UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

A Double-Blind, Cross-Over, Placebo- Controlled Efficacy and Tolerability Study of oral cannabidiol (CBD) and tetrahydrocannabinol (THC) for Essential Tremor (ET)

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

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4. ESTIMATED DURATION OF THE STUDY

24 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Essential tremor (ET) is the most common neurological movement disorder, affecting up to 1% of the population and up to 5% of individuals over the age of 65. ET is characterized by often disabling tremors that occur when an individual moves. The tremors most commonly affect the hands, head, voice, and legs in order of frequency, leading to impairment in activities of daily living and morbidity. No pharmacological agent has been developed for ET, though existing agents such as propranolol and primidone are used off-label to reduce tremor amplitude. Deep brain stimulation surgery is often reserved for only individuals with the most severe tremors. Patients with ET have long reported tremor benefits with the use of cannabis, though no controlled trials have been conducted. We plan to conduct the first double-blind, placebo-control clinical trial of cannabis in an oral capsule. We will use various validated tremor rating methods to quantify tremor severity, while looking at tolerability and safety.

6. SPECIFIC AIMS

The present study seeks to assess the efficacy and tolerability of TILRAY TN-CT120LM (FDA IND#137400), a pharmaceutical-grade formulation containing THC and CBD, vs. placebo in an Essential Tremor patient population. The study is intended to collect pilot data to determine whether larger studies are warranted and assist in their future design.

Aim 1: To determine if short-term exposure to orally administered THC/CBD improves tremor amplitude in ET patients. ***Hypothesis*** 1: ET patients receiving THC/CBD orally will have reduced peak tremor power (compared with their own baseline measures) by accelerometry and spirography vs. placebo.

Aim 2: To determine acute and short-term tolerability of orally administered THC/CBD. ***Hypothesis 2***: ET patients receiving THC/CBD orally will be associated with more frequent ratings of sedation on the Common Toxicity Criteria compared with placebo.

Aim 3: To characterize the relationship between THC/CBD exposure with clinical response (i.e. tremor amplitude) to define a plausibly useful dose range for evaluation in future confirmatory clinical trials.

7. BACKGROUND AND SIGNIFICANCE

7.1 There is a great medical need for a more effective treatment for essential tremor.
Essential tremor (ET) is traditionally defined as bilateral, generally symmetric postural and kinetic tremor of the upper extremities that is not attributable to identifiable causes, and has been present for at least 5 years. A meta-analysis of prevalence studies indicates that 0.4 to 0.9% of the general population has ET. The figure rises

to 4.6 to 6.3% among those 65 years or older (Louis and Ferreira, 2010). ET is a common cause of embarrassment, social withdrawal, disability, and loss of occupation.
The most commonly utilized medications for ET are propranolol, primidone, topiramate, gabapentin, and benzodiazepines. Unfortunately, the long-term efficacy and tolerability of current medications leave much to be desired. If one surveys hundreds of ET patients, it is found that one-third have stopped all ET medications, even those with the most severe tremor. In other words, many of the most disabled ET patients have abandoned the search for a drug that can help them. Over half the patients who try primidone, propranolol, diazepam or topiramate end up stopping them, and the percentage is higher with other anti-ET medications (Louis et al., 2010).

This situation arises from lack of knowledge about the cause of ET, so that clinical trials on medications have been performed on the basis of guess-work or serendipity, with the majority ending with a negative result. The lack of any new positive recommendations by the 2011 Academy of Neurology evidence-based guideline update on the treatment of ET attests to the poor yield of present approaches to drug discovery (Zesiewicz et al., 2011).

The lack of knowledge about the etiology of ET is clearly a barrier to drug discovery. However drug discovery has proceeded for other neurological conditions in which the precise etiology is not clear, such as epilepsy, migraine and multiple sclerosis. We suspect that another barrier to drug discovery for tremor is the under-appreciation by pharmaceuticals of the social, economic, and clinical significance of ET.
Given that half of ET persons aged 65 and over take medication for tremor (Louis et al., 2000), and 2012 demographic data that, among the 1,006.9 million persons living in the European Union, the United States, Japan, Canada, Australia and New Zealand, 163.7 million persons are aged 65 years and over, it can be estimated that 3.8 million persons in this age group in these countries are seeking or receiving medication for ET. If they are willing to pay $4 a day to treat their tremor, the market size would be $5.5 billion per year. Given that persons under age 65 are not included in this calculation, and another 2-3 billion persons in Asia, Latin America, Africa and the Middle East have joined or will soon join the middle class, the market size is likely much greater, at $10-15 billion per year world-wide. Any new ET medication that is highly effective and well tolerated will likely soon dominate a large market.

In addition to neurologists empirically identifying potential treatments for tremor, ET patients themselves have empirically sought remedies. Numerous patients have identified low-dose alcohol as more effective than any prescribed ET medication for tremor suppression. Of particular interest, many ET patients have identified marijuana as more effective and well-tolerated for tremor than any prescribed ET medication, as discussed in the next section.

[redacted]

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7.3 What is the mechanism by which cannabinoids may suppress tremor?
Although the cause of ET is unknown, we do have some knowledge about the neural circuits that may be involved in tremor initiation and expression. It is therefore appropriate to consider these circuits and how cannabinoids may affect them.

