Official Title: *A Clinical Trial of a Hemp-Derived, High-Cannabidiol Product for Anxiety in Glioblastoma Patients*

IRB Protocol Title: *A Randomized, Double-Blind, Clinical Trial of a Hemp-Derived, High Cannabidiol Product for Anxiety in Glioblastoma Patients*

NCT Number: NCT05753007

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A Randomized, Double-blind, Clinical Trial of a Hemp-Derived, High Cannabidiol Product for Anxiety in Glioblastoma Patients

Protocol Number:	V2.7
Version Date:	01AUG2024
Investigational Product:	Industrial hemp-derived ultra-high cannabidiol sublingual solution
IND Number:	160874
Development Phase:	Pilot
Funding Organization:	Sundry Funds/Department
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Approval:

PI or Sponsor Signature (Name and Title)	*Date*

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Sundry Funds/Department with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: V2.7

Protocol Title: An Open-Label Clinical Trial of a Hemp-Derived, High Cannabidiol Product for Anxiety in Glioblastoma Patients

Protocol Date: 01AUG24

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Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

Address _____

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAI	Beck Anxiety Inventory
BUN	blood urea nitrogen
CBD	Cannabidiol
CFR	Code of Federal Regulations
CRF	case report form
CTCAE	Common terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DTI	Diffusion Tensor Imaging
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
MRI	Magnetic Resonance Imaging
OASIS	Overall Anxiety Severity and Impairment Scale
QOL	Quality of Life
PI	Principal Investigator
SAE	serious adverse experience
SOC	Standard of Care
THC	Delta-9-Tetrahydrocannabinol

PROTOCOL SYNOPSIS

TITLE	An Open-Label Clinical Trial of a Hemp-Derived, High Cannabidiol Product for Anxiety in Glioblastoma Patients
FUNDING ORGANIZATION	Sundry Funds/Department
NUMBER OF SITES	1
RATIONALE	The proposed investigation will be the first of its kind to conduct a clinical trial of an industrial hemp-derived product in patients with glioblastoma. Despite the recent interest in Medicinal Cannabis and cannabinoid-based products, the availability of hemp-derived products in all 50 states, and anecdotal evidence suggesting that hemp-derived products may have a profound anxiolytic effect, no studies have conducted a clinical trial of a hemp-derived product in these patients despite their reported levels of anxiety. The recent passage of the Farm Bill of 2018 has resulted in the exclusion of industrial hemp-derived products (THC content <0.3% by weight) from the Controlled Substances Act (CSA). Accordingly, it is now possible to conduct clinical trials using industrial hemp-derived CBD products, which many thousands of consumers have purchased in recent years. As such, we will assess a proprietary hemp-derived full spectrum product formulated by Dr. Gruber; the custom formulation contains approximately 250 mg/ml of CBD and 1.8 mg/ml THC, along with several other cannabinoids. This investigation will provide information regarding the potential efficacy of an industrial hemp-derived CBD product for anxiety in this population, as well as provide information on the potential for a high-CBD product to impact quality of life ratings and tumor progression.
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled study designed to examine the impact of a custom-formulated, high CBD product compared to standard of care plus placebo (SOC) in newly diagnosed glioblastoma patients undergoing chemoradiation therapy.
PRIMARY OBJECTIVE	To assess clinical ratings of anxiety (using BAI and OASIS scales) in individuals with newly diagnosed glioblastoma undergoing chemoradiation therapy pre- and post-CBD treatment compared to those receiving placebo.

SECONDARY **and** **EXPLORATORY OBJECTIVES**	1) To assess pre and post-CBD treatment ratings of pain in BPI, VAS, PDS, PDI scales among newly diagnosed glioblastoma undergoing chemoradiation therapy compared to the SOC group. 2) To assess pre- and post-CBD treatment ratings of quality-of-life in individuals with newly diagnosed glioblastoma undergoing chemoradiation therapy using QLQ-C30 and BN-20 instruments, compared to the SOC group. 1) **Exploratory Objective 1.** To examine pre- and post-CBD treatment measures of tumor progression, quantified using neuroimaging techniques including structural magnetic resonance (MRI) and diffusion tensor imaging (DTI), and perfusion imaging in individuals with newly diagnosed glioblastoma compared to the SOC group. 2) **Exploratory Objective 2.** To examine pre- and post-CBD treatment measures of inflammation using the 12-plex panel that includes: IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IFN-α2, IFN-γ, and TNF-α 3) **Exploratory Objective 3.** To compare time-to-progression, progression free survival, and overall survival rates between the CBD+SOC and SOC groups. 4) **Exploratory Objective 4.** To assess the utilization of the MyStori Mobile app by patients and compare adverse events and symptoms reported in the app to those reported during the in-person patient visit
NUMBER OF SUBJECTS	36 Total subjects: 24 Subjects will be enrolled in the study treatment group (CBD+SOC) 12 subjects will be enrolled in the standard of care plus placebo (SOC) group
SUBJECT SELECTION CRITERIA	**Inclusion Criteria** 1. Male or female ≥ 18 years of age 2. Documentation of newly diagnosed glioblastoma, evidenced by neuropathology report and based on WHO 2021 classification (IDH-mutant glioblastoma grade 4), and who are to undergo SOC (~ 6 weeks of treatment) with radiation and temozolomide (patients using Optune may be included) 3. Written informed consent obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study 4. Fluent in English 5. Scores a minimum of 16 on the Beck Anxiety Inventory (BAI) OR a minimum of 8 on the Overall Anxiety Severity and Impairment Scale (OASIS) at the screening visit. Re-testing is allowed if it is within the stipulated windows (see section 5.1)

6. Stable medication/psychotherapy regimens for at least 1 month prior to starting the study (excluding new glioblastoma treatment-related medications or radiation)
7. KPS of 60 or higher

Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigators would compromise the safety of the patient or the quality of the data.
3. Current substance use disorder, psychotic disorder, bipolar disorder, or eating disorder
4. Current use of recreational cannabis, medical cannabis, or hemp-derived cannabinoid products more frequently than 1x/month; positive urine THC test
5. Presence of a serious or unstable medical illness, including liver, kidney, or cardiovascular disease. The following laboratories will be performed used to confirm normal function of systems within 28 days of day 1 of start study treatment:
    a. Creatinine >1.5 x ULN (Cockroft and Gault)
    b. AST > 3.0 x ULN
    c. ALT > 3.0 ULN
    d. Total bilirubin > 3.0 x ULN
    e. Platelet count outside of normal limits
    f. ANC outside of normal limits
6. Current use of valproate (due to potential for drug-drug interactions)
7. Receiving additional, concurrent, active therapy (including investigational) for glioblastoma other than standard of care.
8. Have received any prior treatment for glioma including but not limited to:

    -Prolifeprospan 20 with carmustine wafer

    -Prior intracerebral, intratumoral, or cerebral spinal fluid (CSF) agent

    -Prior radiation treatment for glioblastoma or lower-grade glioma

    -Prior chemotherapy or immunotherapy for glioblastoma or lower-grade glioma
9. Contraindication to MRI such as non-MR conditional medical devices or ferrous retained foreign bodies.

	10. Additionally, concomitant medications will be assessed on a case-by-case basis with the study physician; a. participants will be excluded if they are taking strong inhibitors or inducers of CYP3A4 (e.g. fluconazole, fluoxetine, fluvoxamine, ticlopidine, St. John's Wort, etc.), CYP2C19 (e.g. ketoconazole, erythromycin, etc.), or CYP2D6 (e.g. paroxetine, buproprion, quinidine, ritonavir, glutethimide, etc.). b. In addition, participants will be excluded if they are taking blood thinners (e.g. warfarin, ticlopidine, rivaroxaban, ticagrelor, apixaban), carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, clobazam, lamotrigine, zonisamide, dexamethasone, dronabinol, or dulcolax. i. It is recognized that patients may require dexamethasone once on clinical trial. If so, they will not be excluded at that point. However, the dose needs to be $\leq$4mg at the start of the trial
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Subjects in both groups will self-administer 1ml of study product sublingually two times daily (BID) for 8 weeks; this corresponds to approximately 250mg of CBD per dose (500mg/day). After an efficacy evaluation after the 9th subject has completed their 8 week trial, will be determine whether dose will escalate to a total of 750mg/day
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 24 months **Screening:** up to 28 days **Treatment:** up to 8 weeks **Follow up:** survival follow-ups (via chart review) will occur at 3 months, 6 months, 12 months, and 24 months post-baseline
CONCOMMITANT MEDICATIONS	Concomitant medications will be assessed on a case-by-case basis with the study physician; participants will be excluded if they are taking strong inhibitors or inducers of CYP3A4 (e.g. fluconazole, fluoxetine, fluvoxamine, ticlopidine, St. John's Wort, etc.), CYP2C19 (e.g. ketoconazole, erythromycin, etc.), or CYP2D6 (e.g. paroxetine, buproprion, quinidine, ritonavir, glutethimide, etc.). In addition, participants will be excluded if they are taking blood thinners (e.g. warfarin, ticlopidine, rivaroxaban, ticagrelor, apixaban), carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, clobazam, lamotrigine, zonisamide, dexamethasone <4mg, dronabinol, or Dulcolax. Dosing schedules may be adjusted in order to offset CBD administration with concomitant medications to decrease the likelihood of any drug-drug interactions. Subjects must have been on stable medication/psychotherapy regimens for at least 1 months prior to starting the study (excluding new glioblastoma treatment-related medications or radiation).

