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CLINICAL STUDY PROTOCOL

Study Title:	Le Rêve 3.0: A Double-Blind, Placebo-Controlled, Randomized, Crossover Investigational Study to Determine if Defined CBD, a Capsule with a Custom Formulation of Cannabidiol (CBD) and Terpenes, Influences Sleep Physiology
Sponsor:	Defined Research Institute 1250 Missouri Street Unit #312 San Francisco, CA 94107
IND Number: ClinicalTrials.gov	N/A NCT05233761
Indication:	Sleep physiology
Protocol ID:	Sleep physiology

Protocol Number: DR-INS-101

National Clinical Trial (NCT) Identified Number: TBD

Principal Investigator: Dr. Paul Muchowski

Sponsor: Defined Research

Funded by: Defined Research

Version Number: v.2

31 January 2022

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

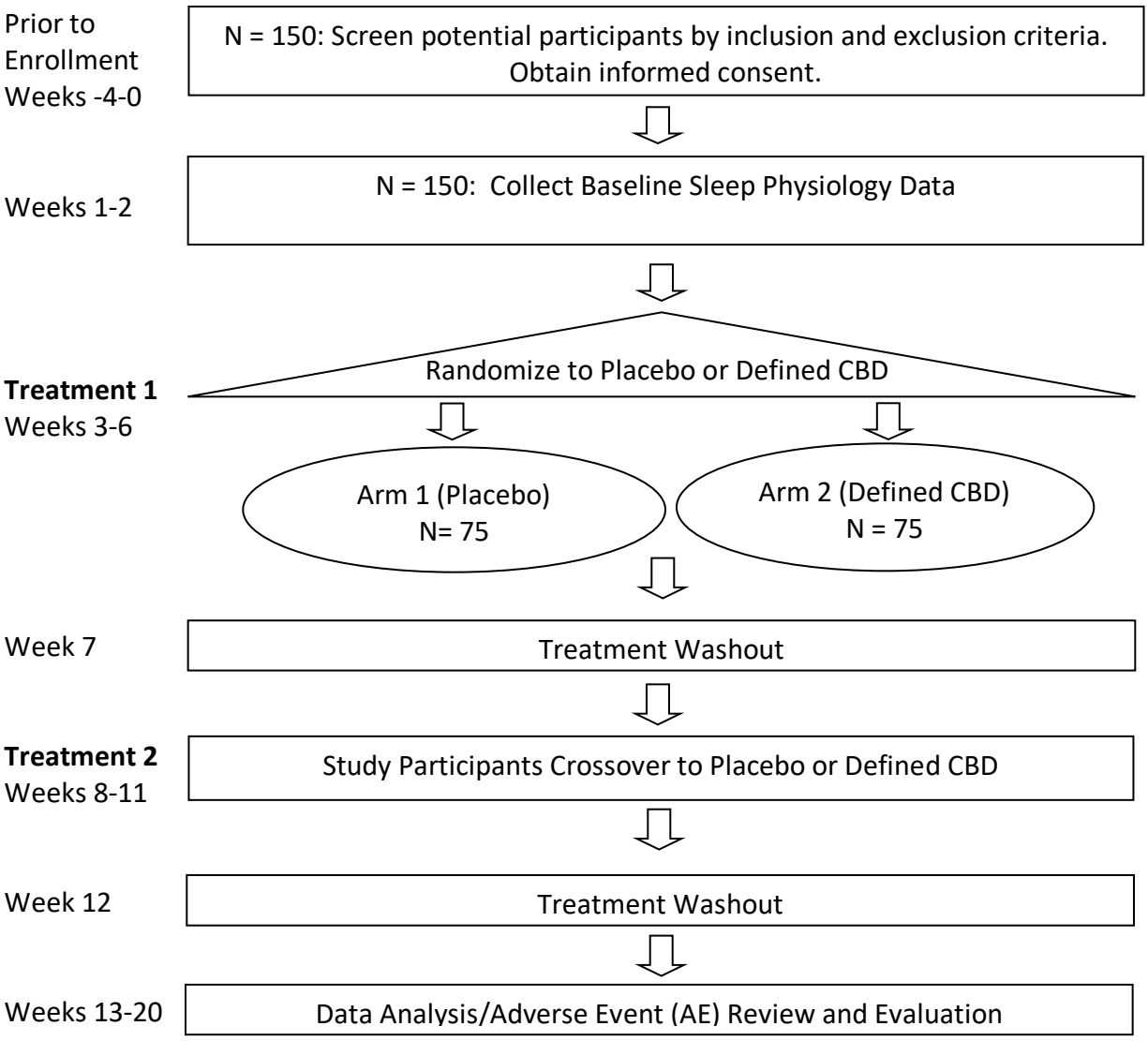
1 PROTOCOL SUMMARY

1.1 PROTOCOL SYNOPSIS

Study Title:	Le Rêve 3.0: A Double-Blind, Placebo-Controlled, Randomized, Crossover Investigational Study to Determine if Defined CBD, a Custom-Formulated Cannabidiol (CBD) Capsule, Influences Sleep Physiology.
Study Description:	Insomnia is a disorder in which people have inadequate or poor-quality sleep due to a number of factors, such as difficulty falling asleep, waking up frequently during the night with difficulty returning to sleep, waking up too early in the morning, or having unrefreshing sleep. Defined CBD is a capsule composed of highly purified (>99.9% purity) hemp-derived CBD and terpenes (>98% purity). Defined CBD contains no Δ-9-tetrahydrocannabinol (Δ-9-THC). Our research study, entitled Le Rêve 3.0, is designed to evaluate the efficacy of Defined CBD on sleep physiology. This trial is not intended to treat, diagnose, prevent, or cure any disease.
Objectives:	Primary Objectives: To determine if Defined CBD influences objective measures of sleep physiology. Secondary Objectives: To determine if Defined CBD influences subjective measures of sleep physiology.
Endpoints:	Primary Endpoint: The percentage of sleep spent in deep [slow wave sleep (SWS)] and rapid eye movement (REM) sleep as determined using an objective wrist-worn sleep-tracking device called Whoop. Secondary Endpoints: Total sleep time, sleep latency, the number of sleep disturbances, time spent in each sleep stage, percentage of time spent in each sleep stage, and subjective measures of sleep physiology as collected via participant surveys.

Study Population:	We will enroll 150 study participants who display chronic insomnia defined as a self-reported difficulty initiating (latency to persistent sleep >30 min) and/or maintaining sleep (>30 min awake, or waking >30 min before desired waking time) on three or more nights per week for at least 3 months. Participants will also complete a brief clinically validated insomnia severity index, and only participants with an Insomnia Severity Index score >15 will be enrolled in Le Rêve 3.0. We will enroll males or females aged 25–70 years that are located in the United States that meet inclusion and exclusion criteria.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Le Rêve 3.0 will be a decentralized study completed by participants in the comfort of their own homes. Recruitment, enrollment, informed consent, and distribution of study materials to participants will all be managed by the contract research organization (CRO) 83 Bar, Inc.
Description of Study Interventions:	Study interventions will include Defined CBD or a placebo control that will be taken orally (p.o.) as two small capsules one hour prior to going to bed. Defined CBD is a capsule made to GMP standards composed of vegetable cellulose (gluten-free, non-GMO, vegan, certified kosher, certified halal) that contains 300 mg >99.9% purity hemp-derived CBD made in a GMP-certified laboratory that is dissolved in coconut oil (USDA certified organic, non-GMO, dairy-free, gluten-free, vegan coconut oil). Defined CBD is a custom chemical formulation that also contains low concentrations (1 mg each) of highly purified (>98% purity) forms of the terpenes linalool, myrcene, phytol, limonene, α-terpinene, α -terpineol, α-pinene, and β-caryophyllene [Food Grade (GRAS), Natural, Organic, non-GMO, dairy-free, gluten-free, vegan) made in GMP-certified laboratories. Defined CBD contains no Δ-9-tetrahydrocannabinol (Δ-9-THC). The safety of CBD[1] and these terpenes[2] at the doses found in Defined CBD is well established.
Study Duration:	The estimated time from when Le Rêve 3.0 opens enrollment until completion of data analyses will be 20 weeks.
Participant Duration:	After enrollment, the participant duration for the entire study will be 12 weeks.

