 14.4) Subjects will complete the measure at Baseline and study Days 7, 14, 21, and 28. The PROMIS upper extremity test utilizes item-response theory and Computer Adaptive Test to efficiently and precisely report patient symptoms and perceived function. Subjects will complete the measure in clinic using an iPad. The PROMIS upper extremity assessment is provided in Attachment 2 (Appendix 14.4). Subjects will complete the PROMIS assessment at Baseline and study Days 7, 14, 21, and 28.

9.2 Safety Assessments

Medical History: Relevant medical history, including history of mental illness, drug or substance abuse, history of hemp-based product usage and other pertinent history will be recorded in the case report form.

Laboratory Testing: At baseline and Study Day 35, blood draws will be performed on all subjects at the UVA Medical Laboratory. The following tests will be ordered and monitored for clinical abnormalities:

- CBC
- Basic metabolic panel (i.e., BUN, creatinine, CO2, Cl, K, Na, and glucose)
- Hepatic function testing (i.e., serum transaminases [ALT/AST], total bilirubin, and alkaline phosphatase)
- Pregnancy Testing (if applicable) (Screening)
- Urine Pregnancy Test (if applicable) (Screening and Day 0 before dosing)

Daily Skin Monitoring: Subjects will be asked to observe the testing site for physiologic changes, skin changes or other adverse events daily. Subjects will be provided with a daily diary to record and monitor any observed changes. The daily diary is provided in Appendix 14.3. They will be instructed to notify the investigator of any sudden changes in skin appearance or increase in their arthritic symptoms that are more than minimally tolerated.

Physician Skin Monitoring: At baseline and at every subsequent visit, the investigator will assess the CBD cream site for adverse events. A score will be given corresponding to the assessment tool below:

Score	Definition
0	No erythema
1	Minimal erythema
2	Moderate erythema with sharply defined borders
3	Intense erythema with or without edema
4	Intense erythema with edema and blistering/erosion

- NOTE: Changes in skin appearance will be evaluated using the standardized skin assessment tool above. A patient will be removed from study with a score >/= 2.

Clinical Evaluations: Subjects will be monitored weekly for the following:

- Vital sign assessments (i.e., heart rate and blood pressure)
- Suicidal behavior and thoughts as a specific question using the Columbia-Suicide Severity Rating Scale (C-SSRS). The full questionnaire is provided in Attachment 3 (Appendix 14.4).
    - Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on study drug Subjects will be asked if they feel more, less, or no change in their level of fatigue during the time they were administering study drug.

Adverse Event Monitoring: Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study intervention will be recorded.

10 DATA AND SAFETY MONITORING PLAN

10.1 Adverse Events and Serious Adverse Events

10.1.1 Definition of Adverse Events (AE)

An adverse event will be considered any undesirable sign, symptom, medical, or psychological condition even if the event is not considered to be related to the investigational drug/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational drug that adversely affects the rights, safety or welfare of subjects.

10.1.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) is considered a serious adverse reaction (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.1.3 Classification of an Adverse Event

10.1.3.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

10.1.3.2 Relationship to Study Intervention

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other

drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge).

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.1.3.3 Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

10.1.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition (including a laboratory abnormality) that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

10.1.5 Adverse Event Reporting

AEs must be recorded into the case report forms per the following guidelines (Table 1).

Table 1

Type of Event	**To whom will it be reported:**	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance *The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form
Data Breach	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure,

	Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	time the incident is identified. IMMEDIATELY.	https://security.virginia.edu/report-information-security-incident UVa Police-Phone- (434) 924-7166
UVA PI HELD IND			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

10.2 Unanticipated Problems

10.2.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs) (may include a data breach) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical Hypotheses

Outcomes between the two groups will be compared and in a within-subject analysis will be performed given the crossover design. A descriptive analysis of the variables will be performed by calculating mean and standard deviation (SD), as appropriate, and absolute and percentage frequency. Differences between pre- and post-treatment scores (delta scores) will be assessed with the Wilcoxon signed-rank test. Correlations between delta scores and the variables considered [age, gender, body mass index (BMI), radiographic features] will be evaluated with the Spearman, Mann-Whitney, and Kruskal-Wallis tests. The significance threshold will be set at 0.05.