EFFICACY EVALUATIONS	Clinical response will be evaluated after the 9th subject has completed their 8 week trial. If no clinical improvement is observed based on a review of clinical scales, a dose escalation will be considered to a total of 750mg CBD per day (1ml TID). Clinical improvement is defined as a 15% reduction in BAI scores compared to baseline.
PRIMARY ENDPOINT	• Reduction in Anxiety scales (BAI, OASIS)
SECONDARY ENDPOINTS	• Improvement in Quality of life (QLQ-C30 and BN20) scores. • Improvement in Pain (BPI, VAS, PDS, PDI) scales • Quantification of tumor change/progression using structural magnetic resonance (MRI), diffusion tensor imaging (DTI), and perfusion imaging measures
OTHER EVALUATIONS	• Other clinical rating scales will be completed which assess other domains of clinical state (BDI), sleep (PSQI), and treatment expectancy questionnaire • Blood samples will be analyzed to measure cannabinoid levels as well as inflammatory markers. • For research subjects that agree to participate in the optional portion of the study, MyStori App will be used to compare symptoms reported at the time of visit to those logged into the app
SAFETY EVALUATIONS	Adverse events will be continuously monitored for all subjects. Subjects will be evaluated at screening/baseline, 1 week, 2 weeks, 4 weeks, 6 weeks and 8 weeks.
PLANNED INTERIM ANALYSES	We will assess clinical response after the first 9 patients have completed their 8-week trial. If we do not see clinical improvement based on a review of clinical scales, subjective reports and performance, we will consider increasing the dose to a total of 750mg CBD per day (1ml TID). Clinical improvement using scales will be defined as a 15% reduction in BAI scores from baseline. An amendment would be submitted to the IRB for approval prior to adjusting the dose of CBD.
STATISTICS **Primary Analysis Plan**	We plan to enroll (i.e. assigned a treatment by randomization) 36 subjects: 24 subjects will be randomized to the treatment arm. This group will receive high-CBD product along with standard of care (SOC) for chemoradiation (CBD+SOC group); 12 subjects will be assigned to receive SOC plus placebo (SOC group). We will analyze the population with an intention to treat (ITT) approach. The intent-to-treat (ITT) group is defined as all the subjects who have valid measurements at baseline and at least one post-baseline visit for at least one of the assessments while on study. The ITT group will be used for all analyses. ITT subjects will be analyzed according to the treatment to which the subject was randomized.

	Standard demographic variables including age, sex and racial/ethnic origin will be summarized by treatment for all randomized subjects. Descriptive statistics for continuous variables will include the number of subjects (n), mean, median, standard deviation, minimum and maximum. For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.
Rationale for Number of Subjects	Power analyses indicate that, assuming a correlation coefficient of the outcome overtime of 0.5, a sample size of at least 12 individuals per group is required for 2x6 mixed model analyses to detect medium effect sizes (Cohen's f=.35) at power 80% and alpha level 0.05.

1 BACKGROUND

Cannabis sativa has been used medically for a range of disorders for thousands of years, including anxiety. Cannabis is comprised of more than 100 phytocannabinoids; D^9-tetrahydrocannabinol (Δ9-THC) is the major psychoactive constituent of the plant, while cannabidiol (CBD) is a major non-intoxicating constituent often touted for a variety of potential therapeutic benefits. Industrial hemp is a specific variety of the *Cannabis sativa* plant, which until recently was grown for industrial applications, such as textiles. Hemp-based cultivars have much lower concentrations of THC than cannabis cultivars, defined as THC levels of <0.3% by weight. In recent years, some hemp cultivars have been bred to produce particularly high concentrations of CBD with very low concentrations of THC, virtually eliminating the potential for intoxication. Extracts from these hemp cultivars are manufactured into a variety of oils, capsules, sprays, etc., available for legal sale in brick-and-mortar stores across the country as well as on the Internet.

Previous studies have demonstrated CBD's anxiolytic potential in both animals and humans, generally in acute-administration models. Fusar-Poli et al. (2009) demonstrated that 600 mg of CBD reduced anxiety in healthy subjects viewing fearful faces while undergoing functional magnetic resonance imaging (fMRI); the authors concluded that this effect was likely due to modulating the activation of limbic and paralimbic regions. This same group later reported that CBD alters subcortical prefrontal connectivity via the amygdala and anterior cingulate (Fusar-Poli et al. 2010). Additionally, in a model of experimentally induced anxiety in healthy subjects, Zuardi et al. (1993) found that 300mg of CBD attenuated anxiety, as did the anxiolytic drugs diazepam and ipsapirone. To induce anxiety, the authors used the simulated public speaking test (SPST), which involves a subject speaking in front of a video camera for several minutes while physiological correlates of anxiety are measured (including heart rate and blood pressure), and self-report scales are administered to measure subjective anxiety. This model has also been used to induce anxiety in patients with social anxiety disorder (SAD); Bergamaschi et al. (2011) demonstrated that pretreatment with a single dose of CBD results in an anxiolytic effect for SAD patients. This single dose (600mg) was sufficient to reduce subjective anxiety, cognitive impairment, and discomfort in SAD patients completing the SPST, compared to placebo, and reduced anxiety in the CBD-treated patients to a level similar to that of healthy controls. Crippa et al. (2011) confirmed CBD's effects in SAD and further investigated the basis of CBD's anxiolytic effect in SAD patients using neuroimaging. Relative to placebo, a single dose of CBD (400mg) was associated with significantly decreased subjective anxiety scores in SAD patients.

These studies used non-plant-derived or plant-derived single extracted compounds (e.g. CBD isolate), rather than a full or broad spectrum product which may confer greater clinical effect since they contain multiple cannabinoids, terpenoids, and flavonoids; these full or broad spectrum products are more analogous to the products generally used in the 'real world'. Recently, our group began the first ever clinical trial of a high-CBD full-spectrum compound for patients with anxiety. This trial, studied under IND #126898, examines the impact of a custom-formulated high-CBD, low-THC cannabis-derived sublingual solution on measures of anxiety, mood, quality of life, and cognition over a 4-week treatment period in individuals with moderate to severe anxiety. Data from the open-label phase of this study are extremely promising; analyses indicate that patients reported a 79.93% reduction in anxiety symptoms on the primary outcome measure, the Beck Anxiety Inventory (BAI), from the baseline to final visit. Patients also reported a 77.94% reduction in depression symptoms on the Beck Depression Inventory from the baseline to final visit. The study product is well-tolerated, with no serious adverse events occurring to date.

Glioblastoma (GBM) is incurable, and the most common malignant brain tumor among adults, with an estimated 5-year survival rate of >6% (Ostrum et al., 2016). Patients with brain tumors often suffer from comorbid conditions which impact their quality of life, including depression and anxiety (Pringle et al., 1999). Interestingly, patients with lower tumor grade have demonstrated a *higher* risk of neuropsychiatric conditions, specifically anxiety (Arnold et al., 2008). Despite this finding, only a percentage of patients report the use of conventional medication for anxiety or depression which may be the result of a failure to accurately diagnose the condition or inadequate assessment of brain tumor patients at clinical visits (Arnold et al, 2008). In a recent study, Schloss et al. (2021) reported that GBM patients who utilized a single daily dose of a 1:1 THC:CBD product for 12 weeks demonstrated improved sleep and quality of life. Accordingly, alternative treatments for anxiety are indicated.

Interestingly, GBM tumors express both CB1 and CB2 receptors (Ellert-Miklaszewsk et al., 2013), with higher grade tumors expressing greater levels of CB2, suggesting that the endocannabinoid system may be implicated in GBM pathology. Recent preclinical work has demonstrated that exogenous cannabinoids may impact GBM tumor growth. Specifically, CBD has been shown to destroy GBM cells by inducing DNA binding of a modified nuclear factor kappa B (NF-κB) subunit and exhibited the best cytotoxic activity from a panel of non-intoxicating cannabinoids (Volmar et al., 2021). Interestingly, a study of an inhalable 985 mg broad-spectrum CBD product in mice resulted in inhibition of GBM tumor growth by regulating the dynamics of several important tumor signaling pathways (Khodadadi et al., 2021). Other cannabinoids such as cannabigerol (CBG) may also act as anti-tumor agents (Lah et al., 2021). Accordingly, a whole-plant, full-spectrum, high-CBD product containing a range of cannabinoids, terpenoids and other compounds at doses similar to those previously used may confer clinical benefit in this population.

1.1 MyStori App background

Subjects living with brain tumors often experience a wide range of disease and treatment-related symptoms, as noted by Armstrong et al. (2016). Effectively managing these symptoms is crucial throughout the entire disease trajectory, as studies have shown that symptom burden at brain tumor diagnosis can predict important clinical outcomes such as overall survival (OS) and progression-free survival (PFS) (Armstrong et al., 2013).

Recognizing the significance of symptom management across various cancer types, experts in the field and relevant organizations have recommended the inclusion of a standardized set of core symptoms for routine assessment in oncology research and clinical care (Basch et al., 2013). It is worth noting that caregivers of brain tumor patients can also identify symptoms, and previous research has demonstrated a high level of agreement between patient and caregiver assessments regarding severe symptoms. However, discrepancies arise when comparing more subtle symptoms that may indicate patient function (Armstrong et al., 2012).

To address these challenges, the MyStoriTM app was developed specifically for brain tumor patients and their caregivers to facilitate symptom management. Research conducted by Armstrong et al. (2021) has shown that providing caregivers and patients with user-friendly tools to track symptoms can help identify triggers and enhance communication with clinicians, thereby improving the effectiveness of clinical visits. This not only leads to better patient outcomes but also alleviates burden on caregivers and patients.