1.2 SCHEMA


Prior to Enrollment Weeks -4-0
N = 150: Screen potential participants by inclusion and exclusion criteria. Obtain informed consent.
Weeks 1-2
N = 150: Collect Baseline Sleep Physiology Data
Treatment 1 Weeks 3-6
Randomize to Placebo or Defined CBD
Arm 1 (Placebo) N= 75
Arm 2 (Defined CBD) N = 75
Week 7
Treatment Washout
Treatment 2 Weeks 8-11
Study Participants Crossover to Placebo or Defined CBD
Week 12
Treatment Washout
Weeks 13-20
Data Analysis/Adverse Event (AE) Review and Evaluation

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Weeks -4 to -1	Enrollment Day 1	Collect Baseline Data Weeks 1-2	Treatment 1 Weeks 3-6	Treatment Washout Week 7	Treatment 2 Weeks 8-11	Treatment Washout Week 12	Post-Treatment Weeks 13-20
Informed consent	X							
Medical history	X							
Randomization				X				
Administer study intervention				X		X		
Adverse event review and evaluation								X

2 INTRODUCTION

2.1 STUDY RATIONALE

Insomnia is a disorder in which people have inadequate or poor-quality sleep due to a number of factors, such as difficulty falling asleep, waking up frequently during the night with difficulty returning to sleep, waking up too early in the morning, or having unrefreshing sleep. The majority of over-the-counter (OTC) supplements used to treat insomnia (e.g. melatonin, valerian root, lavender) have limited efficacy, while the best-selling prescription drugs for insomnia (e.g. Ambien, Halcion, Sonata, Lunesta) have serious and undesirable side effect profiles that limit their utility. There is a strong scientific rationale to support the hypothesis that CBD might positively impact sleep physiology, and our study, entitled Le Rêve 3.0, is designed to fill that void in knowledge.

2.2 BACKGROUND

A survey of 1,267 adults by Consumer Reports indicates that nearly 80% of Americans have trouble sleeping at least once a week. Insomnia is the most common sleep disorder and is an established risk factor for anxiety, depression and other diseases. Insomnia is defined clinically as the perception or complaint of inadequate or poor-quality sleep due to a number of factors, such as difficulty falling asleep, waking up frequently during the night with difficulty returning to sleep, waking up too early in the morning, or having unrefreshing sleep. Insomnia causes significant distress and/or impairment in daytime functioning in people who suffer from it. The prevalence rates of clinically diagnosed insomnia have increased in recent years to ~19% of the adult U.S. population, representing ~46 million. Some studies suggest that the rate of undiagnosed insomnia in the US may be as high as 25% (~80 million)[3].

CBD is the active ingredient of Epidiolex®, a drug approved by the FDA in 2018 for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS). In 2018, the U.S. congress passed the Hemp Farming Act of 2018 (the Farm Bill), which removed remove hemp (defined as cannabis with less than 0.3% THC) from Schedule I controlled substances, and made it an ordinary agricultural commodity. This Bill immediately led to the widespread purification, sale and interstate commerce of CBD, a molecule obtained from hemp (~$4.7 billion in U.S. sales in 2021). The result has been that storefronts and online retailers have flooded the market with CBD products, many with unsubstantiated therapeutic claims. Sadly, U.S. consumers are currently using

CBD to treat a variety of ailments in the absence of rigorous clinical studies. Indeed, ~14% of the U.S. adult population (~29 million adults) admit to using CBD (Gallup Survey, U.S. News & World Report). Nonetheless, rigorous clinical research on products that contain CBD is desperately lacking. Our research study aims to test the effects of a Defined CBD, a capsule with high purity (>99.9%) CBD, on the structure and function of sleep physiology.

There is a strong scientific rationale to test a CBD-based product on sleep physiology in a properly controlled, well-powered and rigorous study in humans. Preclinical studies in rats indicate CBD increases total sleep time in a dose-dependent manner[4]. In one early but small (N = 10) placebo-controlled clinical study in Brazil, subjects with insomnia that received 160 mg of CBD reported having slept significantly more than those who had been given a placebo control[5]. However, the study was only performed in an extremely small number of subjects, and did not use any objective measures of sleep physiology. More recently, a larger study in 72 adults with clinically diagnosed anxiety, CBD (25-75 mg/day) improved sleep in 66% of the patients as determined by a sleep quality questionnaire [the Pittsburgh Sleep Quality Index (PSQI)][6]. However, this was an open label study (i.e. not blinded), lacked a placebo-control, and also did not include any objective measures of sleep physiology. As such, no strong scientific conclusions regarding causality can be drawn from the clinical data.

In a survey by Consumer Reports, ~45% of adults who reported trying CBD said they used it to help them sleep, and a majority of those people said they believed that it worked. Nonetheless, to this date a rigorous, properly-controlled, and well-powered study to determine if CBD influences sleep physiology has simply never been reported in the scientific literature. The Le Rêve 3.0 study is designed to fill this important void in scientific knowledge.

We hypothesize that a novel CBD-based formulation in the form of an orally administered capsule will positively impact sleep physiology metrics in subjects with insomnia, as determined using an objective sleep-tracking device called “Whoop”. The capsule we will test is composed of >99.9% purity hemp-derived CBD with a custom chemical formulation that also contains low concentrations (1 mg each) of highly purified (>98%) forms of the terpenes linalool, myrcene, phytol, limonene, α-terpinene, α-terpineol, α-pinene, and β-caryophyllene. Preclinical studies in animals have shown that these terpenes are sedating[7], but their potential effects on sleep physiology in humans have not been established. The capsules do not contain any Δ-9-THC.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Based on a large amount of published clinical data, the World Health Organization (WHO) has established that CBD (the active ingredient in Defined CBD) is non-intoxicating and has an excellent safety profile in humans[8]. Previous clinical studies indicate that adverse reactions with CBD are rare[9]. The most common adverse reactions that occurred with CBD when given at a high dose [e.g., at the recommended dose for the FDA approved CBD drug Epidiolex® (20 mg/kg/day), were somnolence (sleepiness); decreased appetite; diarrhea; transaminase elevations; fatigue; malaise; asthenia (abnormal physical weakness or lack of energy); rash; insomnia; sleep disorder; poor quality sleep; and infections. However, these adverse reactions were only observed in <15% of patients at a CBD dose (20 mg/kg/day or ~1,800 mg for a 90 kg male) that is approximately six times greater than the dose that will be used in Le Rêve 3.0 study (300 mg or ~3 mg/kg/day for a 90 kg male) (see supplemental file with Epidiolex® Safety Information). Moreover, the frequency of these adverse events decreased significantly when Epidiolex® was administered at a lower dose (10 mg/kg/day or ~900 mg for a 90 kg male), a dose that is still three times greater than the dose we will use in Le Rêve 3.0. A recent meta-analysis of AEs

from 12 clinical trials with CBD indicated that associations with abnormal liver function tests, somnolence, sedation and pneumonia were limited *exclusively* to childhood epilepsy studies, where CBD may have interacted with other medications such as clobazam and/or sodium valproate[10]. After excluding studies in childhood epilepsy, the only adverse outcome associated with CBD treatment was diarrhea. And, again, this was only observed at doses well above the CBD dose that will be evaluated in Le Rêve 3.0. Therefore, due to the low dose of CBD that will be tested in Le Rêve 3.0 (300 mg p.o.), if AEs are observed with Defined CBD, we presume that they will be minor and occur at a lower frequency than what was observed in previous clinical studies.

Although rare, some adults display hypersensitivity to CBD. Participants with known hypersensitivity to CBD will be excluded from participating in Le Rêve 3.0. As noted above, some recent studies indicate that extremely high doses of CBD (much higher than what will be used in Le Rêve 3.0) might impair liver function. Therefore, as a precaution, study participants in Le Rêve 3.0 will be required to refrain from the use of any of the following contra-indicated drugs for at least one week prior to and for the duration of the study: erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, telaprevir, boceprevir, amlodipine, gemfibrozil, cyclosporine, danazol, amiodarone, verapamil, diltiazem, rifampin, theophylline, tizanidine, bupropion, efavirenz, diflunisal, propofol, fenofibrate, lamotrigine, morphine, lorazepam, diazepam, clobazam, stiripentol, valproate, everolimus, sirolimus, or tacrolimus, and niacin (vitamin B3 greater than 1g/ day). Participants who cannot refrain from the intake of these contra-indicated drugs prior to and throughout the study will be excluded from participating in Le Rêve 3.0.

Defined CBD also contains low concentrations (1 mg each) of highly purified (>98%) forms of the terpenes linalool, myrcene, phytol, limonene, α-terpinene, α-terpineol, α-pinene, and β-caryophyllene. Terpenes are widely used as fragrances and flavors in consumer products such as perfumes, cosmetics and cleaning products, as well as food and drink products. For example, the aroma and flavor of hops comes, in part, from sesquiterpenes (mainly α-humulene and β-caryophyllene), which are used to make beer. Importantly, the terpenes in Defined CBD are designated by the FDA as GRAS (Generally Regarded as Safe) for oral consumption. Although rare, some adults display mild skin allergies to terpenes when applied topically. As a precaution, participants with known hypersensitivity to terpenes will be excluded from participating in Le Rêve 3.0.

Defined Research confirms the molecular composition of every batch of Defined CBD (including the Defined CBD to be used in Le Rêve 3.0) by an ISO-10725-accredited analytical testing laboratory. These analytical tests confirm the concentration and purity of Defined CBD, and ensure that it is free from any contaminants, including pesticides, residual solvents and heavy metals. Electronic records that document these lab tests are stored at Defined Research and are available upon request.