ET tremor does not disappear with anesthesia of the limb, or the frequency change with mechanical loading, indicating that it arises from a central generator. Magnetoencephalography during tremor in ET subjects reveals an oscillatory network involving the cerebellum, thalamus, motor cortex, and brainstem (Schnitzler et al., 2009). In ET, PET scans show increased blood flow in the cerebellum even at rest (Boecker et al., 1996). ET patients have many anomalies of cerebellar function, including imbalance, irregular finger tapping, and subtle eye movement abnormalities, some of which improve with successful tremor treatment. The highly effective deep brain stimulation therapy acts by blocking outflow from the cerebellum to the motor thalamus. Transcranial magnetic stimulation of the cerebellum improves tremor (Popa et al., 2013).
Our concept of the circuits involved in excessive cerebellar oscillatory activity underlying action tremor is displayed in Figure 3. A key concept is that these circuits form feedback loops, so that disease processes could occur at one or more of several sites within the loops to unleash and sustain the abnormal oscillations.

Likewise, interventions that dampen the oscillation could be applied at one or more points within these loops, and need not coincide with the site of disease.

In considering the role of various components of the cerebellar system in tremor, we consider a ventral tier, likely involved in oscillation initiation, and a dorsal tier, involved in oscillation amplification.

Inferior olive (IO) PET scans of ET patients have shown increased IO glucose utilization, and increased IO blood flow when patients are given alcohol (Boecker et al., 1996). Eyeblink conditioning, which depends on the olivo-deep cerebellar nuclei (DCN) projection, is impaired in ET patients, but improves after thalamic DBS. The IO is a natural pacemaker, and offers a mechanism for providing rhythmicity to cerebellar oscillatory activity.

Deep cerebellar nuclei (DCN) The excitatory DCN neurons are the sole output neurons of the cerebellum, and in ET tremor an oscillatory loop involves DCN-motor thalamus-motor cortex-IO/pons-cerebellum. It is thus not surprising that strokes that severely damage the DCN, motor thalamus, frontal white matter or internal capsule can eliminate tremor in ET patients (Dupuis et al., 2010). The participation of DCN in tremor is demonstrated by PET imaging in ET and by c-fos imaging in rodents given the tremorigenic drug harmaline. Interestingly, partial lesions of the DCN produce action tremor in patients with head trauma and tremor in rats after chemical DCN lesions. An extensive literature has documented that action tremor ensues after lesions of DCN in monkeys (Gemba et al. 1980). Thus the DCN may be involved in both the initiation and propagation of the oscillations that underlie tremor.

Cerebellar cortex *Pcd* mice that lose all Purkinje neurons still respond to harmaline with tremor, but the tremor is of lower amplitude and frequency compared to wild-type, indicating that Purkinje cells have a role in amplifying tremor. PET scans in ET patients demonstrate increased blood flow in the cerebellar cortex, present at rest, and increased with tremor. This increase is abolished by alcohol (Boecker et all, 1996). In the harmaline model, granule cells express c-fos early. Strokes involving the pons, which interrupt mossy fiber projections to granule cells, abolish tremor in ET (Dupuis et al., 2010). In summary, the components of the cerebellar cortex appear to be important for the amplification of hyperoscillations that underlie action tremor.

How might cannabinoids affect tremor in ET? Endocannabinoids are released by post-synaptic neurons to act retrogradely on pre-synaptic cannabinoid receptors to modulate the release of excitatory and inhibitory neurotransmitters. The CB1R is intensely expressed on the terminals of parallel fibers derived from granule cells that contact Purkinje cells. CB1Rs are also expressed on terminals of basket and stellate interneurons, and on climbing fibers, all projecting to Purkinje cells. The Purkinje cells themselves do not express CB1Rs. Aside from the rubro-olivary projection to inferior olive, there is little CB1R expression in the DCN or inferior olive. CB2Rs are also expressed in the terminals of parallel fibers and basket cells, but are also intensely expressed in the mossy fibers to the granule cell layer, neuropil of DCN, and in spinal cord terminals within the inferior olive (Suarez et al. 2008). Given this strong expression of cannabinoid receptors within all the components of the cerebellar system that have been implicated in tremor initiation and expression, it can be seen that endogenous or exogenous cannabinoids could be expected to influence the hyperoscillations that underlie tremor.

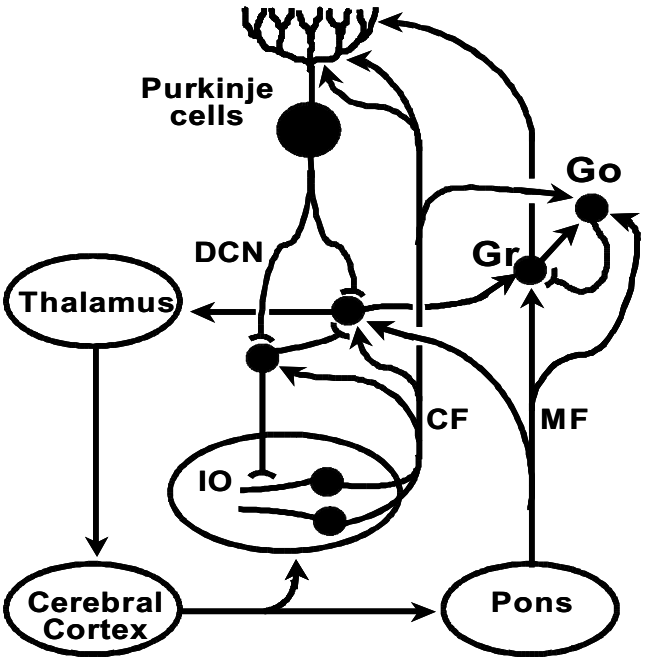
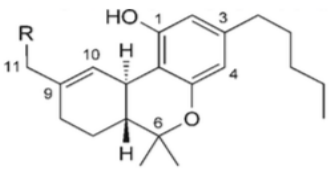
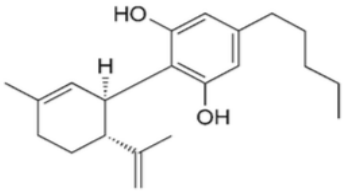