The purpose of including the MyStori^{TM} app in our study protocol is to compare the number and severity of symptoms recorded within the application by caregivers and patients with those reported during clinic visits (whether conducted remotely or in-person). This comparison will enable investigators and patients to more accurately monitor their symptoms and evaluate the safety of the investigational product. Moreover, it will allow us to assess the feasibility of implementing this application in future research studies to streamline reporting systems and reduce the burden on patients when providing self-reported information.

2 STUDY RATIONALE

The proposed investigation will be the first of its kind to conduct a clinical trial of an industrial hemp-derived product in patients with glioblastoma. Despite the recent interest in Medicinal Cannabis and cannabinoid-based products, the availability of hemp-derived products in all 50 states, and anecdotal evidence suggesting that hemp-derived products may have a profound anxiolytic effect, no studies have conducted a clinical trial of a hemp-derived product in these patients despite their reported levels of anxiety. The recent passage of the Farm Bill of 2018 has resulted in the exclusion of industrial hemp-derived products (THC content <0.3% by weight) from the Controlled Substances Act (CSA). Accordingly, it is now possible to conduct clinical trials using industrial hemp-derived CBD products, which many thousands of consumers have purchased in recent years. As such, we will assess a proprietary hemp-derived full spectrum product formulated by Dr. Gruber; the custom formulation contains approximately 250 mg/ml of CBD and 1.8 mg/ml THC, along with several other cannabinoids. This investigation will provide information regarding the potential efficacy of an industrial hemp-derived CBD product for anxiety in this population, as well as provide information on the potential for a high-CBD product to impact quality of life ratings and tumor progression.

3 RISK / BENEFIT ASSESSMENT

3.1.1 Risks Associated with Clinical Assessment/Rating Scales

Although unlikely, it is possible that during the structured assessment or rating scales, subjects may become distressed when recalling periods of their lives or their current mood state. Subjects are informed that they can take a break and/or can choose to stop answering questions at any time. To mitigate any risks associated with the clinical ratings, clinical staff will be available to evaluate and advise the subject during study visits.

3.1.2 CBD Administration

CBD has been shown to have an extremely low side effect profile and since the total amount of THC will not exceed 0.3% by weight, we do not expect significant side effects or psychoactive effects. CBD is not a scheduled substance, and there is no risk of intoxication or addiction to CBD. As with any clinical trial, there are risks of experiencing side effects from the administration of CBD; these side effects are very rare. Epidiolex, the first and only FDA-approved CBD product developed for pediatric intractable seizure disorders, has dosing recommendations of up to 20 mg/kg/day; this dose has been shown to be reasonably well-tolerated. Cunha et al. (1980) reported no signs of toxicity or serious side effects; in this two-part, placebo-controlled, double-blind study, healthy volunteers

were given 3 mg/kg of CBD or placebo per day for 30 days, and patients with epilepsy were given 200-300mg CBD or placebo per day for 4.5 months. Other studies have reported no adverse effects of CBD in patients with Huntington's disease, schizophrenia, and Parkinson's disease after repeated administration (Consroe et al. 1991; Leweke et al. 2012; Zuardi et al. 2006 and 2009). Some reports of increased liver function tests (LFTs) have been reported following CBD administration; however, a recent industry-based investigation did not find evidence for increased LFTs (Kaufmann et al., 2021). Dr. Gruber has conducted several clinical trials of whole plant, full spectrum high-CBD products, and no serious adverse events have been reported to date. Dr. Gruber has conducted several clinical trials of whole plant, full spectrum high-CBD products, and no serious adverse events have been reported to date. Subjects will have the opportunity to report adverse effects at their check-in visits via direct contact with the PI and study staff. This reporting will reduce the likelihood that subjects experience significant negative side effects for any significant period of time, and the Pis/study physicians will be reachable by page 24 hours a day 7 days a week. In addition, SOC includes a full laboratory panel concurrent with the screening visit, which will be reviewed prior to inclusion in the study; patients taking concomitant anticonvulsants will also complete LFT blood draws at baseline, 4, and 8 weeks.

Sublingual solutions are unlikely to be viewed by the public as analogous to recreational smoked marijuana, thus decreasing the risk of the subject experiencing any potential negative appraisal arising from perceived notions associated with marijuana use while partaking in this study.

The safety of CBD administration in pregnant women and fetuses is unknown. Female participants capable of child-bearing will be asked to provide a sample of urine before the study is begun and at each subsequent study visit in order to screen for pregnancy. If the pregnancy test is positive at any point during the study, the subject will be immediately disqualified and participation in the study will cease. Participation requires that the participant uses contraception methods (such as abstinence, diaphragm, condom, or an intrauterine device) to prevent pregnancy for the duration of the study. The participant will be asked to notify study staff immediately if she misses a period or thinks she might be pregnant. In this case, the participant may have to withdraw from the study.

3.2 Potential Benefits

There may be no direct benefits to the subjects; however, based on previous research, it is reasonable to expect that some subjects may experience an improvement in clinical state or quality of life related to a reduction in anxiety.

It is reasonable to expect that this study will contribute to overall knowledge in this field and potentially provide benefits to society in general through improvements in treatment and management as a result of this increased level of understanding.

Subjects are informed that there may be no direct benefit to them from participating in this study. Subjects may benefit from knowing that the results of this study may improve the future care of people prescribed medicinal marijuana, particularly those with anxiety.

4 STUDY OBJECTIVES

4.1 Primary Objective

1) To assess clinical ratings of anxiety (using BAI and OASIS scales) in individuals with newly diagnosed glioblastoma undergoing chemoradiation therapy pre- and post-CBD treatment compared to those receiving placebo.

4.2 Secondary Objectives

2) To assess pre and post-CBD treatment ratings of pain in BPI, VAS, PDS, PDI scales among newly diagnosed glioblastoma undergoing chemoradiation therapy, compared to the SOC group.

3) To assess pre- and post-CBD treatment ratings of quality-of-life in individuals with newly diagnosed glioblastoma undergoing chemoradiation therapy using QLQ-C30 and BN-20 instruments, compared to the SOC group.

4.3 Exploratory Objectives

5) To examine pre- and post-CBD treatment measures of tumor progression, quantified using neuroimaging techniques including structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and perfusion imaging compared to the SOC group.

6) To examine pre- and post-CBD treatment measures of inflammation using the 12-plex panel that includes: IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IFN-α2, IFN-γ, and TNF-α

7) To compare time-to-progression, progression free survival, and overall survival rates between the CBD+SOC and SOC groups.
8) To assess the utilization of the MyStori Mobile app by patients and compare adverse events and symptoms reported in the app to those reported during the in-person patient visit

5 STUDY OVERVIEW

This study is a single center, randomized, double-blind, placebo-controlled study of an industrial hemp-derived high-cannabidiol product that will include 36 subjects with diagnosis of glioblastoma. Eligible participants will sign an informed consent form that describes all study procedures in detail. After being deemed eligible by the Principal Investigators or designee, subjects will be randomized on a 2:1 ratio. As such, 24 patients will be randomized to receive the high-CBD sublingual study product, and 12 patients will act as a control group, completing the same study measures and will continue to receive SOC as well as placebo. Subjects will complete study visits at the UCSF Neuro oncology Clinic (400 Parnassus Ave, 8th floor, San Francisco, CA) as well as remotely via REDCap. Following a preliminary screening process, and prior to any evaluation, all study subjects will be required to sign an informed consent form that describes all study procedures. The screen includes questions related to medical history, substance use history, demographics, and screening questions from the OASIS (see below) to determine whether the subject has anxiety.

All clinical ratings and questionnaires into their first 6 weeks of radiation/temozolomide. The trial will continue until they are nearing the end of their post-radiation break. See below for study timeline:

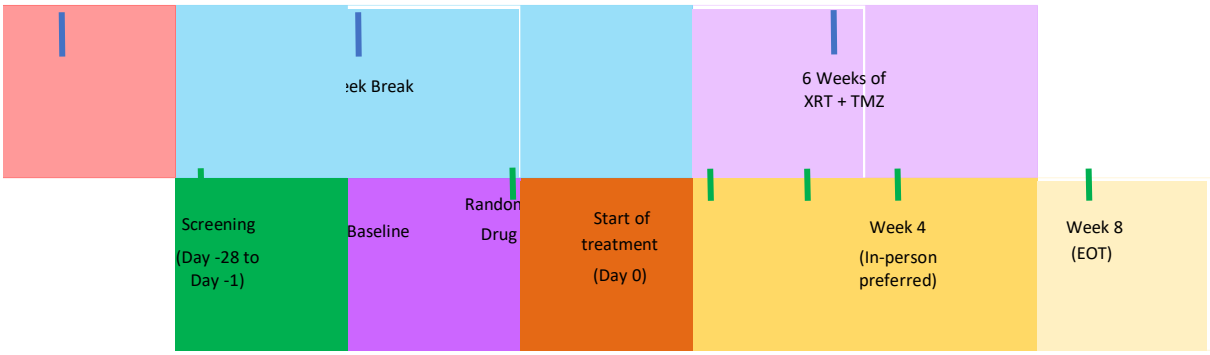


Figure 1. *Study timeline compared to SOC timeline. Note that the Screening and baseline procedures may overlap. Additionally Start of treatment can take place from day 1 to day 14 of chemoradiation treatment*

5.1 Screening (Day -28 to Day -1 to start of study agent, In-person);

Eligible patients from the UCSF neuro-oncology clinic will sign an informed consent form prior to any screening procedure.