2.3.2 KNOWN POTENTIAL BENEFITS

Epidiolex® is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older. Given that the most common adverse reaction in patients treated with Epidiolex® is somnolence, one potential benefit that study participants may receive in Le Rêve 3.0 when treated with Defined CBD is a change in their sleep physiology that increases their somnolence. Several clinical studies indicate that CBD can decrease acute anxiety[11]. Participants with social anxiety disorder and controls were blindly allocated to receive CBD or a placebo control before a simulation public speaking test. CBD resulted in significantly reduced anxiety, cognitive impairment and discomfort, and significantly decreased hyper-alertness in anticipatory speech[12]. Δ-9-THC is well established as having anxiogenic (anxiety-promoting) properties in clinical studies, and these effects can be blocked by CBD[13]. Therefore, as some clinical studies indicate that CBD

may decrease acute anxiety, it is also possible that study participants in Le Rêve 3.0 treated with Defined CBD might feel less anxious.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

As described above, the potential risks of participating in Le Rêve 3.0 relate to potential adverse reactions that may occur in response to CBD or terpenes. However, given the relatively low dose of CBD found in Defined CBD (300 mg or ~3.3 mg/kg/day for a 90 kg male) that will be used in Le Rêve 3.0 relative to that used clinically with Epidiolex® (20 mg/kg/day or 1,800 mg total for a 90 kg male), we anticipate that if AEs are observed, they will occur at a much lower frequency lower than in patients treated with Epidiolex®. Although the potential safety risks in Le Rêve 3.0 are extremely low, the information gained in the study on how CBD may affect sleep physiology may benefit millions of current CBD consumers.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is to determine if Defined CBD influences objective measures of sleep physiology.	The primary endpoint is the percentage of time spent in slow wave (Deep) and REM sleep as quantified by a non-invasive wrist-worn sleep-tracking device called Whoop.	Deep and REM sleep are thought to contribute significantly to restorative sleep. We will use an unbiased approach to collect objective data on these sleep stages to determine if Defined CBD increases deep and REM sleep.
Secondary		
The secondary objective(s) are to determine if Defined CBD influences objective and subjective measures of sleep physiology.	Additional objective secondary outcome measures that will be collected on the Whoop device include: Total sleep time, sleep latency, the number of sleep disturbances, time spent in each sleep stage, and the percentage of time spent in each sleep stage. A modified version of a clinically validated questionnaire entitled the Participant Global Impression (PGI)[14] will be used to track subjective measures of sleep physiology. This data will be collected from study participants in the form of a brief five-minute survey that will be completed on their smartphone at the end of each four-week treatment period. This survey measures the perception of the study participants of the effects of treatment.	Although some early clinical studies suggest that CBD might help people with insomnia, no studies have addressed if it influences objective and subjective measures of sleep physiology. Therefore, we will include a number of objective and subjective secondary outcome measures in this study to fill this void in knowledge.

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesize that Defined CBD, a novel CBD-based formulation in the form of a small orally administered capsule, will increase the percentage of time participants spend in deep (SWS) and REM sleep, as measured by an objective sleep-tracking device called "Whoop". Our research study, entitled Le Rêve 3.0, is a double-blind, placebo-controlled, randomized, crossover investigational study to determine if Defined CBD, a Custom-Formulated CBD Capsule, influences sleep physiology. This capsule contains no Δ-9-THC. As this study is only designed to evaluate the effects of Defined CBD on the structure and function of sleep physiology, the phase of the trial is not applicable. This trial is not intended to treat, diagnose, prevent, or cure any disease.

The Le Rêve 3.0 study will involve a cross-over design in which study participants will cycle through two independent treatments, each for four weeks (Treatment 1: Placebo; Treatment 2: Defined CBD). The placebo will look, smell and taste the same as the Defined CBD capsule. The study participants will initially be randomized with respect to the treatment arm, and every participant will cycle through both treatment arms. We will use a double-blind design in which the investigator and study participants will both be blinded to the treatments. Baseline data for each participant will be collected for two weeks prior to initiating treatments, as well as for a one-week washout period following each treatment arm. The entire study duration will be 12 weeks (for Schema see section 1.2).

Primary data for Le Rêve will be obtained in a completely unbiased manner from a non-invasive sleep-tracking wrist-worn device called "Whoop" (https://www.whoop.com), that electronically collects and transmits sleep data from study participants in the comfort of their own beds.
The wristband collects hundreds of data points per second from a 3-axis accelerometer, 3-axis gyroscope, and heart rate sensor. The wristband can accurately measure the latency to fall asleep, total sleep time, sleep fragmentation, as well as the time spent in each sleep stage [Light, Slow Wave (Deep), Rapid Eye Movement (REM), and Awake]. The device also collects data using photoplethysmography (PPG), a technique that involves measuring blood flow by assessing superficial changes in blood volume. Heart rate, heart rate variability and respiratory rate, can all be derived from PPG data, and all of these metrics are used in Whoop's sleep detection and staging algorithms. Importantly, two recent publications, published independently from Whoop, show that data on sleep stages collected from the Whoop device are highly accurate and correlate well with polysomnography (PSG), the gold-standard of sleep tracking used in clinical studies conducted in sleep clinics[15].

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

To date, a rigorous, properly-controlled, and well-powered study to determine if CBD influences sleep physiology has simply never been reported in the scientific literature. Defined Research's Le Rêve 3.0 study is designed to fill this important void in scientific knowledge.

Summary Of Data From Previous Clinical Studies With Defined CBD

Defined Research recently completed two smaller independent clinical studies to determine the effects of a Defined CBD on the structure and function of sleep physiology. Each of these independent studies were performed as a double-blind, placebo-controlled, randomized, crossover investigational study to determine if Defined CBD influences sleep physiology in humans. These in-house studies were performed under informed consent, but did not go through the IRB approval process.

Summary of Data From Le Rêve 1.0

In our first study, entitled Le Rêve 1.0, participants (N = 23) were randomized to take a placebo control or Defined CBD (300 mg CBD, 8 mg terpenes) once daily, one hour before bedtime, for seven consecutive nights. An example of one participant's data is shown in Figure 1. Participant DR11 showed a significant increase in REM sleep, restorative sleep (the combination of REM and deep sleep), and the percentage of time spent in REM and restorative sleep (Fig. 1). Indeed, on average, over seven days of treatment, participant DR11 benefitted from nearly an extra hour of restorative sleep each night relative to the placebo control (Fig. 1B). Furthermore, participant DR11 was also able to perceive an improvement in their sleep quality and duration relative to the placebo control when they responded to a clinically validated sleep survey at the end of the treatment periods (data not shown).

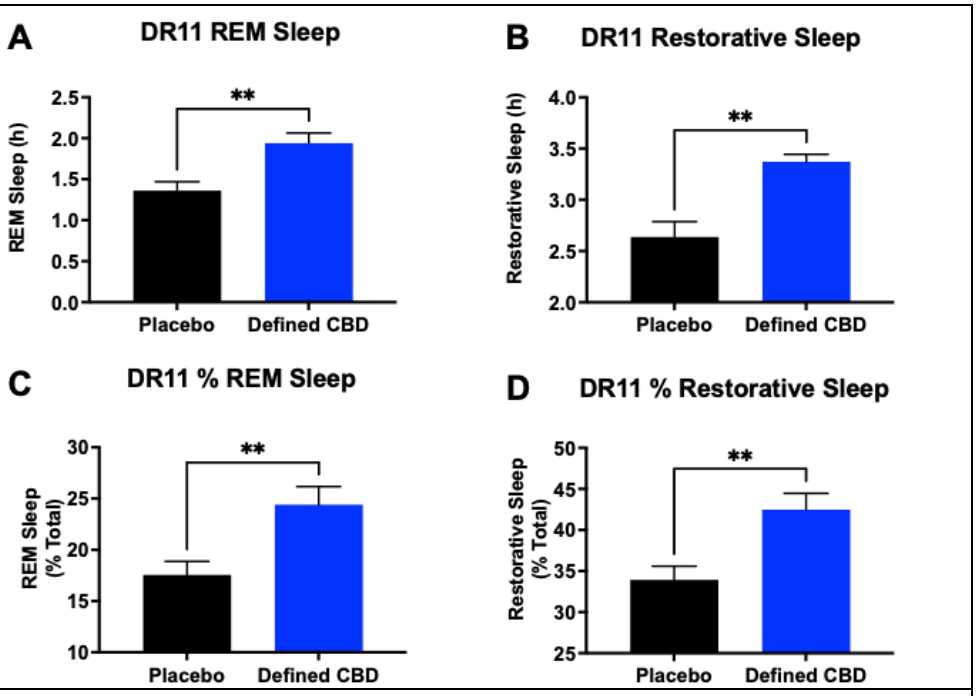


Figure 1: Defined CBD increases (A) REM and (B) Restorative Sleep in study participant DR11 from Le Rêve 1.0, as well as the percentage of time DR11 spends in (C) REM and (D) restorative sleep [**p < 0.01 (t test). n = 7 days per treatment group. Values are means ± SEM].