11.2 Sample Size Determination

Based on a 95% confidence interval to show a 50% reduction effect (as shown in the literature) and receive 80% power with a population variance of 0.25, sample size analysis resulted in a sample size of at least 16. The UVA Hand Center performed 421 operative procedures in 2018 for the management of thumb basal joint arthritis among our 6 fellowship trained hand surgeons, and consequently has a volume sufficient to accrue 40 patients during the study period.

11.2.1 Randomization

The study participants will be randomized to either the treatment group or placebo group (1:1 ratio) once consent is signed and inclusion/exclusion criteria are satisfied. Randomization will be not be stratified. All investigators and subjects will be blinded.

11.2.2 Safety Analyses

All adverse events will be recorded and categorized according to severity, relationship to study treatment. Any subject who receives the study drug will be considered Intent to Treat (ITT) for safety assessments. All AEs will be assessed for their relationship to the treatment.

12 REGULATORY AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory and Ethical Considerations

12.1.1 Informed Consent Document and Process

Once a potential subject is identified, they will be interviewed in a quiet and private place and may have family or friends with them if they choose. If there is concern that the potential subject may not be able to read the potential subject will be asked to read the first sentence of the consent form to determine if they are capable of reading. Depending on the response they will either be offered the opportunity to read the consent form or have the consent form read to them. Once the consent has been read the person obtaining consent will summarize the consent form verbally, asking open ended questions to determine if the potential subject understands what is being covered in the consent form. Questions might include:

- Would you summarize for me what you believe will be done to you if you are in this study?
- Would you benefit from this study?
- What do you feel are the risks of being in this study?

Potential subjects will be given an opportunity to ask questions. Their level of understanding will dictate how much time will be spent covering each item. Once all of their questions have been answered, if they decide to participate, they will be asked to sign the consent form. The person obtaining consent will sign the form and subjects will be given a copy of the signed consent form. Study procedures will then begin. The informed consent process for each individual subject will be documented in the subject's medical record.

12.1.2 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. The study protocol, documentation, data, and all other information generated will be held in strict confidence. Consents will be maintained in a confidential manner in accordance with the code of federal regulations and HIPAA. No information concerning the study or the data will be released to any unauthorized third party without prior written approval.

All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, and institutional policies.

12.1.3 Safety Oversight and Monitoring

Any study under the purview of the University of Virginia HSR-IRB is subject to review. Studies are chosen for post-approval monitoring either a) at random or b) requested by a study team member or any member of the IRB-HSR.

The purpose of post-approval monitoring audits is to ensure that documentation of clinical research studies is of the highest quality, verify protocol adherence, and ensure that all Federal and local rules concerning clinical research are being fulfilled. Post-approval monitoring is done by staff within the office of the Vice President for Research

(VPR) in accordance with their Standard Operating Procedures. The conduct of an on-site review may include but is not limited to:

- requests for progress reports from investigators,
- examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
- contacts with research subjects, or
- observation of the consent process and/or research procedures. Examples of when observation of the consent process could occur are:
    - Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
    - IRB is made aware of a complaint or concern with regard to the informed consent process; or
    - IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

12.1.4 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion according to institutional policies.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing and inspection by local and regulatory authorities.

12.2 Data Handling and Record Keeping

12.2.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study records will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Microsoft Excel for data analysis. Clinical data will be entered directly from the source documents.

12.2.2 Study Records Retention

Record retention will be in accord with 21 CFR 312.62 and HIPAA regulations.

An Environmental Assessment is not required because the action requested qualifies for a categorical exclusion per 21 CFR 25.31(e). To the applicant's knowledge, no extraordinary circumstances exist per 21 CFR 25.15(d)

13 REFERENCES

1. Wolf et al. Sick Leave After Surgery for Thumb Carpometacarpal Osteoarthritis: A Population-Based Study. Journal of Hand Surgery. 2018. 43(5):439-447.

2. Gamble et al. Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. Frontiers in Veterinary Science. 2018. 5(165): 1-9.

3. Iffland and Grotenherhermen. An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. Cannabis Cannabdinoid Res. 2017. 2(1): 139-154.