The screening procedure includes review of medical history, substance use history, demographics, and review of concomitant medications. A complete physical exam will be performed including vital signs, height, weight, performance and performance status. Additionally, subjects will complete the Beck Anxiety Inventory (BAI) and Overall Anxiety and Impairment Scale (OASIS) instruments. **Subjects must score a minimum of 16 on the BAI or 8 on the OASIS to be considered eligible.** If at the time of screening, potential subjects do not meet the anxiety threshold(s), re-assessment may be done if it is within the screening windows.

Urine samples will be collected at the screening visit to ensure patients are negative for THC. Women of child bearing potential (WOCBP) who enroll in the study will be informed that their sample will also be used to confirm negative pregnancy (HCG) status.

Laboratory tests (see SOE Table 3) will be performed as part of the SOC pre-chemoradiation and collected prior taking any study product(s)

The clinical rating scales to be completed at this time are:

Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Overall Anxiety Severity and Impairment Scale (OASIS), the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and module QLQ-BN20, the Pittsburgh Sleep Quality Index (PSQI), the Brief Pain Inventory (BPI), a Pain Visual Analog Scale (VAS), the Pain Distress Scale (PDS), the Pain Disability Index (PDI), the Medical Cannabis Treatment Expectancy Questionnaire (Tx Exp Questionnaire), and a questionnaire designed to assess previous cannabis/cannabinoid exposure.

All patients will undergo a blood draw to determine levels of circulating endocannabinoids (AEA, 2-AG), which may be a predictor of treatment response, and blood levels of cannabinoids ; patients

who are on concomitant anticonvulsants will also submit a blood sample for liver function tests (see below). Additionally, a urine sample will be collected to measure the presence of Cannabis in urine.

Patients will complete a post-surgery MRI scan as part of their SOC that meets minimum consensus recommendations for a standardized brain tumor imaging protocol as described by Ellingson et al. (2015). Using this imaging, review will be performed by the PI or UCSF neuro-radiologist applying established response assessment criteria, RANO (Wen et al., 2010). The recommended protocol is as follows (though per the PI exceptions can be made due to technical limitations of some MRI scanners and or availability of sequences on certain MRI scanners):

- 2D axial and coronal diffusion weighted imaging (b = 1000)
- 3D axial T1 gradient recalled echo (eg MP-RAGE)
- 3D axial susceptibility weighted imaging (eg SWAN)
- 3D axial arterial spin labelling perfusion
- 2D axial T2 spin echo
- Post-contrast 3D axial T1 gradient recalled echo (eg MP-RAGE)
- Post-contrast 2D coronal T1 spin echo
- Post-contrast sagittal T2 fluid-attenuated inversion recovery (FLAIR)

5.2 Baseline visit *(In-person)*

Following eligibility confirmation by the principal investigators or designee, the patient will perform a baseline visit within 2 weeks (14 days) of having initiated study therapy. The visit may overlap with the screening visit. If these procedures were performed at screening within the time window mentioned before (day -14 to day -1 to start of study agent), they do not need to be repeated unless otherwise directed by the treating physician.

At this time patients will answer the clinical rating scales: BAI, BDI, OASIS, EORTC QLQ-C30 and QLQ-BN20, PSQI, BPI, VAS, PDS, PDI, Side effect symptom questionnaire (SEQ), Treatment Expectancy Questionnaire, and a questionnaire designed to assess previous cannabis/cannabinoid exposure (if this was not administered in the screening visit).

After completing the study assessments, patients will be randomized to receive study product (N=24) or placebo (N=12).

Patients will receive detailed administration instructions along with study drug diaries to document product use over the course of the study; they will be instructed how to draw one full dropper of study product, deposit the amount in the dropper under the tongue, hold for at least two minutes, then swallow.

Only after a subject has been assigned a study ID but prior to any study product administration, blood specimens will be collected to perform (~2 teapoons) to perform endocannabinoid analysis and inflammatory biomarkers (see Appendix 3 and section 10.2 for details on specific markers). Safety laboratories may be repeated if they are > 3 weeks from day 1 of treatment unless otherwise indicated by the investigator. Urine collection does not need to be repeated if a sample was collected within 4 weeks of beginning of treatment unless otherwise indicated by the investigator (see Table 3).

5.3 Treatment period

The treatment period begins at the first day of dosing and for up to 8 weeks (56 days +/-3). Study agent should start within day 1 to day 14 of radiation therapy. All patients will self-administer 1mL of study product (approximately 250mg of CBD) or placebo sublingually two times daily (BID) for 8 weeks.

All patients will complete remote clinical ratings every 2 weeks (14 days +/-3) throughout the study. At each timepoint patients will answer the clinical rating scales: BAI, OASIS, BDI, the EORTC-QLQ-C30 and QLQ-BN20, VAS, PDS, PDI, patient global impression of change scale (PGIC), PSQI, SEQ, the Treatment Expectancy Questionnaire, and a questionnaire designed to assess study drug compliance. To reduce patient burden, only a subset will be required at each timepoint (e.g. at weeks 2 and 6, only the BAI, BDI, VAS, and SEQ will be administered). Refer to Table 3 for details on instruments administered at each timepoint.

All participants will complete a brief remote visit (toxicity check) by phone or video visit after 1 week (7 days +/-3) of the first dose in order to assess potential adverse events, to ensure compliance and to check general mood and quality of life.

The 4 -week (28 days with treatment with study agent, +/-3) visit may take place in person (preferred) or remotely according to the clinic's ability. Additionally, at this timepoint standard of care safety laboratories data will be collected (CBC, liver function tests) from safety laboratories performed per SOC during chemoradiation. These tests can be performed at a local laboratory(see Table 3)

Subjects will receive sufficient study product (placebo or High-CBD product) from the investigational at the beginning of the treatment period and at week 4.

Adverse events will be monitored continuously throughout the study. Subjects will be encouraged to contact the investigator or study team with any questions regarding the study or concerns about side effects. Additionally, for subjects who decide to participate in the optional research activity using MyStori™ mobile application, they will be asked to use the application continuously throughout the study (see details in section 5.5).

5.4 End of Study *(In-person)*

Participants will return for an end-of-study visit after 8 weeks (56 days +/-3)of treatment with the study product. The end-of-study visit will include additional clinical rating scales:

BAI, BDI, OASIS, EORTC QLQ-C30 and QLQ-BN20, PSQI, BPI, VAS, PDS, PDI, SEQ, the PGIC, Treatment Expectancy Questionnaire, and a questionnaire designed to assess medication compliance.

Subjects will undergo a blood draw to assess levels of both circulating endocannabinoids, which may be a predictor of treatment response, and exogenous cannabinoids, in order to ensure study drug compliance and help confirm that no additional cannabinoid products were used during the trial.

A review of their post radiation MRI will take place; this may occur at a separate visit from the final study visit depending on SOC treatment plan. The review of the MRI does not require the participant to take any actions beyond what is established in their SOC treatment plan.

Additionally, safety laboratory tests (will be performed as per Table 3 SOE). Similarly, a blood specimen will be obtained to test for endocannabinoid analysis and inflammatory biomarkers (see appendix 3 for details)

5.5 MySTORI™ mobile application (Optional)

Subjects will be offered to opt-in to use the MySTORI™ mobile application as an optional research activity. The application was developed for brain tumor patients and caregivers by the Neuro-Oncology Branch (NOB) at the National Cancer Institute (NCI). With the objective of tracking and managing symptoms, side effects, organize and manage self-care activities as well as clinical care. Subjects who agree to participate in this section will be instructed on how to use the application either in-person or in remote sessions. Subjects will be asked to use the side effect, symptom logging, and medication intake tracker (at minimum) function of the application. At each visit they will be instructed to generate a report using this function in the application and send it to the investigators. This report can be sent using secure communication channels: secure e-mail, MyChart, or upload directly in to their electronic record on RedCap.

The objective of using this application is to compare asynchronous symptom and adverse event reporting at the time of clinic visit with near real-time reporting.

This mobile application is intended to be used as symptom tracker and journaling for the patients. Given that the mobile application stores data locally in the participant's device, it does not communicate with 3rd parties.

6 CRITERIA FOR EVALUATION

6.1 Primary Endpoint

- The primary endpoint for this study will be the difference between baseline and 8 week clinical rating scores on the BAI and OASIS in the CBD+SOC group compared to the SOC group. Clinical improvement will be defined as greater than or equal to 15% reduction in baseline scores on the BAI.

6.2 Secondary and Exploratory Endpoints

- The secondary endpoints for this study will be improvement on measures of pain and quality of life (BPI, VAS, PDS, PDI, PSQI, EORTC QLQ-C30 and QLQ-BN20, PGIC) after 8 weeks of treatment with CBD compared to patients in the SOC group.
- Additionally, we will describe tumor progression differences between the CBD+SOC and SOC groups by using MRI, including where feasible diffusion tensor imaging (DTI), and perfusion imaging.

6.3 Safety Evaluations

SOC includes a full laboratory panel concurrent with the screening visit, which will be reviewed prior to inclusion in the study – see Table 3 SOE.. If patients present with transaminases $\geq$3 times UNL at screening, laboratory tests may be repeated. Patients may not be enrolled if transaminases are above the stated limit $\leq$24 hours prior to day 1 of treatment. Patients will be discontinued if they have elevated levels (>3x the normal upper limit) while taking the study drug. Additionally, patients

will be tested for kidney function measuring creatinine calculated using the Cockroft and Gault formula (>1.5 x ULN).