Figure 3. Schematic of neural circuits involved by hyper-oscillatory activity in action tremor. See text for discussion. Arrowheads connote excitation and bar endings connote inhibition. A reciprocal loop involving stellate and Purkinje cells is omitted. CF: Climbing Fibers; DCN: Deep Cerebellar Nuclei; Go: Golgi interneurons; Gr: Granule cells: IO: Inferior Olive; MF: Mossy Fibers



R = H Δ^9-Tetrahydrocannabinol (THC)



Cannabidiol (CBD)

Figure 4. Chemical structures of THC and CBD

An alternative mechanism could be the activation of glycine receptors. Glycine receptors are pentamers made of alpha and beta subunits. There are 4 isoforms of alpha, and one of beta. Δ^9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) (see Figure 4) act as positive allosteric modulators of glycine receptors, including alpha1, alpha2 and alpha3 receptors (Ahrens et al., 2009; Hejazi et al., 2006). It has been suggested, for example, that CBD and related compounds exert analgesic effects against chronic pain via spinal alpha-3 glycine receptors, as these compounds suppress pain in CB1 knockout mice, but not in alpha3 glycine receptor knockout mice (Xiong et al., 2012). In the cerebellum, Purkinje cells and deep cerebellar nucleus neurons strongly express messenger RNA for glycine receptors (Fujita et al., 1991). The deep cerebellar nuclei, from which all cerebellar outlow emanates, including tremor-associated oscillations, are composed of three types of neurons: (1) large, glutamatergic output neurons, (2) GABAergic neurons that project to the inferior olive, and (3) glycinergic or mixed glycinergic/GABAergic interneurons. All three types receive Purkinje afferents. The glycinergic interneurons project to the large DCN output neurons, and thus are positioned to play an important role in cerebellar output (Pedroarena and Kamphausen, 2007).

These glycine receptors, composed of alpha1 and beta subunits, might be allosterically potentiated by cannabinoids, thereby suppressing tremor.

7.4 Objective assessment of efficacy can be performed with a relatively small number of ET subjects
Tremor is reliably elicited during posture and movement in persons with ET, thus permitting assessment of efficacy with relatively few subjects compared to other medical or neurological conditions that are characterized by intermittent events. Cross-over Phase 2 trials for ET that use rating scales typically employ 20 to 60 subjects. Moreover, the use of digital spirography and accelerometry provide greater power at smaller sample sizes, as these measures appear to be more sensitive and reliable than the use of rating scales.
In the ET field, the standard is to include placebo in the first reported trial of a treatment. The reason for this is that in the 1980's and 1990's numerous open-label positive results could not be replicated in controlled trials. Given the paucity of new treatments for ET in the past 10 years, knowledge of a positive result with even a small trial will rapidly become disseminated within the ET community. It may be noted that none of the medications currently prescribed for ET are FDA-approved for that condition. A single positive Phase 2 study can result in a marketed drug gaining access to the $5-15 billion global ET market.

8. PROGRESS REPORT

Based on preliminary date from the first 5 subjects enrolled, we have learned a number of things to date that are being integrated into this protocol amendment:

- The dosing maximum that we have selected was poorly tolerated at 3 capsules administered concurrently, while it was tolerated by some subjects at the 2-capsule dose. We are modifying the protocol to limit the maximum concurrent administration of study drug to 2 capsules QAM and providing the last capsule in the evening.
- The only adverse effect to date took place when a subject did not take the study drug after a meal. This is already specified in both the protocol and consent, and we are simply emphasizing this and providing regular reminds to subjects.
- The frequent monitoring of vital signs, efficacy measures, and adverse effects within the first 3 hours of each study visit are excessive since the onset of effect in all subjects has been 2-3 hours post-dose. We are modifying the protocol to reduce the number of initial assessments and extending the duration of each study visit to 4 hours to allow for an enhanced sensitivity in identifying adverse effects and efficacy.

9. RESEARCH DESIGN AND METHODS

9.1 Rationale for Study Design Selection
The overall goal of this pilot trial is to determine whether TILRAY TN-CT120LM (FDA IND#137400), a pharmaceutical-grade formulation containing THC and CBD, is a viable therapeutic option for the management of ET. The primary endpoints will include safety and efficacy. Since the therapeutic dose of THC/CBD to manage ET is unknown, the study is designed to include a titration of the investigational drug to determine therapeutic doses. The protocol allows for a maximum dose of 15mg of THC and 300mg of CBD.

9.2 Strategies/Procedures for recruitment
Subjects with a diagnosis of ET will be recruited from the UCSD Movement Disorder Center and the general community. There will be an emphasis on obtaining a diverse sample composed of equal numbers of males and females, as well as an equal number of subjects above and below the age of 50.

9.3 Description of Screening and Study Design
SCREENING VISIT
After being screened for inclusion/exclusion criteria and providing informed consent, subjects will undergo a complete neurological examination to confirm their diagnosis of ET and exclude other neurological disorders. Additional measures collected during this visit are listed in Appendix 1. Note that subjects will need to have been on a stable dose of their medications for a minimum of 6 weeks prior to the screening visit and will be

encouraged to remain on these doses for the remainder of the study period. Subjects will be asked about their other tremor medication doses at each follow-up visit to confirm stable doses.