It is important to emphasize that these preliminary clinical studies with Defined CBD were designed and performed as feasibility studies, and were not statistically powered to show any significant clinical benefits. Nevertheless, analysis of the pooled data from all of the participants (N = 23) from Le Rêve 1.0 indicated that Defined CBD showed a trend to increase the percentage of REM (Fig. 2) and restorative sleep (data not shown).

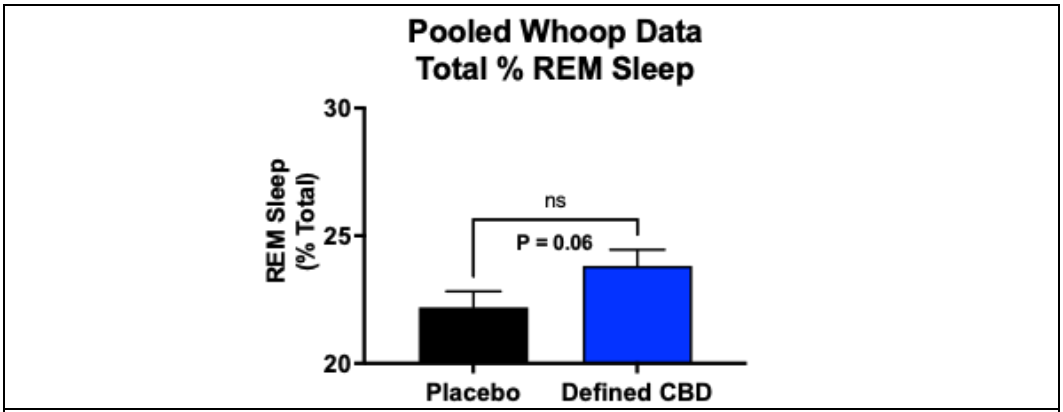


Figure 2: Defined CBD shows a trend to increase the percentage of REM sleep in Le Rêve 1.0 [p = 0.06; (t test). n = 23 participants per treatment group. Values are means ± SEM].

Analysis of the pooled data from our first clinical study indicated that participants could be stratified into "responders" and "non-responders". Pooled data from "responders" showed a highly significant increase in the percentage of REM and restorative sleep in study participants who received Defined CBD relative to the placebo control (Fig. 3). Indeed, when only "responders" were analyzed, they exhibited a ~10% increase in restorative sleep when treated with Defined CBD (Fig. 3B).

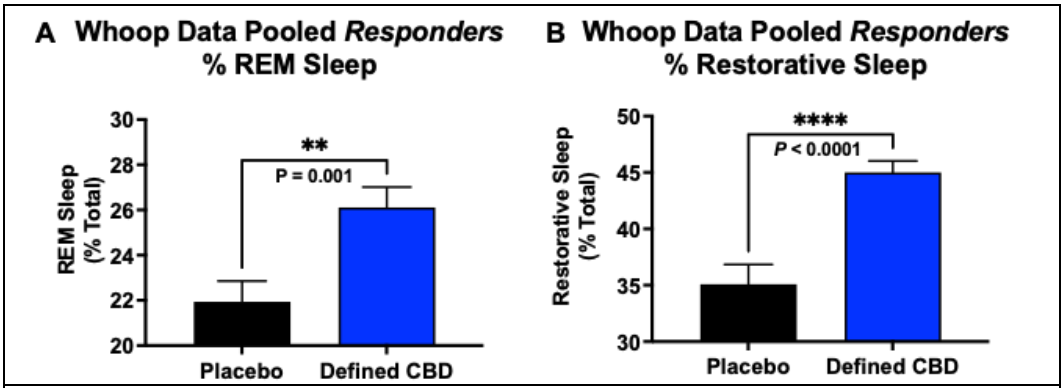


Figure 3: Defined CBD increases the percentage of REM and Restorative Sleep in pooled responders in Le Rêve 1.0 [**p = 0.001; ****p < 0.0001 (t test). n = 11 responders per treatment group. Values are means ± SEM].

After more careful scrutiny of the clinical data from Le Rêve 1.0, we determined that of the participants who responded to treatment with Defined CBD, 9/11 exhibited insomnia or subthreshold insomnia as defined by a clinically validated insomnia severity index [the Pittsburgh Sleep Quality Index (PSQI)][16] that was completed prior to the clinical study being conducted. After taking Defined CBD, participants who scored as having moderate insomnia in the PSQI exhibited an increase in the percentage of restorative sleep that narrowly missed statistical significance, and a significant increase in the percentage of restorative sleep relative to the placebo control (Fig. 4).

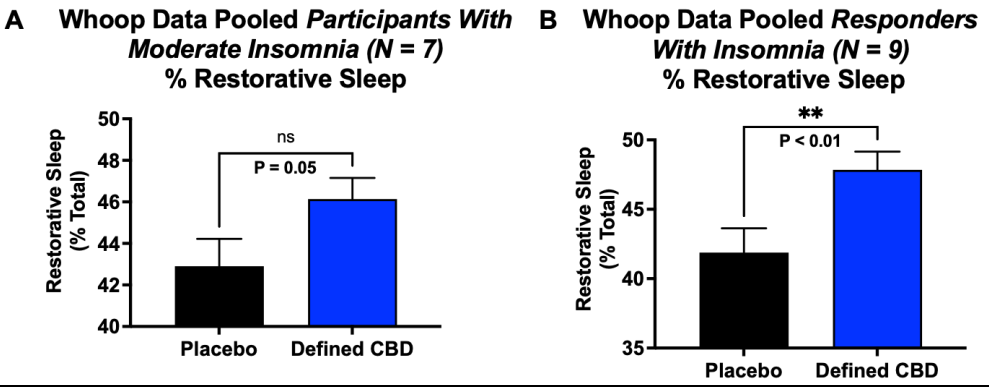


Figure 4: Defined CBD increases the percentage of (A) REM in participants with moderate insomnia and (B) Restorative Sleep in pooled responders with insomnia in Le Rêve 1.0 [**p < 0.01; (t test). n = 7-9 responders per treatment group. Values are means ± SEM].

At the end of each treatment period in our clinical studies, participants completed a modified version of a clinically validated questionnaire entitled the Participant Global Impression (PGI)[14]. PGI assessments are based on the participant's global perception of the effects of treatment on sleep during each treatment period, as compared to their sleep during the baseline period of the study. Using the PGI assessment, participants perceived that they slept better after taking Defined CBD relative to the placebo control, although this effect did not achieve statistical significance (Fig. 5). Nevertheless, based on post-hoc power analysis we have performed, we believe that this effect would achieve statistical significance with a larger sample number. Importantly, no AEs whatsoever were reported in Le Rêve 1.0.

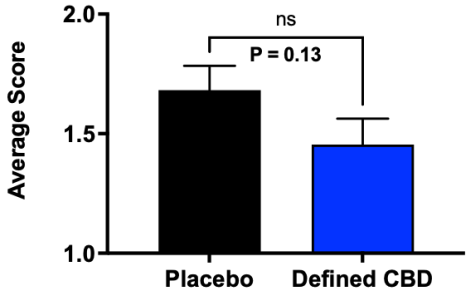


Figure 5: Study Participants in Le Rêve 1.0 Perceived That Defined CBD Helped Them Sleep Better [p = 0.13; (t test). n = 23 responders per treatment group. Values are means ± SEM]. At the end of each treatment period, study participants used a PGI questionnaire to determine if the treatment influenced their sleep relative to a baseline period before the treatments were initiated. Scoring Matrix: 1= Treatment Helped; 2-No Effect of Treatment; 3-Treatment Worsened. With this data, a lower score indicates a potential benefit to help sleep. The results showed that Defined CBD appeared to improve the perception of better sleep relative to the placebo control.

Summary of Data From Le Rêve 2.0

After the successful completion of Le Rêve 1.0, we attempted to replicate this study in an independent cohort of participants. As data from our Le Rêve 1.0 indicated that participants with insomnia most benefitted from treatment with Defined CBD, for Le Rêve 2.0 we only enrolled study those who exhibited moderate or severe insomnia as defined by a clinically validated insomnia severity index (the PSQI)[16].

In Le Rêve 2.0 participants (N = 13) were randomized to take a placebo control or Defined CBD (300 mg CBD, 8 mg terpenes) once daily, one hour before bedtime, for at least four nights per week, for a total treatment period of three weeks.

In pooled data from Le Rêve 2.0, Defined CBD increased the percentage of REM and restorative sleep in participants treated with Defined CBD relative to the placebo control, although only the effect on restorative sleep reached statistical significance (Fig. 6). Similar to Le Rêve 1.0, our second study was not powered to obtain statistical significance, and, as such, we believe that this data represents an encouraging replication of Le Rêve 1.0 in an independent cohort of participants. Moreover, based on post-hoc power analysis we have performed, we believe that the effects of Defined CBD on REM sleep would achieve statistical significance with a larger sample number. As in Le Rêve 1.0, no AEs whatsoever were reported in Le Rêve 2.0.