Suicidality will be assessed using question #9 of the BDI. Investigators and staff must follow the suicidality SOP will be followed in the event that suicidal ideation is disclosed **(see appendix 1).**

All adverse events will be queried and reported at study visits. Further, all adverse events will be graded using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE V5.0) and relatedness to the study product will be recorded.

For a subset of patients who opt-in, the MySTORI™ app will be used to log-in symptoms, symptom impact on physical functions, track self-care activities, track treatments and clinical appointments. At each clinic visit, participants will be asked to generate the PDF report and share it with researchers. The MySTORI™ app will be used as an additional resource for patients and does not replace appointment systems and symptom reporting established by the neuro-oncology clinic.

7 SUBJECT SELECTION

7.1 Study Population

Subjects with newly diagnosed glioblastoma (IDH-wildtype glioblastoma, grade 4) who meet the inclusion and exclusion criteria will be eligible for participation in this study.

7.2 Inclusion Criteria

1. Male or female ≥ 18 years of age
2. Documentation of newly diagnosed glioblastoma, evidenced by neuropathology report and based on WHO 2021 classification (IDH-mutant glioblastoma grade 4), and who are to undergo SOC (~ 6 weeks of treatment) with radiation and temozolomide (patients using Optune may be included)
3. Written informed consent obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study
4. Fluent in English
5. Scores a minimum of 16 on the Beck Anxiety Inventory (BAI) OR a minimum of 8 on the Overall Anxiety Severity and Impairment Scale (OASIS) at the screening visit. Re-testing is allowed if it is within the stipulated windows (see section 5.1)
6. Stable medication/psychotherapy regimens for at least 1 month prior to starting the study (excluding new glioblastoma treatment-related medications or radiation)
7. KPS of 60 or higher

7.3 Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigators would compromise the safety of the patient or the quality of the data.

3. Current substance use disorder, psychotic disorder, bipolar disorder, or eating disorder
4. Current use of recreational cannabis, medical cannabis, or hemp-derived cannabinoid products more frequently than 1x/month; positive urine THC test
5. Presence of a serious or unstable medical illness, including liver, kidney, or cardiovascular disease. The following laboratories will be performed used to confirm normal function of systems within 28 days of day 1 of start study treatment:
    a. Creatinine >1.5 x ULN (Cockroft and Gault)
    b. AST > 3.0 x ULN
    c. ALT > 3.0 ULN
    d. Total bilirubin > 3.0 x ULN
    e. Platelet count outside of normal limits
    f. ANC outside of normal limits
6. Current use of valproate (due to potential for drug-drug interactions)
7. Receiving additional, concurrent, active investigational drug for glioblastoma other than standard of care. Dietary therapies, like ketogenic etc.do not exclude patients.
8. Have received any prior treatment for glioma including but not limited to:
    a. Prolifeprospan 20 with carmustine wafer
    b. Prior intracerebral, intratumoral, or cerebral spinal fluid (CSF) agent
    c. Prior radiation treatment for glioblastoma or lower-grade glioma
    d. Prior chemotherapy or immunotherapy for glioblastoma or lower-grade glioma
9. Contraindication to MRI such as non-MR conditional medical devices or ferrous retained foreign bodies.
10. Additionally, concomitant medications will be assessed on a case-by-case basis with the study physician;
    a. participants will be excluded if they are taking strong inhibitors or inducers of CYP3A4 (e.g. fluconazole, fluoxetine, fluvoxamine, ticlopidine, St. John's Wort, etc.), CYP2C19 (e.g. ketoconazole, erythromycin, etc.), or CYP2D6 (e.g. paroxetine, buproprion, quinidine, ritonavir, glutethimide, etc.).
    b. In addition, participants will be excluded if they are taking blood thinners (e.g. warfarin, ticlopidine, rivaroxaban, ticagrelor, apixaban), carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, clobazam, lamotrigine, zonisamide, dexamethasone[+], dronabinol, or dulcolax.

[+] It is recognized that patients may require dexamethasone once on clinical trial. If so, they will not be excluded at that point. However, the dose needs to be $\leq$4mg at the start of the trial

Dosing schedules may be adjusted in order to offset CB administration with concomitant medications to decrease the likelihood of any drug-drug interactions. Subjects must have been on stable medication/psychotherapy regimens for at least 1 months prior to starting the study (excluding new glioblastoma treatment-related medications or radiation).

8 CONCURRENT MEDICATIONS

Standard of care for anxiety treatment includes medications, such as antidepressants, buspirone, and benzodiazepines, as well as psychotherapy. This study is an investigation of a plant-derived compound that has promise in the treatment of anxiety. Subjects will not be asked to change their current treatment regimen to participate in this study (i.e. discontinue other medications); this study will add an ultra-high CB custom-formulated study product to their current regimen. Patients will also not be asked to modify their glioblastoma treatment plan in order to participate.

Common Medications in Glioblastoma Patients

*patients on these medications will be excluded (see exclusion criteria 10)

CYP3A4 enzyme-inducing AEDs:

Carbamazepine*

Oxcarbazepine*

Phenytoin*

Fosphenytoin*

Phenobarbital*

Primidone*

Clobazam*

Non-CPYP3A4 enzyme-inducing AEDs:**

Valproic acid*

Lamotrigine*

Zonisamide*

Other concomitant medications commonly used:

Dexamethasone

Dronabinol*

Dulcolax*

Additional Exclusions*

Blood thinners (Warfarin*, Ticlopidine*, Rivaroxaban*, Ticagrelor*, Apixaban*)

Strong inducers or inhibitors of 3A4, 2C19, or 2D6 (https://drug-interactions.medicine.iu.edu/MainTable.aspx)

8.1 Allowed Medications and Treatments

Standard therapy for newly diagnosed glioblastoma is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

Concomitant medications will be allowed and will be assessed on a case-by-case basis with the study physician (see above).

9 STUDY TREATMENTS

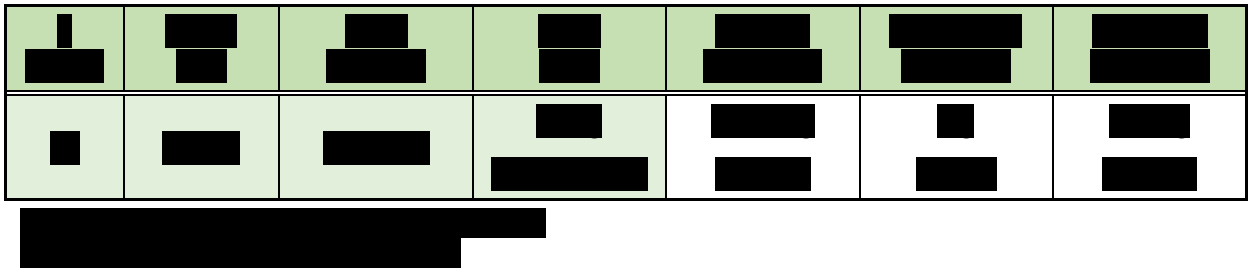
9.1 Method of Assigning Subjects to Treatment Groups

Up to 36 eligible patients will be randomly assigned to high-CB product or standard of care alone groups in a 2:1 ratio. Formulation of Test Product

We will use the staff and expertise of the Marijuana Investigations for Neuroscientific Discovery (MIND) Program at McLean Hospital, directed by co-PI Dr. Staci Gruber, to accomplish randomization as they have successfully done this for FDA-approved clinical trials using similar study products.

The ultra-high CBD study product will contain approximately 250 mg/ml of cannabidiol (CBD), and will be formulated in medium chain triglyceride (MCT) oil. The solution will also include a small amount of THC (approximately 0.6 mg/ml). Participants will self-administer 1 mL of the solution BID.

The based used to formulate the high-CBD study product was derived from a proprietary strain of industrial hemp grown and processed by [redacted]. Ethanol extraction was used to create a distillate, which allows for the retention of some terpenes and flavonoids. The final solution was made by diluting the extract [redacted], and mixing with MCT oil.



9.2 Packaging and Labeling

Packaging: The study product will be bottled into 30-mL glass bottles with calibrated droppers. A tamper-evident heat-shrink band will be used to secure the cap.

Labeling: The bottles will be labeled with the batch ID, contact information for the PI, directions for use, and the statement "Caution: New Drug – Limited by Federal law to investigational use." See below for mock-up of label:

Protocol ID:

PIs: Dr. Butowski, Dr. Gruber

Phone: (415) 353-2966, (617) 855-2762

Directions for use: Deposit 1 dropper under the tongue, hold for approximately 2 minutes, then swallow. Take two times daily: once in AM, and once in PM.

Caution: New Drug – Limited by Federal law to investigational use

Placebo study products will be packaged and labeled in an identical manner to the active study product.

9.3 Supply of Study Drug at the Site

Study Drug will be shipped or delivered by local courier to the investigational sites. The initial study drug shipment will be delivered after approval. Subsequent study drug shipments, if necessary, will be made after request for resupply and it is subject to product availability.

9.3.1 Dosage/Dosage Regimen

Patients will self-administer 1 ml (approximately 250mg/ml for the CBD group) of study product sublingually two times daily (BID).

1.3.2 Dispensing

UCSF Investigational Drug Services (IDS) will manage drug accountability records for UCSF study supply of investigational product(s).