VIDEOTAPED TETRAS
As part of each study visit (1-3), subjects will complete a TETRAS rating scale while being videotaped. This is intended for rating purposes by two blinded raters at the completion of the study.

RANDOMIZATION
After completion of the screening visit, subjects will be assigned to one of two possible treatment arms based on a pre-set randomization matrix. Only the research pharmacy who will be responsible for dispensing the doses will be aware of which of two treatment options will be provided, but not the identity of the particular agent. The equivalence of the THC/CBD and Placebo will be equally matched by the manufacturer, making it difficult for the subject to discriminate which arm they are on. Subjects will be asked which arm they are receiving at each assessment visit and on telephone follow up to assess for potential unblinding.

DOSE TITRATION AND TREATMENT
On visit 1 and 5, subjects will receive 1 capsule of IMP every morning. On visit 2 and/or 6, if the subject tolerated 1 capsule then they would receive 2 capsules every morning. Alternatively, if 1 capsule was not tolerated, the timing of the administration would be changed to 1 capsule in the evening. At visit 3 and/or 7, if the single nightly capsule was not tolerated, the subject would be dropped at this visit. If the 2 capsules every morning were tolerated, the subject would then receive 2 capsules in the morning and 1 capsule in the evening. If 2 capsules in the morning were not tolerated, the subject dosing would be changed to 1 capsule in the morning and 1 capsule nightly. Subjects will remain on the highest tolerable dose for the duration of the period until visit 4 or 8 (See Appendix 2).

The starting dose, titration schedule and target dose were selected based on safety, tolerability and efficacy data reported in previous studies using cannabinoids to treat pain (Langford et al., 2013; Portenoy et al., 2012; Johnson et al., 2010). Adverse effects will be inventoried at each study visit. If the patient or investigator feel that the higher study drug dose is causing troublesome side effects, the dosage may be lowered. Food intake can affect systemic exposure of cannabinoids (Zgair et al. 2016). Subjects will be advised to schedule their dose at a similar time every morning after breakfast to maintain similar systemic exposure throughout the study. Regular reminders will be provided to subjects to ensure they are taking the study drug post-meals. During study visits when drug is administered, subjects will be provided with a standardized FDA high-fat, high-calorie meal prior to taking the study drug.

DOSE TAPER AND WASHOUT
After completing a 2-week course on 15/300 mg/day of THC/CBD or placebo, subjects will return on this dose for assessment and completion of the various measures detailed in Appendix 1. After completion of this visit, subjects will taper from the treatment gradually over 1-week, in similar fashion to the dose titration up to the target dose. Subjects will then complete a 3-week washout period prior to being crossed-over to the alternate arm. This is to allow subjects to return to their baselines. The duration selected is conservative and takes into consideration the known elimination half-life of THC/CBD.

9.4 Assessment Measures
DIGITAL SPIROGRAPHY
This functional measure of kinetic tremor in subjects with ET has been validated by a group at NINDS, including Dr. Nahab. In this technique, the subject is asked to draw a spiral between the loops of a pre-printed spiral with an unsupported hand, proceeding from inside the figure to outside. This measure offers an objective measure of functional tremor, and may enable detection of efficacy with fewer subjects (Haubenberger et al.,

2011). As this methodology is recent, it has not yet found widespread application ET clinical trials. Subjects with severe tremor who have difficulty keeping the inking stylus in contact with the paper are not suited for this test. Based on our experience, we consider this scale to be appropriate as a primary outcome measure.

ACCELEROMETRY
This functional measure of tremor allows objective measurement of postural tremor. During this task, subjects are asked to maintain each arm in an isometric posture with the arm in a 'winged' position in front of the chest. Tri-axial accelerometers are used to collect the tremor frequency and magnitude. Tremor severity is derived from the time domain of a Fourier transformation. This measure allows for standardization across time and 1-minute of data is collected for each limb to minimize variability.

TETRAS
This scale evaluates tremor of various body parts during postures, kinesis and tasks. Items are scored from 0 to 4, with 4 representing the highest degree of severity. The maximum score is 64 (Elble et al., 2012). Although this scale was recently published, it is a refinement of the long-used Fahn-Tolosa-Marin scale. Based on the authorship, this scale has clearly received widespread endorsement from the opinion leaders in the field of essential tremor. To achieve maximum credibility with any result from this clinical trial, it is appropriate to include this scale as a second primary measure. One difficulty with on-site blinded examiners is that they may be prone to placebo effects in their ratings, as they are aware which visit is baseline and which is the treatment visit, although the latter may be with placebo or active drug. To eliminate such order effects, we will videotape the subject undergoing this rating and provide the videos to a minimum of two blinded raters unfamiliar with which visits are baseline and treatment visits.

GLOBAL IMPRESSION OF CHANGE
This is a standardized and commonly used 7-point scale in which both the subject (PGI) and blinded clinician (CGI) rate the degree of change from baseline.

PATIENT REPORTED OUTCOMES OF THE COMMON TERMINOLOGY CRITERIA
All adverse events will be assessed and recorded using the Patient Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) version 1.0. This is a standardized tool for identifying adverse events across all organ systems and includes severity classification.