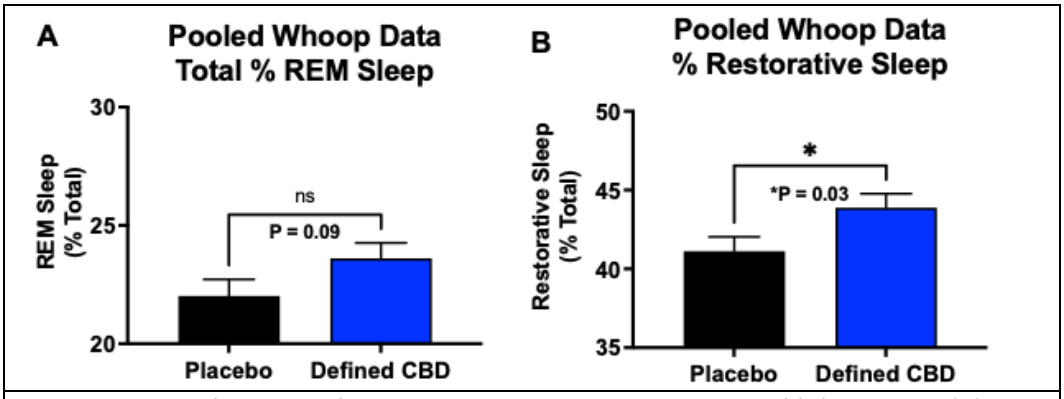


Figure 6: In Le Rêve 2.0 Defined CBD increases the percentage of (A) REM and (B) restorative sleep in an independent cohort of participants with moderate to severe insomnia [*p < 0.05; (t test). n = 13 participants per treatment group. Values are means ± SEM].

Our two clinical studies were performed in a decentralized manner in which study participants self-administered treatments and collected sleep data in the comfort of their own homes. We therefore decided to quantify the effects of Defined CBD on sleep physiology when we combined the data from our two small clinical studies. In the combined data set, Defined CBD significantly increased the percentage of time study participants spent in REM and restorative sleep (Fig. 7). The effects of Defined CBD on deep sleep in the combined data set narrowly missed statistical significance (data not shown). As noted previously, based on post-hoc power analysis we have performed, we believe that the effects of Defined CBD on deep sleep would achieve statistical significance in a larger sample number.

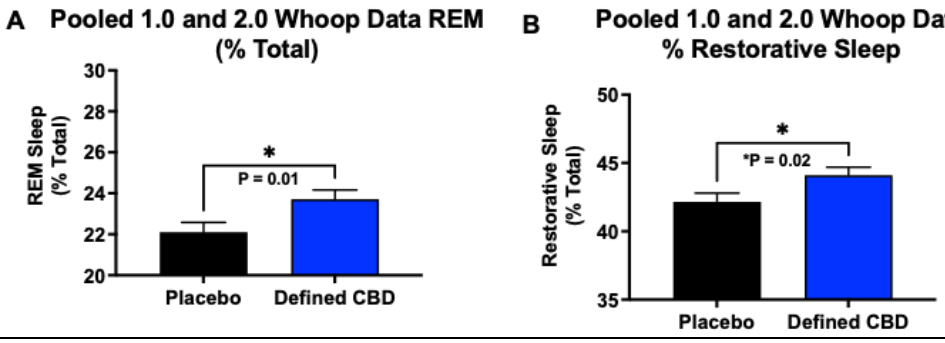


Figure 7: Defined CBD increases the percentage of (A) REM and (B) restorative sleep in a combined data set from clinical studies Le Rêve 1.0 and 2.0 [*p < 0.05; (t test). n = 36 participants per treatment group. Values are means ± SEM].

Conclusions and Clinical Significance Of Research Findings

Our clinical data with Defined CBD indicates that it significantly increases the percentage of time people spend in REM and restorative (deep plus REM sleep), and that these effects are most pronounced in people suffering from insomnia. Importantly, we were able to replicate the effects of Defined CBD on these sleep physiology parameters in two independent participant cohorts. Furthermore, participants who took Defined CBD could also perceive a benefit of the treatment on their sleep quality, and not a single AE was reported in either clinical study.

REM and restorative sleep appear to be critically important for good brain health, and their absence in human populations is often associated with chronic ailments and diseases. For example, REM sleep has an essential role in the process of learning and memory in the hippocampus, and disruption of REM sleep can lead to cognitive impairment and other manifestations[17]. During sleep, the brain is able to repair and grow cells, tissue, and nerves that regenerate and boost the hormone and immune system. Along with good nutrition, exercise and stress reduction, restorative sleep is vital for your optimal physical, mental, and emotional health. Insufficient restorative sleep increases the risk of disorders, such as high blood pressure, diabetes, obesity, stroke and depression. It's also associated with cognitive decline and Alzheimer's disease.

Defined CBD is composed of a novel formulation of CBD and terpenes that we have shown significantly increases REM and restorative sleep in people with insomnia, and these people could correctly perceive the benefit of this treatment (even though they were blinded to the treatments). We would now like to replicate these exciting preliminary findings in a larger participant cohort under IRB approval.

4.3 JUSTIFICATION FOR DOSE

The justification for the route of administration and planned dosage for the Le Rêve 3.0 study is based on published scientific literature and in-house dose range-finding studies completed at Defined Research. In one early but small (N = 10) placebo-controlled clinical study in Brazil, subjects with insomnia that received 160 mg of CBD p.o. reported having slept significantly more than those who had been given a placebo control[5]. More recently, a somewhat larger study in 72 adults with clinically diagnosed anxiety, 25-75 mg/day p.o. CBD improved sleep in 66% of the patients as determined by a sleep quality questionnaire[6]. Unfortunately, this particular study was an open label study (i.e. not blinded), lacked a placebo-control, and did not include any objective measures of sleep physiology. Furthermore, the study was only performed in participants with clinically diagnosed anxiety, adding a further confound. Previous clinical studies with Epidiolex® (which contains 99.9% CBD) indicated that

CBD may cause somnolence and sedation at doses between 10 mg/kg/day-20 mg/kg/day (900-1,800 mg/day for a 90 kg male)[9]. In-house dose-ranging pilot studies conducted at Defined Research under informed consent demonstrated that Defined CBD (300 mg p.o.) was well tolerated and significantly increased the percentage of time participants spent in deep and REM sleep (data not shown). These studies formed the basis for the dose of CBD used in Le Rêve 1.0-3.0. As described above, based on a large amount of published clinical evidence, the WHO has established that CBD is non-intoxicating and has an excellent safety profile in humans[1], and based on previous clinical studies with Epidiolex®[9] we anticipate that the dose of Defined CBD that will be used in Le Rêve (300 mg/day) will result in no or minimal AEs.

4.4 END OF STUDY DEFINITION

The Le Rêve 3.0 study will span 12 weeks in time (for Schema see section 1.2). The end of data collection for Le Rêve 3.0 will be defined as the last day of drug washout on the seventh day of the twelfth week.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1) Has provided a signed and dated informed consent form.

2) Presence of chronic insomnia defined as self-reported difficulty initiating (latency to persistent sleep >30 min) and/or maintaining sleep (>30 mins awake during the middle of the night, or waking >30 mins before desired waking time on three or more nights per week) for at least 3 months.

3) Insomnia Severity Index score >15.

4) Male or female aged 25–70 years.

5) Is willing to comply with *all* study procedures throughout the entire study, including:

-Wearing a sleep-tracking device on their wrist throughout entire clinical study.
-Ensuring that the sleep-tracking device is connected to their smartphone via Bluetooth on a daily basis so that sleep data can be collected on a daily basis.
-Ensuring that the sleep-tracking device is charged before going to bed each night, ensuring that sleep data can be collected on a daily basis.
-Is willing to receive and respond to daily text (SMS) notifications for the duration of the entire clinical study.
-During the treatment phases of the study, is willing to take the treatment for at least four nights in each week.

6) On the nights in which the participant takes the treatment, is willing to abstain from excessive alcohol intake (>two drinks/day).

7) On the nights in which the participant takes the treatment, is willing to refrain from drinking alcohol two hours before bedtime.

8) Female subjects who:

-Are postmenopausal, with amenorrhea for at least one year before the screening interview, OR

-Are surgically sterile, OR

-If of childbearing potential agree to practice effective double barrier methods of contraception (e.g., condom + diaphragm; condom or diaphragm + spermicidal gel or foam), from the time of the signing of informed consent through the last dose of study treatment, or agree to completely abstain from intercourse.

9) Self-reported bedtime between 9 pm and midnight on four-seven nights per week.

10) Owns a smartphone.

5.2 EXCLUSION CRITERIA

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

1) Self-reported body mass index > 32 calculated from patient's height (m) and weight (kg); weight (kg)/square height (m^2).