9.3.3 Administration Instructions

Patients will receive detailed administration instructions along with study drug diaries to document product use over the course of the study; they will be instructed how to draw one full dropper of compound, deposit the amount in the dropper under the tongue, hold for at least 2 minutes, then swallow.

9.3.4 Storage

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the Sponsor or designee and captured as a deviation. Subjects will be instructed to store the medication in original packaging at room temperature according to the instructions outlined on the Drug Administration Instructions.

As this product was created from industrial hemp, per the Agricultural Improvement Act of 2018 it is not scheduled under the Controlled Substances Act.

9.4 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug

dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The principal investigators and/or their designee will verify these documents throughout the course of the study.

9.5 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any adverse event. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

For the subset of participants who opt-in to the use of MySTORI™ app, they will be asked to log their study medication intake in the mobile application.

10 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Table 3.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative.

10.1 Clinical Assessments

10.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline and each study visit at weeks 1,2,4,6,8 and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

10.1.2 Demographics

Demographic information (date of birth, gender, race/ethnicity) will be recorded at Screening.

10.1.3 Medical History

Relevant medical history, including history of current disease, and information regarding underlying diseases will be recorded at Screening

10.1.4 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

10.2 Clinical Laboratory Measurements

10.2.1 Pregnancy Test

A urine or serum pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

10.2.2 Urinalysis

Urine will be obtained at screening only for determination of THC

10.2.3 Cannabinoid and endocannabinoid analysis

A blood sample of ~3mL will be collected on a properly labeled K2 EDTA 5.4mg at baseline, prior to start study treatment and at the end of study visit to test for the 12-plex panel that includes: IL-1 beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-19, IL-12, IL-13, IL-17, IFN-γ, TNF-α.

Samples will be processed according to the guidelines stated on Appendix 3.

The samples will be processed for analysis at the Center for Medicinal Cannabis Research (CMCR):

University of California, San Diego
ATTENTION: CMCR Lab
220 Dickinson Street, Suit B
Mail Code8231
San Diego, CA 92103-8231

Whole blood Will be aliquoted into cryovials, barcoded into the labs biorepository system, and stored at -80^{o}C until analysis.

Note: standard laboratory tests for patients under temozolomide treatment will be performed at customary timepoints as per standard of care practice and at the discretion on the treating physician and data will be recorded.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigators will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

Additionally, a subset of subjects who agree to participate will be identified to enroll in the MySTORI^{TM} mobile application to track and log symptoms and adverse events. At each visit, participants will share the report generated by the app with the investigators and will be included in the study record. This tool will not replace the investigator's discussion with the subject for occurrence of AE during each visit.

11.2 AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be

used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

11.3 AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.4 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death

- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.4.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF IRB Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigators will report SAEs to the IRB/IEC.

All serious adverse events are entered into OnCore, as well as submitted to the IRB. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every eight weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore.

If a death occurs during the study and is determined to be possibly, probably, or definitely related either to the study procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair and DSMC Director within one business day.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigators, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

Study Termination Criteria

Patients may withdraw at any time and for any reason, and the PIs may discontinue a patient based on their clinical judgment. In addition, a patient's participation in the trial will end if any of the following criteria are met:

a) Completion of the study
b) Patient reports adverse effects of study product and wishes to leave the study, or if study staff determine that study termination is appropriate based on the development of significant anxiety or paranoia, reports of undesired intoxication, reports of significant changes in heart rate (ie. palpitations, tachycardia) or blood pressure, initiation of contraindicated concomitant medication, or any suicidal ideation; while occurrence of these events is very unlikely, they will be monitored at each visit and the SOP included in appendix 1 will be followed.
c) Patients taking anticonvulsants with elevated transaminases >3x the normal upper limit will be discontinued if they exhibit elevated levels while taking the study drug
d) Patient does not use solution as directed; if a patient endorses taking more study product than directed, the study team will first go through the standard dosing instructions with them again and re-iterate the amount to be taken and how often. If, at the next visit, the patient is still taking significantly more than directed (i.e. >50% increase in daily total dose), they will be terminated from the study
e) Any study exclusions are met (i.e. change in medical status, pregnancy, other cannabinoid use, etc.)
f) Inpatient hospitalization >48hrs or hospice care is initiated

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigators until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigators to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigators, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigators to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 7) should have an early discontinuation visit. Refer to Section 10 for early termination procedures.

12.3 Replacement of Subjects

Subjects who withdraw from the study (both arms) will be replaced.

Subjects who are withdrawn from the study by the investigator will be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigators fail to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

-Enrollment of a subject who failed to meet inclusion/exclusion criteria

-Use of a prohibited concomitant medication without the Principal investigator's approval

-Major deviations from the protocol that pose a safety risk for the subject

When a protocol violation or incident occurs, it will be discussed with the investigators and a Protocol Violation Form detailing the violation will be generated. The HDFCCC DSMC will review the report to ensure that there is a sufficient root cause analysis and a corrective and preventive action plan in place to address the violation or incident. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

14 DATA AND SAFETY MONITORING

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) DSMC will be the monitoring entity for this trial (see DSMC Monitoring Plan in Appendix 2).

15 STATISTICAL METHODS AND CONSIDERATIONS

15.1 Descriptive Statistics

Descriptive statistics will be summarized for all randomized subjects. For continuous variables will include the number of subjects (n), mean, median, standard deviation, minimum and maximum. For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

15.2 Analysis of Primary Endpoints

The primary endpoint of the trial will be **change in anxiety scores measured by the BAI and OASIS** instruments. Instruments will be administered to eligible subjects as per the schedule of events (Table 3). Analysis will be conducted in a hierarchy, first testing the change in scores based only on randomization, then stratified by MGMT methylation status and finally stratified by IDH status. This will be evaluated by applying a mixed effects multivariate regression model with all relevant variables that include but not limited to: age, sex, race/ethnicity and extent of resection.

Clinical response (defined as >15% reduction in BAI scores from baseline) will be evaluated after the 9th subject has completed their 8 week trial. If >15% reduction in average BAI scores has not been achieved, the dosing will increase to three times per day (TID) for a total daily dose of 750mg CBD in the CBD+SOC group.

15.3 Analysis of Secondary Endpoints

Secondary endpoint, **change in quality of life score measured by the EORTC-QOL** will be assessed in the randomized population at baseline, and over the treatment course of the trial. Similar to the primary endpoint, a mixed effects multivariate regression model containing all relevant variables will be used for analysis.

Disease state and response to therapy will be determined using Response Assessment in Neuro-Oncology (RANO) criteria (DOI: 10.1200/JCO.2009.26.3541) based on structural MRI. We will observe PFS at 6 and 12m and OS over 24m.

Additionally, advanced MRI including DTI and perfusion imaging will be obtained at scheduled standard of care MRI timepoints. Qualitative diffusion and perfusion characteristics will be used to support the evaluation of changes in structural MRI that may represent tumor growth (progressive disease) or post-treatment changes ("pseudoprogression") commonly seen in glioblastoma in the period immediately following chemoradiotherapy. Further, quantitative measures of diffusion (mean diffusivity, MD; fractional anisotropy, FA) and perfusion (relative cerebral blood volume, rCBV) will be used to assess changes between control and treatment groups.

Response assessment as well as DTI and perfusion processing and analysis will be performed by the study neuroradiologist, Javier Villanueva-Meyer, and his laboratory.

15.4 Analysis of Exploratory Endpoint

Disease state and response to therapy will be determined using Response Assessment in Neuro-Oncology (RANO) criteria (Wen et al., 2010) based on structural MRI and interpreted by Dr. Butowski with any necessary assistance provided by UCSF Neuroradiology.

Additionally, advanced MR techniques including DTI and perfusion imaging will be obtained at scheduled SOC MRI timepoints. Qualitative diffusion and perfusion characteristics will be used to support the evaluation of changes in structural MRI that may represent tumor growth (progressive disease) or post-treatment changes ("pseudoprogression") commonly seen in GBM in the period immediately following chemoradiotherapy. Further, quantitative measures of diffusion (mean diffusivity [MD], fractional anisotropy [FA]) and perfusion (relative cerebral blood volume [rCBV]) will be used to assess changes between the CBD+SOC and SOC groups.

15.5 Sample Size and Randomization

We plan to enroll (i.e. assigned a treatment by randomization) 36 subjects: 24 subjects will be assigned to receive high-CBD along with SOC for chemoradiation (CBD+SOC) and 12 to receive SOC plus placebo.

Power analyses indicate that for 2x6 mixed model analyses (2 groups with 6 time points each) to detect medium effect sizes (Cohen's f=.35) at power 80% and alpha level 0.05, a minimum of 12 individuals per group is required assuming a correlation coefficient of the outcome over time of 0.5. Given the pilot nature of this investigation, a larger sample size in the active treatment group confers additional statistical power for monitoring safety and efficacy, and is justified given the likelihood of clinical benefit.