PHARMACOKINETIC ANALYSES
Established nonlinear mixed-effects modeling methods will be used to evaluate the population pharmacokinetic and pharmacodynamic properties of CBD, THC, and 11-OH-THC. The correlation between plasma concentrations and/or PK parameters with demographic factors (age, sex, body size, race) will be investigated, along with analysis of any relationship between exposure and the resulting efficacy and/or safety response. Different relationships (linear, log-linear, Emax and Sigmoidal Emax) will be explored to correlate exposure with pharmacodynamic metrics (assessment measures of tremor). In addition, as prior studies have shown a hysteresis between THC plasma concentration and drug effect, we anticipate modeling the effect(s) using a hypothetical effect compartment, i.e. $dCe/dt = ke0 \cdot (Cp - Ce)$, where Cp is the plasma concentration, Ce is the concentration in the effect compartment, and ke0 is the a first-order rate constant describing transport into the effect compartment. The final population pharmacokinetic model will be used to perform Monte Carlo simulations to determine the distribution of CBD, THC, and 11-OH-THC at various oral doses.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)
Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al. 2011). The C-SSRS is a standardized suicidal rating system conducted by a certified rater. The interview measures presence of suicidality and consists of four categories: suicide ideation, intensity of ideation, suicidal behavior and answer

for actual attempts only. This scale will be used for screening as well as to assess for the occurrence of any suicidal ideation and/or behavior during the study.

9.5 Subject Monitoring

Subjects will be monitored using PRO-CTCAE. The principal investigator and sponsor will also select a committee of up to 4 qualified individuals to serve on a Data Safety and Monitoring Board. The DSMB will receive regular updates on adverse events and will have access to unblinded data should they decide to explore whether a frequent or serious adverse event is associated with the study drug. Assessment of suicidal ideation and/or behavior will be conducted using the Columbia-Suicide Severity Rating Scale (C-SSRS).

9.6 Outcome Measures

Primary Outcome Measures

The primary outcome measures will be change from baseline of tremor power by digital spirography for drug vs. placebo.

Secondary Outcome Measures

The secondary outcome measures will include the TETRAS, CGI, PRO-CTCAE, plasma concentrations of CBD/THC, Common Toxicity Criteria for adverse effects, and Columbia-Suicide Severity Rating Scale.

9.7 Sample Size Estimation

A power analysis was performed to estimate the minimum number of subjects for enrollment. We assumed the following: Significance ($p<0.01$ or $p<0.05$, corrected), Power=0.80, minimum expected group difference of 15%, and an estimated standard deviation of 10%. Based on these assumptions, we will require a minimum of 14 participants to complete the study. For purposes of this study, 16 subjects will be enrolled and will complete all aspects of this study. To account for drop-outs due to various causes, we plan to have an accrual ceiling of 20 subjects.

9.8 Data Analysis

Data analysis will be performed by a consulting statistician who will also provide guidance in the final experimental design. Each subject will serve as their own control. We will collect baseline tremor severity using the various outcome measures described and will utilized paired-sample t-tests for evaluation of statistical significance between drug and placebo vs. baseline. Descriptive statistics will also be performed in an exploratory fashion.

10. HUMAN SUBJECTS

10.1 Subjects

Description of Study Population

16 patients with Clinically Definite or Clinically Probable ET will complete the study. We will have an accrual ceiling of 20 to allow for dropouts. This will be a single site investigator-initiated trial with all aspects of the study taking place at UCSD. Subject selection will be equitable among adult men and women. We plan to enroll a wide selection of ages (≥21) and ethnicities to enhance our sample diversity and generalizability. Pregnant or lactating females will be excluded due to the unknown teratogenicity of THC/CBD. Any women of childbearing potential will undergo a urine pregnancy test prior to receiving study medication and will be required to use some form of contraception during the course of the trial.

10.2 Inclusion/Exclusion Criteria

Inclusion criteria

- Subjects with ET diagnosed by a Movement Disorder Neurologist aged 21 and older
- Subjects on a stable dose of tremor medication for a period of at least 6 weeks prior to screening
- Subjects with upper limb tremors
- Subjects with a minimum score of 2 on the TETRAS Question 2.4 (amplitude of at least 1-3cm)

Exclusion criteria

- Subjects with significant non-ET related abnormal findings on neurological exam.
- Subjects with a tremor at rest.
- Subjects with a diagnosis of mild cognitive impairment or dementia
- Subjects who are pregnant or nursing, or suspect that they might be
- Women of childbearing potential unable or unwilling to use a form of contraception during course of the trial
- Subjects on medications known to interact with cannabinoid-type agents
- Subjects with a history of alcohol use disorder (based on DSM-5 criteria) or substance abuse.
- Subjects with exposure within the past 21 days to primidone or within the past 7 days to benzodiazepines, ketoconazole, ritonavir, clarithromycin, rifampin, carbamazepine, St. Johns Wort, digoxin or other agents known to be strong inducers or inhibitors of CYP3A, CYP2C19, and CYP2C9.
- Subjects unwilling to abstain from consumption of grapefruits, grapefruit juice or grapefruiting-containing products that are known to strongly inhibit CYP3A4.
- Subjects taking concomitant medications that are highly protein-bound with a narrow therapeutic index (e.g. warfarin, cyclosporine, and amphotericin B).
- Subjects who do not wish to take a cannabis-derived agent
- Subjects who an allergy or sensitivity to sorbitol, xylitol, stevia or other natural sweeteners
- Subjects with an allergy or sensitivity to cannabis.
- Subjects actively using cannabis or a cannabis-derived product (within 4 weeks of screening) or who are unwilling to discontinue its use during the course of the study.
- Subject with a history of significant Axis I psychiatric disorder (e.g., mania, bipolar depressive disorder, schizophrenia, schizoaffective disorder, or other major psychiatric disorder)
- Subject with active or prior history of suicidal ideation and/or behavior.
- Subject with significant coagulopathy, immunologic, gastrointestinal, respiratory, cardiovascular (e.g., uncontrolled hypertension, myocardial infarction in the last 18 months, significant bundle branch block, congestive heart disease), or endocrine (e.g., uncontrolled diabetes, hyperthyroidism) disorder
- Subject with current or chronic infection.
- Subject with renal insufficiency (GFR <60)