4. Nitecka-Buchta A, Nowak-Wachol A, Wachol K, Walczynska-Dragon K, Olczyk P, Batoryna O, Kempa W, Baron S. Myorelaxant Effect of Transdermal Cannabidiol Application in Patients with TMD: A Randomized, Double-Blind Trial. J Clin Med, 2019 Nov 6, 8(11).2)

5. Xu DH, Cullen BD, Tang M, Fang Y. The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. Curr Pharm BIotechnol. 2019 Dec 1(3)

14 APPENDICES

14.1 Schedule of Activities (SoA)

Visit	Visit 1 (Screening and Baseline)	Visit 2 (Baseline)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Study Day	-7[1]	0	7 (+/- 1)	14 (+/- 1)	21 (+/- 1)	28 (+/- 1)	35 (+/- 1)
Informed Consent	X						
Review study eligibility	X						
Blood Draw[2]	X[3]						X
Urine Pregnancy Test (if applicable)	X	X					
Hand Functional Assessment		X	X	X	X	X	
Patient Reported Outcome Measures		X	X	X	X	X	
Physician Skin Monitoring		X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	X	X	X	X	X	X	X

[1] Screening may take place within one week of baseline visit to allow for results of bloodwork and pregnancy testing.
[2] Blood pregnancy test to be ordered during screening visit only.
[3] Baseline blood testing (Hemoglobin and Platelet count, Creatinine, AST/ALT) will be obtained at the screening blood draw.

Monitor for somnolence and sedation			X	X	X	X	X
Study Medication Dispensed		X		X			
Diary dispensed		X		X			
Diary Review			X	X	X	X	X
Study Medication Collected			X	X	X	X	
Assessment of Adverse Events		X	X	X	X	X	X

14.2 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
02	11/23/19	Addition of PI address and CRC contact information	Protocol clarification
02	11/23/19	Addition of relevant abbreviations	Protocol clarification
02	11/23/19	Clarification and addition of secondary safety endpoints	FDA Clinical Hold response
02	11/23/19	Addition of one-week follow-up visit	FDA Clinical Hold response
02	11/23/19	Corrected literature references	Protocol clarification
02	11/23/19	Duration of subject participation changed to up to seven (7) weeks	FDA Clinical Hold response
02	11/23/19	Clarified study schema	FDA Clinical Hold response
02	11/23/19	Added "There has yet to be a randomized controlled trial demonstrating benefit of topical CBD products in this patient population. The risks involved as detailed above are mitigated by safety monitoring and are outweighed by the ability to add to the current research in Cannabidiol products, which are currently understudied."	Added risk/benefit analysis.
02	11/23/19	Added inclusion/exclusion criteria.	FDA Clinical Hold response
02	11/23/19	Clarified product packaging information.	Protocol clarification
02	11/23/19	Added Physician Skin Monitoring Scale	FDA response
02	11/23/19	Clarified clinical blood labs drawn	FDA Clinical Hold Response
02	11/23/19	Relevant changes made to Schedule of Activities	FDA Clinical Hold Response
03	04/27/20	Addition of relevant abbreviations	Protocol clarification
03	04/27/20	Dosage increase from once to BID	Literature review
03	04/27/20	Added change from baseline to endpoints	Protocol clarification
03	04/27/20	Added additional information and references to Background section	Literature review

03	04/27/20	Removed “oil” throughout	Protocol clarification
03	04/27/20	Additional information provided in **Section 5.2 Justification for Dose**	Information added to support dosage increase
03	04/27/20	Added “Subject is blind” to **Section 6.2 Exclusion Criteria**	Protocol clarification
03	04/27/20	Added medication examples for Exclusion criteria #15.	Protocol clarification
03	04/27/20	Addition of **Section 6.4 Lifestyle Considerations**	Protocol clarification
03	04/27/20	Section 7.2 Dosing and Administration – changed dosing to BID. Investigational product is given in three 10mL syringes.	Information changed to support dosage increase
03	04/27/20	Provided list of attachments	Protocol clarification

14.3 Daily Sin Monitoring Diary

Day X	Time of onset	Time of symptom improvement	Time of symptom resolution
Itching			
Redness			
Red bumps/hives			
Swelling			
Diarrhea			
Nausea			
Change in appetite			
Fatigue			
Other concerning signs/symptoms			

Signature:

_____

14.4 List of Attachments

1. PROMIS-29
2. PROMIS Upper Extremity Assessment
3. Columbia-Suicide Severity Rating Scale