Randomization will take place on a 2:1 fashion (CBD+SOC: SOC plus placebo) following the procedure below (figure 2):

After subjects have signed the informed consent form and have been deemed eligible, the investigator or designee will administer the BAI instrument and collect demographic and disease information in the corresponding CRFs. Alternatively, the BAI instrument can be performed on a self-administered fashion by sending the instrument's link to the participant's preferred e-mail.
We will utilize block randomization with covariate-adaptive methods to ensure that the treatment and control groups are matched based on their baseline anxiety level (measured by BAI), age and sex. Each block will be size 3.
For the first three randomization blocks (n=9), the statistician will supply the randomization schedule a priori to the investigational pharmacy.
After the 9th subject has completed the trial, subjects will be randomized matched by age and clinical symptomatology (i.e. based on BAI scores). To perform this, the database will trigger a series of communications with the study team that includes the study statistician. In addition, the investigator or designee will contact the study's statistician (Dr. M. Kathryn Dahlgren) with at least 48 hours before but no more than 120hours (5 calendar days) with de-identified demographic and clinical status information to perform the matched randomization process and assign treatment group, in turn, this will be communicated and coordinated to the investigational pharmacy.

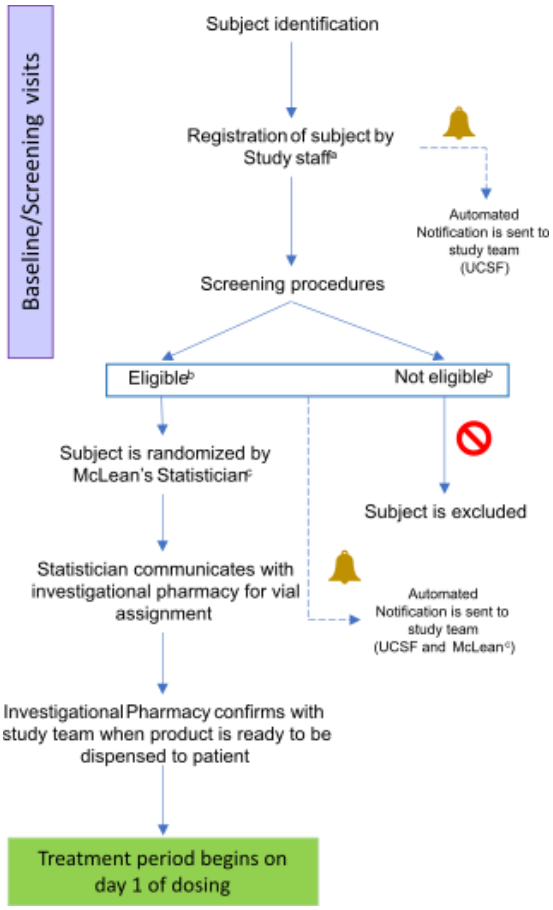


Figure 2. Randomization flow. a. Patients will be registered in Oncore and Redcap. b. Eligibility will be determined by PI or designee and documentation should be included in shadow chart. c. All information sent to study team members from McLean Hospital will be de-identified

15.6 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose (the Safety Population) will be included in the safety analysis.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigators will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Data from participants will be stored in REDCap a secure web-based database. Subjects will be assigned a sequential number following randomization to identify them in the database. Only the research team will have access to such data.

In the event that a survey is e-mailed to the participants the data will be de-identified and the PI, co-PI and/or their designee(s) will have a key to be able to identify the data in case an authority requires so and for data analysis. Given the sensitivity of the information collected on the questionnaires, the patient will be advised that the information shared will be strictly for research and will remain de identified and confidential.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number and initials.

The Investigators are responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigators' site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigators must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

Monitoring visits will be conducted by representatives of the UCSF Hellen Diller Cancer (HDCC) Center according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigators grant permission to the UCSF HDCC (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigators must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigators will keep the IRB/IEC informed as to the progress of the study. The Investigators will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigators before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigators to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.2 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigators will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigators must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigators will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

17.3 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigators agree to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).

3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

TABLE 3. SCHEDULE OF ASSESSMENTS

Study visit	Screening[q]	Baseline[r]	Treatment period				End of Treatment	Follow up
	Day -28 to -1 of study agent	Up to 14 days of start of RT	Treatment Week 1[a]	Treatment Week 2	Treatment Week 4[b]	Treatment Week 6	Treatment Week 8	
Day			**7 (± 3 days)**	**14 (±3days)**	**28 (± 3 days)**	**42 (± 3 days)**	**56(± 14 days)[s]**	**Month 3, 6, 12, 24 post-baseline(+/- 14 days)[t]**
Informed Consent	X							
Medical History	X[p]							
Complete Physical Exam	X						X[o,p]	
Karnofsky Performance Status	X	X						
Abbreviated Physical Exam		X[n]			X (optional)		X[o,p]	
Height	X							
Weight	X	X						
Vital Signs	X	X						
Urine sample[j]	X							
Standard lab tests[k] (data collection)	X	X			X		X	
Research biomarkers[l]		X[l]					X[k,l]	
Pregnancy Test (Urine Or Serum)[c]	X	X[c]	X[c]					
Randomization	X							

Drug Dispensation		X			X			
Drug Administration		X	→ X[s] →					
Subject Diary Review and Drug Accountability [m]			X	X	X	X	X	
Concomitant Medication Review	X	X	X	X	X	X	X	
Adverse Events Evaluation[m]	X		X	X	X	X	X	
Self-administered questionnaires [d]	X[f,i]	X[f,i]	X[e,g]	X[h]	X[e,g]	X[h]	X[e,g]	
Survival Follow up (Via Chart review)								X

a. First dose should occur between day 1 and 14 of radiation therapy.

b. Week 4 visit may be completed in person if the patient or investigators choose to do so. While remote visit is allowed , in-person visit is preferred if feasible.

c. For Women of Child Bearing Potential only. It is mandatory at study entry. Test may be repeated if treating physician deems it appropriate.

d. The instruments: Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Overall Anxiety Severity and Impairment Scale (OASIS), the European Organisation for Research and Treatment of Cancer(EORTC) QLQ-C30 and brain module (BN20), the Pittsburgh Sleep Quality Index (PSQI), the Brief Pain Inventory(BPI), a Pain Visual Analog Scale (VAS), the Pain Distress Scale (PDS), the Pain Disability Index (PDI), the Tx Expectancy questionnaire, Patient's Global Impression of Change scale (PGIC), and a questionnaire designed to assess previous cannabinoid exposure. Instruments will be completed on a self-administered fashion. Patients will be provided with a link to complete measurements online. If patients are unable to answer online, they will be provided with paper versions.

e. Patients will be administered with Side Effects Questionnaire (SEQ) and a questionnaire designed to assess dosing compliance.

f. BAI, BDI, OASIS , QLQ-C30, QLQ-BN20, PSQI, BPI, VAS, PDS, PDI, Treatment Expectancy questionnaire

g. BAI, BDI, OASIS, QLQ-C30, QLQ-BN20, PSQI, BPI, VAS, PDS, PDI, Treatment Expectancy questionnaire, PGIC

h. BAI, BDI, VAS, SEQ

i. Questionnaire to assess previous cannabis/cannabinoid exposure.

j. Screening for THC in urine.

k. CBC, liver function tests and chemistry tests will be completed at customary standard of care timepoints and or at the discretion of the treating provider as needed with data recorded at screening or baseline (before taking study product(s)), approximately week 4 and week 8 with windows as stated in table. If screening labs within 14 days of baseline they do not neeed to be repeated

l. Patients will submit blood samples for endocannabinoid analysis and inflammatory biomarkers (Plex-12 panel) at the beginning of treatment but prior to dosing on day 0 and at the final visit (see section 8.2.3). Research blood will be processed following the guidelines on Appendix 3.

m. As an optional item subjects will be asked to enter symptoms and side effects using the MySTORI^{TM}App on their personal mobile devices. For those subjects who opt-in to use the mobile application, they will be asked to generate the PDF reports and hand them to the investigator at the time of visit.

n. Abbreviated exam may be performed at baseline (but after screening) if the investigator deems it appropriate.

o. End of treatment imaging and safety laboratories will be performed as per customary standard of care practice or at the discretion of the treating provider. The resulting data will be recorded accordingly. Abbreviated physical exam may be used in place of complete physical exam if the investigator deems it appropriate

p. A post-surgical MRI scan will be reviewed as per delineated in section 5.1 (if/when available). This is not a requirement for study enrollment. Similarly, a post-radiation MRI scan will be reviewed on or after end of treatment.

q. If screening procedures are performed when starting radiation therapy (Day 0 +2weeks) the tests can be used as baseline and may be omitted unless otherwise noted by the investigator.

r. This visit may overlap with the screening visit. If the procedures on this visit were performed at screening within the time window, they may be omitted unless otherwise directed by the investigator.

s. Drug administration marks the start of treatment and it will be continuous through day 56. Surveys will be answered at the 56 day (week 8) timepoint ($\pm$ 3 days)t. Follow up period visits will be completed via chart review

I. APPENDICES

Appendix 1. Suicidality policy for subjects with suicidal Ideation

All assessments will be performed electronically or by interview at the clinic. If subjects endorses suicidal ideation or screens positive for suicidal ideation (as per the guidelines below) at an in-person visit the guidelines below should be followed.

If the subject is found positive for suicidal ideation during an electronic, self-administered screener, it will trigger urgent communications (e-mail and notifications) to the Investigators and designated staff. Upon receipt of such communication the Investigator or designee will contact the subject via phone to further evaluate using the Suicidality Assessment and the protocol will continue as delineated below.

The protocol for situations in which subjects report suicidal ideation at screening, during a visit, or on the BDI is as follows:

Screen/Spontaneous Expression of Suicidality During Visit

- If the subject endorses recent or current thoughts about death, assess current risk level following steps outlined in safety planning guidelines, below.