2) Insomnia associated with clinically diagnosed sleep apnea (AHI greater than 15 events/hour), or movement disorders such as restless legs, periodic limb movement (PLM) (greater than 30 events/hour or greater than five events/hour with associated PLM arousals).

3) Are currently participating in a formal behavioral therapy program to facilitate sleep.

4) History of epilepsy or seizures.

5) History of liver disease.

6) Serious head injury or stroke within the past year.

7) Psychiatric disorders including major depression, bipolar, anxiety, or schizophrenia.

8) History of suicide attempt or current suicide ideation.

9) Evidence of any clinically significant, severe or unstable, acute or chronically progressive medical or surgical disorder (including planned medical procedures that may impact sleep), or any condition that may interfere with the absorption, metabolism, distribution, or excretion of the study drug.

10) Patients with a history of cardiovascular disease including poorly controlled hypertension, ischemic heart disease, arrhythmia, or severe heart failure.

11) Untreated metabolic disorder such as diabetes.

12) Medical conditions that result in frequent need to get out of bed (e.g. nocturia).

13) History of drug or alcohol abuse, including past or present history of cannabis dependence.

14) Inability to refrain from greater than two standard drinks/day of alcohol consumption for study duration.

15) Current cigarette smoker.

16) Currently chronic (daily) cannabis user.

17) Use of any substance with psychotropic effects or properties known to affect sleep/wake, including neuroleptics, morphine/opioid derivatives, antihistamines, stimulants, anti-depressants, clonidine, within one week prior to screening.

18) Use of any over-the-counter sleep medications including tryptophan, valerian root (Valeriana officinalis), kava (Piper methysticum Forst), melatonin, St John's Wort (Hypericum perforatum), Alluna (herbal sleep supplement with valerian root), and hemp within one week prior to screening.

19) Inability to refrain from use of any of the following contra-indicated drugs for at least one week prior to and for the duration of the study: erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, telaprevir, boceprevir, amlodipine, gemfibrozil, cyclosporine, danazol, amiodarone, verapamil, diltiazem, rifampin, theophylline, tizanidine, bupropion, efavirenz, diflunisal, propofol, fenofibrate, lamotrigine, morphine, lorazepam, diazepam, clobazam, stiripentol, valproate, everolimus, sirolimus, or tacrolimus, niacin (vitamin B3 greater than 1g/ day), grapefruit juice.

20) Consumption of xanthine-containing beverages (i.e., tea, coffee, energy drinks or cola) of more than five cups or glasses per day.

21) Inability to refrain from greater than 400mg/day of caffeine consumption for study duration.

22) Participation in any other clinical trial within 30 days before the screening visit.

23) Night shift workers (during the 12 months prior to the study and during the study).

24) Individuals who nap three or more times per week over the preceding month.

25) Current delayed sleep phase syndrome where wake-up time is regularly (>5x/week) later than 9:00 a.m.

26) Individuals having to travel across more than two time zones or outside of their country of residence at any time during the study.

27) Females who are pregnant, are planning to become pregnant, or are breastfeeding.

28) History of allergies particularly to plant-based products containing terpenes, i.e. flavors and aromatic natural oils for example citrus, mango, lavender, thyme, cedarwood and pine products.

29) Known hypersensitivity to cannabinoids, including CBD.

30) Individuals may be excluded from participating in the study based on the investigator's professional judgement.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from ingesting greater than two standard drinks/day of alcohol consumption for study duration.
- Refrain from drinking alcohol two hours before bedtime.
- Abstain from ingesting greater than 400 mg/day of caffeine consumption for study duration.
- Abstain from ingesting caffeine after 3 pm for study duration.
- Abstain from ingesting more than five cups or glasses per day of xanthine-containing beverages (i.e., tea, coffee, energy drinks or cola) for study duration.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment Strategies

Participant recruitment and enrollment for Le Rêve 3.0 will be performed entirely by a CRO named 83Bar, Inc., who has extensive experience in managing all aspects of clinical trials. Recruitment materials will include (for details see Supplemental materials):

• Digital advertisements to appear on Facebook / Instagram and Google Search

• Landing pages

  o Landing page with embedded lead generation survey

  o Qualified results landing page

  o Not qualified results landing page

• Lead Generation Survey

• Emails

• Text messages

• Call script

• Privacy Policy

• Social Media Editorial Calendar

• Social Media Comment Moderation

Design and Procedure: Prospective candidates will see a digital ad on Facebook, Instagram, or Google search. After a prospective candidate clicks on the ad, they will be directed to a dedicated landing page that includes an embedded survey. The survey is designed to pre-screen prospective candidates. Survey respondents that are "survey qualified" will next receive a phone call from an 83bar Contact Center agent. If the prospective candidate answers the call, the agent will dialogue with the prospective candidate using an IRB-approved script (see supplemental materials). The script is designed to provide additional screening for prospective candidates. Interested participants will be provided with electronic consent forms. Information will then be sent to the study activation team for enrollment. Study candidates will also receive confirmation and reminder via email and text message. 83Bar predicts that upon receiving IRB-approval, the recruitment process will take approximately four weeks.

Target Population:

- Self-identify as meeting the study inclusion/exclusion criteria

Subject Recruitment:

- Potential candidates will be recruited from the general population using IRB-approved Facebook/Instagram and Google search advertisements. Potential candidates will complete an IRB-approved online pre-screening survey.
- Pre-screened potential candidates will be contacted by the 83bar Contact Center. The Contact Center will conduct verbal pre-screening using an IRB-approved script (see supplemental materials). If the candidate is interested in participating in the study, candidates that qualify based on online pre-screening and verbal pre-screening will be invited to participate in the study.

Participant Compensation:

- Participants who successfully complete Le Rêve 3.0 will receive a $100 gift card immediately upon completion of the study. Participants will also be allowed to keep their Whoop™, a non-invasive wearable fitness and health coach, which will be active for a period of up to two months. After this period, if participants desire to continue using the Whoop strap they will be required to obtain a subscription for its use directly from Whoop™.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Defined CBD is composed of small capsules made with vegetable cellulose (gluten-free, non-GMO, vegan, certified kosher, certified halal) that contain >99.9% purity hemp-derived CBD dissolved in coconut oil (USDA certified organic, non-GMO, dairy-free, gluten-free, vegan coconut oil) with a custom chemical formulation that also contains highly purified (>98% purity) forms of the terpenes linalool, myrcene, phytol, limonene, α-terpinene, α-terpineol, α-pinene, and β-caryophyllene [Food Grade (GRAS), Natural, Organic, non-GMO, dairy-free, gluten-free, vegan). Participants will be required to take two small capsules one hour before they go to bed. These capsules will contain a total of 300 mg CBD and 8 mg of terpenes (1 mg of each terpene). Defined CBD contains no Δ-9-THC.The capsules that

contain the placebo control will look, feel and smell exactly the same as the capsules that contain Defined CBD, but will contain no CBD or terpenes.

6.1.2 DOSING AND ADMINISTRATION

The dose participants will take in the study is two small capsules, that contain a total of 300 mg CBD and 8 mg of terpenes (1 mg each of the terpenes linalool, myrcene, phytol, limonene, α-terpinene, α-terpineol, α-pinene, and β-caryophyllene) that will be taken orally with a glass of water one hour before bedtime. The participants will be required to take the study medication on a minimum of four nights per week for each of the four-week treatment phases of the study.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The CRO 83Bar will handle all of the study materials, including Defined CBD and the placebo control. They will ship these materials directly to study participants.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The treatments will come in two independent blister packs labeled “Defined Research Treatment 1” and “Defined Research Treatment 2”. The blister packs contain a sufficient number of capsules for a total of 28 days of treatment (either Defined CBD or the Placebo Control).

6.2.3 PRODUCT STORAGE AND STABILITY

The study treatment should be stored in a cool dry location, but do not require refrigeration.

6.2.4 PREPARATION

The study treatments will require no preparation. The capsules are simply removed by the study participants from the blister packing before taking the treatment.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

After enrollment, study participants will be assigned a study participant number, and will be randomized to receive Defined CBD or the Placebo control first. As Le Rêve 3.0 is a crossover study, participants who are randomized to receive Defined CBD as the first treatment will cross-over to receive the Placebo Control as the second treatment, and vice-versa. Both the study participants and the PI will be blinded to the study treatments. Unblinding will occur at the completion of the study by the PI. In certain rare instances (e.g. for a SAE), the blind may be broken for an individual participant by the PI.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol by study participants will be assessed by two independent approaches. In the first approach, a CBD Sleep Study team member will be checking Whoop data (stored on the cloud)

on a daily basis for each participant to ensure that the data is being collected consistently and accurately. In the second approach, study participants will be required to answer a text (SMS) message on a daily basis to confirm whether or not they took the study treatment.