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Subjects will be recruited primarily through print and online advertising (advertisement language is also attached for approval) with the assistance of the International Essential Tremor Foundation and the local UCSD Movement Disorders clinic. In addition, we would request a partial waiver of individual authorization for use of Protected Health Information (PHI) by the IRB as this component meets the requirements outlined by the HIPAA Privacy Rule, 45 CFR 164 section 512(I). Specifically, we would request a waiver pertaining to targeted EMR queries of UCSD Epic to identify individuals with Essential Tremor and collecting the following variables: name, contact info, birthdate, diagnosis of essential tremor, presence of parkinson's disease (as an exclusion variable), and use of primidone. Data from the EMR query will be used to inform treating physicians that they may have eligible patients and to assist in making patients aware of the study. We will not contact patients directly without having received prior consent to be contacted.

12. INFORMED CONSENT

Interested patients and their caregivers will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language. If still interested in participating after receiving an explanation of the study, patients and their caregivers will be given an opportunity to review and inquire about the study-specific written informed consent form. Patients and their caregivers will have ample time to think about the information in the written informed consent form and have a chance to discuss it with family members or other people. Any patient and caregiver who has difficulty understanding the information contained in the written informed consent form will be asked to reread the misunderstood portion(s) of the consent and discuss it with a research staff member until s/he shows complete understanding of the information discussed in the informed consent form, and may thus give full consent. Research staff will work closely with patients and their caregivers in an effort to help them understand the requirements of study participation. Patients' and caregivers' questions must be answered fully by trained and qualified staff. Any patient or caregiver who is unable to demonstrate understanding of the information contained in the informed consent form will be excluded from study participation.

Prior to a patient's participation in the study, the written IRB approved informed consent form will be signed and personally dated by the patient) and by the person who conducted the informed consent discussion. In addition, a statement to document the informed consenting process will be recorded in the patient's source documents.

The consent form and any other information provided to patients will be revised whenever important new information becomes available that is relevant to a patient's consent and continued participation in the study. The revised consent form and information will receive IRB approval prior to use. The Investigator, or study coordinator should fully inform all patients of all pertinent aspects of the study and any new information relevant to the patients' willingness to continue participation in the study. This communication with the patient should be documented by the patient signing and personally dating the revised consent form and by written documentation of this discussion with the patient in the Investigator's study files available to Sponsor for onsite review.

Each patient who consents to participate in the study will receive a copy of the signed and dated written informed consent form and any other information provided to patients prior to the participation in the study. The original signed forms will be maintained in the Investigator's study file. After providing and documenting consent on the IRB approved written informed consent form, patients will be assigned their patient screening number and proceed to the Screening Period.

A copy of the informed consent and HIPAA form has been uploaded for review and approval.

The signed informed consent includes the following information:

1. Who is conducting the study
2. Procedures
3. Potential risks and discomforts
4. Benefits
5. Expense to subjects
6. Confidentiality
7. Voluntary participation/withdrawal
8. Emergency and study contact
9. HIPAA discussion

No study procedures will occur including screening until informed consent is obtained. The patient may withdraw his/her consent to participate in the study at any time. A patient is considered as enrolled in the study when he/she has signed the informed consent form. The entire consenting process will take place in a private exam room to ensure the participant's privacy and confidentiality is protected.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to participation in this study is to not participate and continue with any prior clinical care.

14. POTENTIAL RISKS

GENERAL ADVERSE EFFECTS

The risks and discomforts known to occur from the use of cannabis include but may not be limited to the following: coordination difficulties, dizziness, lightheadedness, eye irritation, increased heart rate (rapid heart beat), decreased blood pressure (low pressure of blood within arteries), sedation (sleepiness), feeling high, reversible effects on your appetite, mood, memory (ability or recall) and judgment (capacity to form an opinion). Specific mood changes may include anxiety, paranoia, and unusual, disturbing thoughts. Individual response to cannabis varies widely.

DEPENDENCE

Few Cannabis users develop dependence. With prolonged use, individuals may experience withdrawal symptoms such as irritability, restlessness, mild agitation, cramping, nausea, vomiting, sleep disturbances, and loss of appetite. Based on the dose of CBD and THC in TILRAY TN-CT120LM (FDA IND#137400), we do not anticipate symptoms of dependence or withdrawal, but will monitor for them nonetheless.

SOCIAL

Subjects are also informed that THC and CBD can be found in the body days or weeks after exposure, leading to a theoretical risk of a positive drug test should the subject be seeking employment, or undergoes testing as a part of their employment.

CARDIOVASCULAR

While the use of one of the cannabinoids (THC) found in the investigational drug is a rare trigger of cardiovascular events, there may be a significant increase in the rate of cardiovascular events (e.g. heart attack) for 1 hour following the use of cannabis.

REPRODUCTIVE RISKS

While THC and CBD are not known to cause birth defects, the investigators do not wish to expose the unborn child to any unnecessary medications, so subjects who are pregnant or unwilling to use a contraceptive during the course of the study will be excluded. A urine pregnancy test will be performed and confirmed negative before women of childbearing potential may participate in the study.

BLOOD SAMPLING

Since a blood sample will be collected at required study visits, subjects are informed about the risks of pain, discomfort, redness, bruising, infection and/or irritation at the needle insertion site, and rare risks of fainting, dizziness, and lightheadedness that may occur.