BDI

- If the subject endorses a "0" for suicidal thoughts or wishes (BDI item 9) no further action is required.
- If the subject endorses a "1" for this item, offer information about community resources for psychological treatment saying, "I noticed on your questionnaire you circled items showing you are feeling distressed." (See Community Resources folder for materials.)
- If a subject endorses a "2" or "3" for this item, assess for current suicidal ideation. (See

SUICIDALITY ASSESSMENT; Determine current level of risk and follow safety planning guidelines. (See RISK ASSESSMENT AND SAFETY PLANNING)

GUIDELINES (*jump to the Risk Assessment section.*)

SUICIDALITY ASSESSMENT

What types of thoughts are you having about death? (Describe suicidal ideation)

Do you have a specific plan? *Note:*

- Time
- Place
- Method (specific & detailed or vague?)
- Access to ___(*method*)___?
- Knowledge of how to implement?
- expressed intent to carry out the plan?

Have you ever felt this way before? (Describe any prior attempts, when these occurred, method used, how they survived (did someone find them?), how lethal was the method)

What has helped you keep yourself safe in the past? (Reasons elicited for living -support)

Are you currently in treatment with a therapist, psychologist, social worker, or psychiatrist?

Have you discussed these thoughts/plans with that person? When was your last appointment with this person? When is your next appointment? Can you request an earlier appointment?

(In addition to, or if no therapist) ***Who can you talk to when you are feeling this way?***

Do you have friends or family that you could call or see now? (Check social support situation - likelihood of someone else being around to detect or intervene - and living situation – do they live alone, with roommate(s), spouse, parents, etc. Are people close to them aware of how they are feeling?)

Do you have any plans/appointments for this week? (Check to see how future-oriented they are. Do they have plans and obligations that they are planning on following through with?)

On a scale of 0-10 (0 = negative/depressed, 10 = positive) how would you rate your current mood?

On a scale of 0-10, what is your current intent to kill yourself? (Assess level of risk: i.e. low, moderate, high, imminent). (**FOLLOW STEPS APPROPRIATE TO RISK LEVEL – SEE BELOW)**

I'm concerned about you and want you to be safe. Can you promise me that you will page your therapist/psychiatrist or go to an ER or call a suicide hotline if you don't think you can keep yourself safe? (Ability to contract for safety)

What hospital will you go to? How will you get there? (Get specific details, make sure the person has a taxi # or their friend's/family member's phone number right in front of them)

After completing the "SUICIDALITY ASSESSMENT", go to "RISK ASSESSMENT AND SAFETY PLANNING GUIDELINES"

RISK ASSESSMENT AND SAFETY PLANNING GUIDELINES

Refer to questions in the Suicidality Assessment section of this document to elicit information about the subject's thoughts of suicide. To determine if current suicidal intent is present ask: "On a scale of 0-10, what is your current intent to kill yourself?"

Assess level of risk as follows:

LOW RISK = No past attempt or current intent

- Validate subject's feelings; offer community resources

MODERATE RISK = past attempt, but current suicidal intent ≤ 6

- Subject to articulate own safety plan (i.e. what to do if thoughts/urges increase)
- Provide subject with emergency contact numbers:
  - 911,
  - find # of their own clinician,
  - National suicide prevention lifeline:1-800-273-TALK (8255)
  - San Francisco Suicide Prevention's hotlines: 415-781-0500
- Call Physician on call at the Neuro Oncology clinic: 415-353-2966 or Nursing line: 415-353-2652 to inform them of level of risk and to enlist their assistance in getting subject to a clinician
- Send MyChart message to physician
- Document safety plan and steps taken to decrease risk

HIGH RISK = Current suicidal intent 7-8, but no plan or access to lethal means.

- Subject to articulate own safety plan (i.e. what to do if thoughts/urges increase)
- Encourage subject to immediately contact support(s) and clinician(s) to inform of risk.
- Provide subject with emergency contact numbers:
  - 911,
  - find # of their own clinician,
  - National suicide prevention lifeline:1-800-273-TALK (8255)
  - San Francisco Suicide Prevention's hotlines: 415-781-0500
- Call Physician on call at the Neuro Oncology clinic: 415-353-2966 or Nursing line: 415-353-2652 to inform them of level of risk and to enlist their assistance in getting subject to a clinician
- Document safety plan and steps taken to decrease risk

IMMINENT RISK = Current suicidal intent > 6 and specific plan/access; OR current suicidal intent 9-10, regardless.

- Call Physician on call at the Neuro Oncology clinic: 415-353-2966 or Nursing line: 415-353-2652 to inform them of level of risk and to enlist their assistance in getting subject to a clinician

If in clinic:

- Subject should not be left alone while supports are being contacted.
- If subject refuses to enlist his/her support network, call the physician and inform them of subject's location and risk level.
- Subject can leave the clinic with family member or friend -- someone able to accompany them to their own clinician; or someone from the staff team can accompany them to ER (located on Parnassus avenue 505 Parnassus Avenue) for an emergency evaluation.

If on the phone:

- Subject should not remain at home alone.
- Staff member keeps the subject on the phone while contacting (or enlisting the help of colleagues to contact) clinician/people in support network to inform them of level of risk and enlist their assistance in getting subject to a clinician or psychiatric emergency room.
- If subject refuses to do this: Call 911 and inform of subject's location and risk level.

- Document safety plan and steps taken to decrease risk

Suicide Risk Factors

- Male gender (females more attempts, males more completions)
- Ethnicity (white attempt and complete more than others)
- Age ≥16 years?
- If male, > 65 years?
- Current psychiatric disorder?
    - Current mood disorder (MDD, Bipolar)
    - Current substance use disorder (Is the person under the influence of alcohol or drugs at this moment?)
    - Current psychotic disorder
    - Current personality disorder (esp. Borderline PD or Anti-Social PD)
- Other risk factors
    - Recent loss, separation/divorce/break-up? Other current stressors?
    - Impulsiveness?
    - Hopelessness about the future?
    - Current distress, irritability, agitation or other "abnormal" mental state
    - Depressed mood (On scale 0-10 [0 = neg, 10 = pos] how would you rate your current mood?)

- Suicide history and present ideation/planning
    - Previous suicide attempt?
    - Family history of suicide/attempts/completions?

- Current plan (SSI item 12)?
- Access to lethal means (firearm, drugs, etc.; SSI #13)?
- Current intent (SSI #14 -15; also, "on a scale of 0-10, what is your current intent to kill yourself?)
- Current suicidal ideation? (BDI score of 3 on item 9 and/or a 5 is endorsed on the MASQ suicide item)

Protective Factors:

- In treatment? If so, is clinician aware of risk?
- Family/roommates/friends aware of risk?
- Means restriction (firearms, drugs, family/social support/monitoring)?
- Presence of children in the home, spouse/partner, or other positive relationships?

CRISIS NUMBERS (Also refer to Community Resources folder for a more resources):

- 911
- National Hopeline Network 1-800-SUICIDE (1-800-784-2433)
- National suicide prevention lifeline:1-800-273-TALK (8255)
- San Francisco Suicide Prevention's hotlines: 415-781-0500
- Suicide Prevention in Spanish: 1-800-SUICIDA (784-2432)
- UCSF Parnassus Emergency Department: 415-353-1037

Appendix 2. Data and Safety Monitoring Plan for a Phase II or III Institutional Trial

A.2.1 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Annual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

A.2.2 Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on an annual basis, with all data from 20% percent of the enrolled participants audited by the DSMC Monitor/Auditor.

The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

A.2.3 Review and Oversight Requirements

A.2.3.a Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** –clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

A.2.3.b Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death
- Life-threatening adverse experience*
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above
- Event that changes the risk/benefit ratio of the study.

* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

A.2.3.c Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

A.*2.3.d Data and Safety Monitoring Committee Contacts:*

Katie Kelley, MD (DSMC Chair)
415-353-9888
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Box 3211
UCSF HDFCCC
San Francisco, CA 94158

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Appendix 3. Research blood procedures for collecting plasma for cannabinoid, endocannabinoid and inflammatory component (Plex-12 panel) analysis

Supplies

1. BD Vacutainer Cat # 367856 (Plasma tube,K2 EDTA 5.4 mg,13 x 75,3.0 mL)
2. Nalgene cryogenic vial, 1.2 mL Millipore catalog number V4507.

Procedure:

1. Print barcode labels for specimen ID. Specimen ID should contain: subject identifier (subject name or study ID#), unique specimen ID, draw date and time. Print one label for the primary tube and each aliquot tube.
2. If drawing blood specimen from an indwelling catheter, flush catheter with 20 mL of saline before and after obtaining blood.
3. Draw 3mL of blood through the catheter and discard.
4. Collect 4 to 6 mL of blood into a properly labeled lavender top vacutainer tube.
5. Invert tube gently 8-10 times (rock slowing by hand).Place on ice.
6. Centrifuge at 1800 RCF for 8 minutes within 30 min of collection.
7. Using a nonsterile pipette, aspirate the plasma, which appears as a clear-yellow liquid above the blood tissue layer. Place plasma into cryovial tubes as 1mL aliquots.
8. Place aliquots into box/bag labeled with ID, visit, and visit date and freeze the plasma samples at -80^{o}C until time of analysis.

Shipping:

Whole blood Will be aliquoted into cryovials, barcoded into the labs biorepository system, and stored at -80^{o}C until analysis.
The samples will be processed for analysis at the Center for Medicinal Cannabis Research (CMCR) and site should send samples to the following address:

University of California, San Diego
ATTENTION: CMCR Lab
220 Dickinson Street, Suit B
Mail Code8231
San Diego, CA 92103-8231