6.5 CONCOMITANT THERAPY

Not applicable.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation of the study intervention may occur in the event of a SAE if the medical monitor on the CBD Sleep Study Team makes that recommendation. In the event that the medical monitor determines that the study intervention should be discontinued for a study participant, they will prepare an electronic Case Report Form (eCRF) that will capture the date and the specific underlying reason for discontinuation of study intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Study participants may voluntarily choose to withdraw from Le Rêve 3.0 at any point before or during the study by sending a text (SMS) message to 415-275-2014 or by sending an email to support@definedresearch.org. If a study participant chooses to withdraw from the study for any reason, they will be required to disclose to the CBD Sleep Study Team the reason that they chose to withdraw. The PI may choose to withdraw a study participant(s) for significant study intervention non-compliance, or in the event of a SAE such that continued participation in the study would not be in the best interest of the participant. In the event that the PI chooses to withdraw a participant from the study, a member of the sleep study team will attempt to reach the participant by phone to inform them that they have been withdrawn from the study. The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to respond to CBD Sleep Study Team.

The following actions must be taken if a participant fails to respond to CBD Sleep Study Team:

- CBD Sleep Study Team will attempt to contact the participant and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, up to 3 telephone calls).
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

We will enroll 150 study participants who display chronic insomnia defined as a self-reported difficulty initiating (latency to persistent sleep >30 min) and/or maintaining sleep (>30 min awake, or waking >30 min before desired waking time) on three or more nights per week for at least 3 months. Participants will also complete a brief clinically validated insomnia severity index, and only participants with an Insomnia Severity Index score >15 will be enrolled in Le Rêve 3.0. We will enroll males or females aged 25–70 years that are located in the United States that meet inclusion and exclusion criteria.

Le Rêve 3.0 will be conducted in an entirely decentralized manner. Primary data for Le Rêve 3.0 will be obtained in a completely unbiased manner from a non-invasive sleep-tracking wrist-worn device called “Whoop” (https://www.whoop.com), that electronically collects and transmits sleep data from study participants in the comfort of their own beds.

The wristband collects hundreds of data points per second from a 3-axis accelerometer, 3-axis gyroscope, and heart rate sensor. The wristband can accurately measure the latency to fall asleep, total sleep time, sleep fragmentation, as well as the time spent in each sleep stage [Light, Slow Wave (Deep), Rapid Eye Movement (REM), and Awake]. The device also collects data using photoplethysmography (PPG), a technique that involves measuring blood flow by assessing superficial changes in blood volume. Heart rate, heart rate variability and respiratory rate, can all be derived from PPG data, and all of these metrics are used in Whoop’s sleep detection and staging algorithms. Importantly, two recent publications, published independently from Whoop, show that data on sleep stages collected from the Whoop device are highly accurate and correlate well with polysomnography (PSG), the gold-standard of sleep tracking used in clinical studies conducted in sleep clinics[18].

The primary endpoint efficacy endpoint in Le Rêve 3.0 is the percentage of time spent in slow wave (Deep) and REM sleep as collected by a non-invasive wrist-worn sleep-tracking device called Whoop. Additional objective secondary outcome measures that will be collected on the Whoop device include: Total sleep time, sleep latency, the number of sleep disturbances, time spent in each sleep stage, and the percentage of time spent in each sleep stage.

A modified version of a clinically validated questionnaire entitled the PGI[19] will be used to track subjective measures of sleep physiology. This data will be collected from study participants in the form of a brief five-minute survey that will be completed on their smartphone at the end of each four-week treatment period. This survey measures the perception of the study participants of the effects of treatment.

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 This is an interventional study to determine the effects of Defined CBD on sleep physiology.

8.2.2 Defined CBD is a small capsule composed of vegetable cellulose (gluten-free, non-GMO, vegan, certified kosher, certified halal) that contains 300 mg of >99.9% purity hemp-derived CBD purified in a GMP-facility that is dissolved in coconut oil (USDA certified organic, non-GMO, dairy-free, gluten-free, vegan coconut oil) with a custom chemical formulation that contains a low concentration (1 mg each) of highly purified (>98% purity) terpenes linalool, myrcene, phytol, limonene, α-terpinene, α-terpineol, α-pinene, and β-caryophyllene [Food Grade (GRAS), Natural, Organic, non-GMO, dairy-free, gluten-free, vegan]. Defined CBD contains no Δ-9-THC.

8.2.3 Defined Research Inc. has >5 years of experience in manufacturing CBD products under GMP-like conditions, and confirms the molecular composition of every batch of Defined CBD (including the Defined CBD to be used in Le Rêve 3.0) by an ISO-10725-accredited analytical testing laboratory. These analytical tests confirm the concentration and purity of Defined CBD, and ensure that it is free from any contaminants, including pesticides, residual solvents and heavy metals. Electronic records of these laboratory tests are stored at Defined Research and are available upon request.

8.2.4 Based on a large amount of published clinical data, the World Health Organization (WHO) has established that CBD (the active ingredient in Defined CBD) is non-intoxicating and has an excellent safety profile in humans[20]. Previous clinical studies indicate that adverse reactions with CBD are rare[21]. The most common adverse reactions that occurred with CBD when given at a high dose [e.g., at the recommended dose for the FDA approved CBD drug Epidiolex® (20 mg/kg/day), were somnolence (sleepiness); decreased appetite; diarrhea; transaminase elevations; fatigue; malaise; asthenia (abnormal physical weakness or lack of energy); rash; insomnia; sleep disorder; poor quality sleep; and infections. However, these adverse reactions were only observed in >10% of patients at a CBD dose (20 mg/kg/day or ~1,800 mg for a 90 kg male) that is approximately six times greater than the dose that will be used in Le Rêve 3.0 study (300 mg or ~3 mg/kg/day for a 90 kg male). Moreover, the frequency of these adverse events decreased significantly when Epidiolex® was administered at a lower dose (10 mg/kg/day or ~900 mg for a 90 kg male), that is still three times the dose we will use in Le Rêve 3.0. A recent meta-analysis of adverse events from 12 clinical trials with CBD indicated that associations with abnormal liver function tests, somnolence, sedation and pneumonia were limited to childhood epilepsy studies, where CBD may have interacted with other medications such as clobazam and/or sodium valproate[22]. After excluding studies in childhood epilepsy, the only adverse outcome associated with CBD treatment was diarrhea. And, again, this was only observed at doses well above the CBD dose that will be evaluated in Le Rêve 3.0. Therefore, if adverse events are observed with Defined CBD in Le Rêve 3.0, we presume that they will be minor and only occur at a lower frequency than what was observed in previous clinical studies.

Although rare, some adults display hypersensitivity to CBD. Participants with known hypersensitivity to CBD will be excluded from participating in Le Rêve 3.0. As noted above, some recent studies indicate that extremely high doses of CBD (much higher than what will be used in Le Rêve 3.0) might impair liver function. Therefore, as a precaution, study participants in Le Rêve 3.0 will be required to refrain from the use of any of the following contra-indicated drugs for at least one week prior to and for the duration of the study: erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, telaprevir, boceprevir, amlodipine, gemfibrozil, cyclosporine, danazol, amiodarone, verapamil, diltiazem, rifampin, theophylline, tizanidine, bupropion, efavirenz, diflunisal, propofol, fenofibrate, lamotrigine, morphine, lorazepam, diazepam, clobazam, stiripentol, valproate, everolimus, sirolimus, or tacrolimus, and niacin (vitamin B3 greater than 1g/ day). Participants who cannot refrain from the intake of these contra-indicated drugs prior to and throughout the study will be excluded from participating in Le Rêve 3.0.

Defined CBD also contains low concentrations (1 mg each) of highly purified (>98%) forms of the terpenes linalool, myrcene, phytol, limonene, α-terpinene, α-terpineol, α-pinene, and β-caryophyllene. Terpenes are widely used as fragrances and flavors in consumer products such as perfumes, cosmetics and cleaning products, as well as food and drink products. For example, the aroma and flavor of hops comes, in part, from sesquiterpenes (mainly α-humulene and β-caryophyllene), which are used to make beer. Importantly, the terpenes in Defined CBD are designated by the FDA as GRAS (Generally Regarded as Safe) for oral human consumption. Although rare, some adults display mild skin allergies to terpenes when applied topically. Participants with known hypersensitivity to terpenes will be excluded from participating in Le Rêve 3.0.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a clinical study participant administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures or special situations (Section 8.3.8).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical consequence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (Section 8.3.8).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented as medical history.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A SAE is defined as an event that, at any dose, results in the following:

- Death.
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were worse or more severe).

- New patient hospitalization due to the investigational product.

- Persistent or significant disability/incapacity.

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgement must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dycrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

The medical monitor is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity using the CTCAE (Common Terminology Criteria for Adverse Events) grading system:

- **Grade 1 Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Grade 2 Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
- **Grade 4 Life Threatening** – Events in which urgent medical intervention is indicated.
- **Grade 5 Death** – If related to the event.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The medical monitor is responsible for assessing the relationship to study drug using clinical judgement and the following considerations:

- **Not related:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

- **Related:** The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

8.3.3.3 EXPECTEDNESS

The medical monitor is responsible will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention (see Section 8.2.4).