QUESTIONNAIRES AND SCALES

Subjects will need to complete questionnaires and scales during the study visits. These ask about quality of life and ability to carry out certain daily activities. Reviewing health related information might be stressful or make the subject feel uncomfortable.

LOSS OF CONFIDENTIALITY
Every effort will be made to keep all information including the results for substance abuse screening confidential; however there is slight risk of loss of confidentiality that may affect a subject's employability, insurability, ability to adopt and possible criminal/civil liabilities. These risks will be minimized to the extent possible.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Subject safety and tolerability will be monitored in this study across multiple dimensions by tracking clinical adverse events; vital signs (including orthostatic pulse and blood pressure); general and neurological physical examinations; standard clinical laboratory safety panels for complete blood counts, chemistry, coagulation, and urinalysis; standard 12-lead electrocardiograms; the Patient Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and Columbia Suicide Severity Rating Scale (C-SSRS). Subjects answering "yes" to Suicidal Ideation item 4 or 5 on the C-SSRS during the study must be withdrawn from the study treatment. The PI will also withdraw subjects from treatment if, in the judgment of the Investigator, the subject develops other indicators of significant risk of suicide. In the event that suicidal ideation is observed in any study subject, the PI will manage the situation as he/she deems medically and psychiatrically appropriate. Further, In the event that a subject reports suicidal ideation, the subject will be withdrawn from the study and personally escorted by a study team member to the UCSD Emergency department for urgent psychiatric evaluation and management. In the event that we are made aware of such suicidal ideation by telephone outside of routine study visits, subjects will be referred to a local ED for evaluation and we will conduct a telephone follow up to ensure the subject followed through with these recommendations.

The specified inclusion/exclusion criteria have been carefully considered to avoid enrollment of subjects for whom exposure to the study drug might pose a hazard, particularly as it relates to individuals with a history of substance abuse.

In order to provide independent oversight over patient safety, the PI will select of committee of up to 4 qualified individuals to serve on a Data Safety and Monitoring Board (DSMB). The DSMB will receive regular updates (minimum of quarterly) on adverse events and will have access to unblinded data should they decide to explore whether a frequent or serious adverse event is associated with the study drug. All serious adverse events (SAEs) meeting criteria for expedited reporting to the US FDA will be reported to the FDA, IRB, and DSMB in accordance with regulatory timelines. In the case of a fatal or life-threatening event, we will notify the FDA by telephone within 3 working days and stop further enrollment until the serious adverse event can be reviewed by the DSMB. In addition, any event that is unexpected will be reported to the FDA and IRB within 7 working days.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Subjects will be given a Health Insurance Portability and Accountability Act (HIPPA) authorization form to sign. This separate consent will authorize the Investigator(s) and his/her/their staff to access medical records and associated information as may be necessary for purposes of this study. The Investigator and his/her collaborators, staff will consider your records confidential to the extent permitted by law. The Sponsor, Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) may review these research records. Records may also be reviewed for audit purposes by authorized UCSD employees or other agents who will be bound by the same provisions of confidentiality.

All study-related data will be maintained securely on UCSD computers based on UCSD Information Security policies outlined by the UCSD Administrative Computing and Telecommunications department (ACT). Subjects will receive a study identification number that will only be available to the principal investigator. All other study databases will only include this anonymous study ID number. This anonymous study data may be

maintained indefinitely. Authorized access will only be granted to study investigators or as otherwise defined by university policy. The study site personnel may use this information to notify subjects of appointments, send appointment reminders, or schedule additional appointments.

17. POTENTIAL BENEFITS

Subjects may or may not directly benefit from participating in this study. However, participation may be beneficial to others by providing information that is useful to our understanding of the study drug and its use in ET. The study drug may or may not have any effect on ET.

18. RISK/BENEFIT RATIO

This research represents a more than minimal risk. While there is the limited prospect of direct benefit to individual subjects who could experience a reduction in their tremors, it is more likely to yield generalizable knowledge. All aspects of this research have been designed to limit risk to the extent possible and provides a favorable risk:benefit ratio.

19. EXPENSE TO PARTICIPANT

There will be no cost to subjects to be in this study. Study drug will be provided to subjects free of charge. The study visits, interviews, and examinations during participation will be provided at no cost to subjects. Participants will not be required to pay for parking. Parking permits will be provided by study staff if necessary. The only expense to the participant will be transportation to UCSD.

20. COMPENSATION FOR PARTICIPATION

Subjects will not receive remuneration for participating in this study.

[redacted]

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23. FUNDING SUPPORT FOR THIS STUDY

Funding is provided by a grant from the International Essential Tremor Foundation. A contract between Tilray and UCSD will provide study drug and funding for the PK portion of this study.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

See attached FDA IND 137400 Permission to Proceed Letter and Investigator's Brochure.

26. IMPACT ON STAFF

This study will utilize existing resources to conduct this study, including the services of the ACTRI clinic.

27. CONFLICT OF INTEREST

The principal investigator and research have report no conflicts of interest with regard to this study.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

N/A

29. OTHER APPROVALS/REGULATED MATERIALS

N/A

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

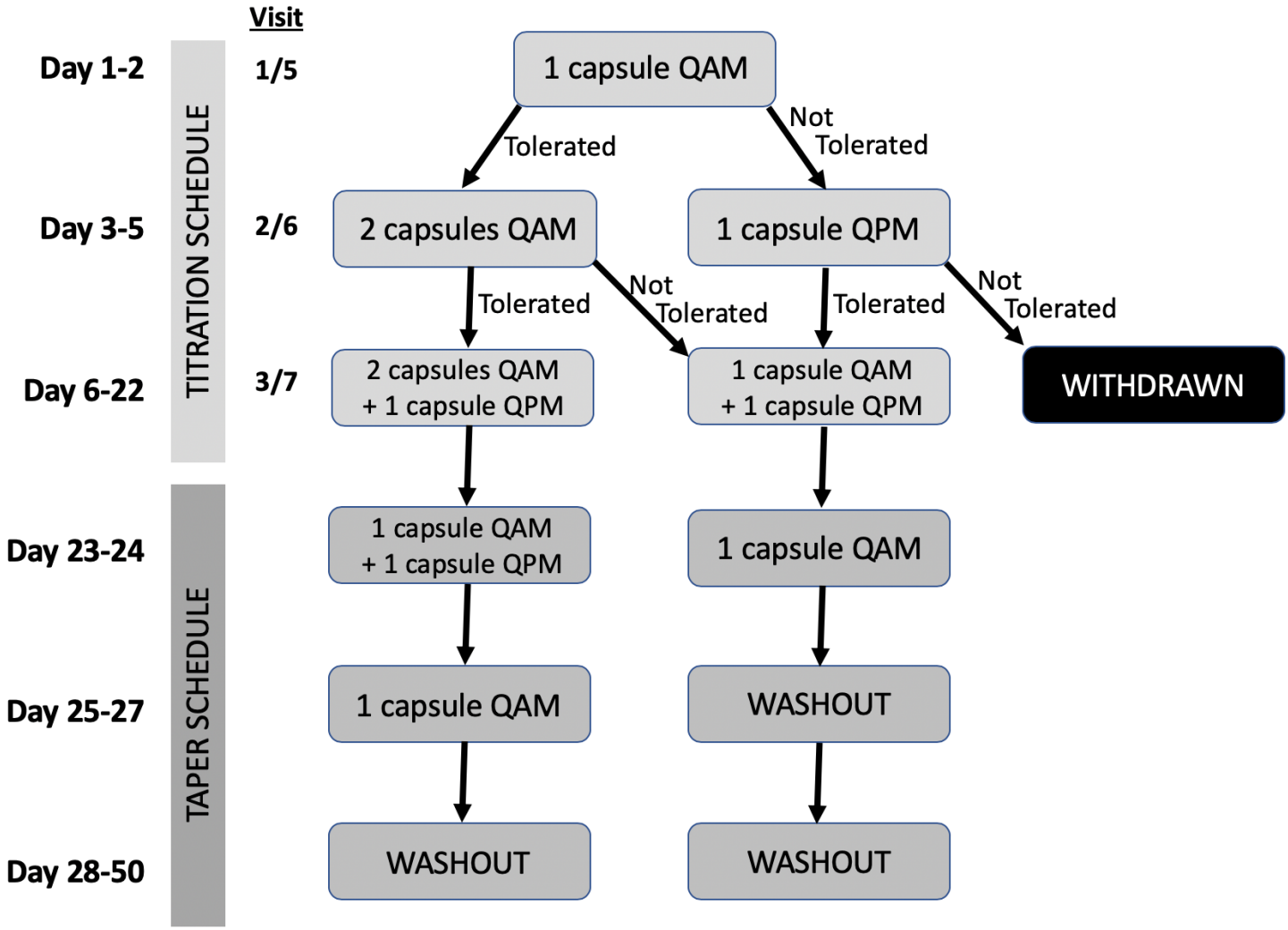
N/A

APPENDIX 1: STUDY OVERVIEW

EVENT	VISIT 0: SCREENING	VISIT 1: DOSE TITRATION	VISIT 2: PK	VISIT 3: PK	TREATMENT PHASE	VISIT 4: ASSESSMENT	TAPER	WASHOUT	VISIT 5: DOSE TITRATION	VISIT 6: PK	VISIT 7: PK	TREATMENT PHASE	VISIT 8: ASSESSMENT	TAPER	TELEPHONE FOLLOW-UP	TOTAL DAYS
TOTAL DAYS	**0**	**5**		**1**	**16**	**1**	**5**	**22**	**5**		**1**	**16**	**1**	**5**	**1**	**77**
DAY NUMBER (±3)	**0**	**1**	**3**	**6**		**22**	**23**	**28**	**50**	**52**	**55**		**71**	**72**	**77**	
Consent	X															
Neurological Exam	X					X							X			
Vital Signs	X	X	X	X		X			X	X	X		X			
TETRAS (video)	X					X							X			
Spirography	X					X							X			
Accelerometry	X					X							X			
CGI/PGI						X							X			
PRO-CTCAE	X	X	X	X		X			X	X	X		X		X	
C-SSRS	X					X							X		X	
Lab Testing - pregnancy, CBC, CMP, Drug screen	X					X							X			
EKG*	X	X	X	X		X			X	X	X		X			
PK Sample(s)			X	X		X				X	X		X			

***** EKG at screening, then post-dose at each subsequent visit.

9.16.2 APPENDIX 2: DOSE TITRATION AND TREATMENT PLAN (THC/CBD*** or PLACEBO)



***Note: THC/CBD formulation will consist of 5mg of THC and 100mg of CBD per capsule.

9.16.3 APPENDIX 3: PHARMACOKINETIC SAMPLING TIMES**

DAY #	TIME
3	Trough
6	Trough
22	Trough + Pseudorandom (1,2,3, or 4 hrs/post-dose) sample

**NOTE: Samples will be collected for drug and placebo to maintain blinding, but PK lab will be unblinded in order to process only drug samples. If subject receive placebo first, PK days will be: #52, 55, and 71.