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate electronic case report form (eCRF). Information to be collected includes event description, time of onset, medical monitor's assessment of severity, relationship to study product, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

The medical monitor will record all reportable events (AEs and SAEs) starting with the first day of the study until the study is completed. The medical monitor will follow up with the study participant up to three times until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Following initiation of study treatments, all AEs, regardless of cause or relationship, throughout the duration of the study will be reported on the eCRFs.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (i.e. the signing of the informed consent) and throughout the duration of the study will be reported on the eCRFs.

The medical monitor will immediately report to Defined Research any SAE, whether or not considered study intervention related, and will include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol. All SAEs will be followed until satisfactory resolution or until the study investigator deems the event to be chronic or the participant is stable.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Events of special interest include all reports of medication error, abuse, misuse, overdose, and product complaints with AE. Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an investigational product while the medication is in the control of a health care professional, patient, or consumer.

Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an investigational product by a participant.

Misuse is defined as any intentional and inappropriate administration of an investigational product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of an investigational product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacturing, packaging, or distribution of the investigational product.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary objective of the study is:

- To determine if Defined CBD influences objective measures of sleep physiology.

The secondary objective of the study is:

- To determine if Defined CBD influences subjective measures of sleep physiology.

The primary endpoint of the study is:

- To determine if Defined CBD increases the percentage of sleep spent in deep [slow wave sleep (SWS)] and rapid eye movement (REM) sleep as quantified with an objective wrist-worn sleep-tracking device called Whoop.

The null hypothesis is that there is no difference in the percentage of sleep spent in deep and REM sleep in participants that received Defined CBD

and the placebo control; the alternative hypothesis is that there is a difference among the two treatment groups. The difference in the percentage of sleep spent in deep and REM sleep in participants that received Defined CBD and the placebo control at the end of the two four-week treatment phases will be compared using a 2-sided test with an alpha level at 0.05 to evaluate superiority. The p-value and 95% confidence interval for the estimate of treatment difference in percentages will be estimated and constructed using the above-mentioned method.

The secondary endpoints of the study are:

- To determine if Defined CBD changes total sleep time, sleep latency, the number of sleep disturbances, time spent in each sleep stage, and the percentage of time spent in each sleep stage as quantified with the Whoop sleep-tracking device, and subjective measures of sleep physiology as collected via participant surveys.

The null hypothesis is that there is no difference in the secondary endpoints in the study in participants that received Defined CBD and the placebo control; the alternative hypothesis is that there is a difference among the two treatment groups. The difference secondary endpoints in participants that received Defined CBD and the placebo control at the end of the two four-week treatment phases will be compared using a 2-sided test with an alpha level at 0.05 to evaluate superiority. The p-value and 95% confidence interval for the estimate of treatment difference in percentages will be estimated and constructed using the above-mentioned method.

9.2 SAMPLE SIZE DETERMINATION

A total of 100 participants will provide at least 90% power to detect a 15% difference in the percentage of time participants spend in deep and REM sleep, as quantified using the Whoop sleep-tracking device after the four-week treatment phase. The CRO 83Bar will recruit 8,000 potential study participants using social media, will screen approximately 800 study participants via online screening surveys, will contact 440 participants from a call center, and will ultimately enroll 150 qualified study participants. Based on our two previous clinical studies with Defined CBD, we anticipate a maximum dropout rate of 33% in Le Rêve 3.0.

9.3 POPULATIONS FOR ANALYSES

Analysis of the primary and second endpoints will be completed after all study participants have completed the 12-week study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. This analysis of the primary and secondary endpoints will serve as the final analysis of the endpoints. A safety analysis dataset will be composed of any AE and SAEs collected by the medical monitor in the form of eCRFs.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For the primary and secondary endpoints, the difference in the means of each endpoint in participants that received Defined CBD and the placebo control at the end of the two four-week treatment phases will be compared using a 2-sided test with an alpha level at 0.05 to evaluate superiority. The p-value and 95% confidence interval for the estimate of treatment difference in percentages will be estimated and constructed using the above-mentioned method.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint that will be analyzed in Le Rêve 3.0 is the percentage of time study participants spend in deep and REM sleep as quantified using wrist-worn sleep-tracking device Whoop. The difference in the mean percentage of sleep spent in deep and REM sleep in participants that received Defined CBD and the placebo control at the end of the two four-week treatment phases will be compared using a 2-sided test with an alpha level at 0.05 to evaluate superiority. The p-value and 95% confidence interval for the estimate of treatment difference in percentages will be estimated and constructed using the above-mentioned method.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The difference secondary endpoints (total sleep time, sleep latency, the number of sleep disturbances, time spent in each sleep stage, percentage of time spent in each sleep stage, and subjective measures of sleep physiology as collected via participant surveys) in participants that received Defined CBD and the placebo control at the end of the two four-week treatment phases will be compared using a 2-sided test with an alpha level at 0.05 to evaluate superiority. The p-value and 95% confidence interval for the estimate of treatment difference in percentages will be estimated and constructed using the above-mentioned method.

9.4.4 SAFETY ANALYSES

The primary analysis set for safety analyses is defined as safety analysis dataset, which includes all participants who are randomized/enrolled and receive any dose of study treatment. All data collected during the study will be included in the safety summaries.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Not applicable.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

Demographic measurements will be summarized using standard descriptive methods by cohort and treatment. Demographic summaries may include sex, race/ethnicity, and age.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

9.4.9 EXPLORATORY ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

An informed consent form describing in detail the study intervention, study procedures, and risks will be given to study participants and written documentation of informed consent will be required prior to initiating Le Rêve 3.0. The informed consent to be used in Le Rêve 3.0 is submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. A member of the CBD Sleep Study Team will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to initiating the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant initiates the study. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and IRB. If the study is prematurely terminated or suspended, the PI will promptly inform study participants and IRB, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable. Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

The investigator must assure that the participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code will be recorded on any data form used in Le Rêve 3.0. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Defined Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by Defined Research's staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Defined Research.

10.1.4 FUTURE USE OF DATA

Data collected for this study will be analyzed and stored at Defined Research.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Paul Muchowski, Ph.D., CEO	*Chetan Gottimukkula, M.D., Medical Monitor*
Defined Research	*Defined Research*
1250 Missouri Street, Unit #312 *San Francisco, CA 94107*	*1250 Missouri Street, Unit #312* *San Francisco, CA 94107*
415-413-8666	*415-413-8666*
paul.muchowski@definedresearch.com	*chetan.g@definedresearch.com*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an independent safety monitor (ISM) named Dr. Chetan Gottimukkula. Dr. Gottimukkula has extensive experience and knowledge with National and International Drug Safety and Pharmacovigilance principles and Regulations (US FDA, EMA, MHRA, MHLW) and Clinical Trials design and development process. The ISM will provide input to Defined Research and the IRB as necessary.

10.1.7 CLINICAL MONITORING

Clinical monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Members of the CBD Sleep Study Team will oversee clinical monitoring via daily text (SMS) messages with study participants to ensure compliance and to capture any AEs and SAEs.
- Members of the CBD Sleep Study Team will oversee clinical monitoring by ensuring that sleep-tracking data is being collected on a daily basis throughout the study.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Le Rêve 3.0 will be conducted in a decentralized manner. All data will be collected electronically via the cloud. Quality control (QC) procedures by the CBD Sleep Study Team will be implemented to ensure that sleep physiology data is being collected appropriately. Data QC checks will be run on a daily basis. If a study participant becomes noncompliant resulting in a lack of sleep physiology data being collected (for example, if the battery on their sleep tracking device runs out of charge; if the participant forgets to wear the sleep tracking device at night; or if the participant forget to connect the sleep-tracking device to their smartphone via Bluetooth), then the lack of data collection will automatically trigger the activation of a text (SMS) based application to communicate directly with that participant to help them resolve the lack of compliance issue. In the event the text-based notification system does not resolve the lack of compliance issue, a member of the CBD Sleep Study Team may also reach out to the study participant by phone or email to help resolve the issues.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

As stated above, all of the data that will be collected in Le Rêve 3.0 will be electronic and captured via the cloud. The investigator and CBD Sleep Study Team are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Clinical data will be collected by a 21 CFR Part 11-compliant data capture system provided by Whoop. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after completion of Le Rêve 3.0.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant or the investigator. As a result of deviations, corrective actions are to be developed by the CBD Sleep Study Team and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the CBD Sleep Study Team to use continuous vigilance to identify and report deviations within one working day of identification of the protocol deviation. All deviations must be addressed in study source documents.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Data from Le Rêve 3.0 will be included a manuscript that Defined Research will submit for publication in a peer reviewed scientific journal. In addition, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. Data from this study may be requested from other researchers three years after the completion of the primary endpoint by contacting Defined Research.

10.1.12 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed, including in a scientific publication that may arise from Le Rêve 3.0. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
DHHS	Department of Health and Human Services
DRE	Disease-Related Event
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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