Clinicaltrials.gov
Record-Title: Combination Drug-Therapy for Patients With Untreated Obstructive Sleep Apnea
Number: 191990
Document Type: Study Protocol and Statistical Analysis Plan
Document Date: 06/17/2021

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

191990, RESCUE-Drug: Rescuing OSA Patients Unable to Tolerate CPAP Using Endotype-Targeted Drug Therapy

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

- Sleep Research Offices and Sleep Research Laboratory in Altman Clinical and Translational Research Institute (ACTRI), 9452 Medical Center Drive, La Jolla, CA 92037

4. ESTIMATED DURATION OF THE STUDY

5 years

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

Obstructive sleep apnea (OSA) is a chronic disorder that affects ~1 billion people worldwide and is associated with many adverse health consequences. Many patients cannot or will not tolerate CPAP (continuous positive airway pressure) and alternatives are limited, thus many patients remain untreated. Consequently, there has been great interest in developing drug therapy for OSA, but single interventions have failed to provide more than just partial relief. Recognizing that individualized multimodal therapy is often required for many conditions (e.g. cancer, diabetes or hypertension) we believe this strategy may also hold the key to help the millions of currently untreated OSA patients.

6. SPECIFIC AIMS

AIM 1: Determine the Efficacy of Dual-Drug Therapy for OSA

OSA is caused by four pathophysiological mechanisms or traits ("endotypes"). Using a cross-over, randomized, double-blind, placebo-controlled mechanistic trial design we will assess the effect of short-term dual-drug-therapy (two drugs that each target a different trait: acetazolamide [loop gain], eszopiclone [arousal threshold]) on the Apnea-Hypopnea Index ($AHI_{NREM,supine}$, primary outcome), endotypes, sleep parameters, sleepiness, and blood pressure in 20 OSA patients.

AIM 2: Explore the Efficacy of Single and Triple-Drug Therapy for OSA

Patients from aim 1 in whom dual therapy resolves OSA ($AHI_{NREM,supine}$ reduction >50% & $AHI_{NREM,supine}$<10/h) will undergo an open-label study on single therapy acetazolamide (AZM)), whereas subjects in whom OSA did not resolve will undergo triple-drug therapy (acetazolamide [loop gain], eszopiclone [arousal threshold], venlafaxine [pharyngeal muscle recruitment]). Outcomes will be the same as in aim 1. This exploratory aim will allow us to estimate which proportion of OSA patients responds to single

vs dual vs triple therapy and facilitate the design of long term trials.

7. BACKGROUND AND SIGNIFICANCE

OSA is Very Common and Associated with Many Adverse Health Outcomes
OSA is characterized by a repetitive collapse of the upper airway during sleep leading to transient hypoxemia and arousals from sleep. Recent estimates suggest that about 10% of the US population suffer from clinically significant OSA, with global estimates approximating one billion. Untreated OSA has been associated with many adverse health outcomes, including neurocognitive (e.g. excessive fatigue/sleepiness, motor-vehicle accidents) and cardiovascular (e.g. hypertension, coronary artery disease and cardiovascular mortality) sequelae resulting in costs of more than 150 billion dollars per year in the United States alone.

Patients with OSA are Often Untreated
The standard of care is CPAP therapy, but most studies report long-term discontinuation rates between 40-60%. Alternative therapies are limited, e.g. oral appliances require adequate dentition, have a more variable response and are generally reserved for patients with only mild-moderate disease. Furthermore, to mitigate side effects such as occlusal changes, administration of a custom-fitted device by a qualified dentist is recommended, resulting in a comparable economic burden as for CPAP and limiting its widespread availability. Other alternatives such as upper airway surgeries and implantation of a hypoglossal nerve stimulator are reserved for even fewer patient populations. It is therefore a clinical reality that a large fraction of OSA patients remain untreated and thus at risk of OSA sequelae.

Endotype-Targeted Therapy as a Potential Rescue Strategy
Thanks to the pioneering work of Dr Malhotra and Dr Owens (PI's mentors & co-investigators) and others it is now accepted that OSA is a multifactorial disease caused by the interplay of an anatomical predisposition and at least three non-anatomical physiological traits or endotypes: poor pharyngeal muscle recruitment, unstable ventilatory control (high loop gain), and low arousal threshold (waking up too easily). A detailed discussion of these endotypes and their various implications can be found in a review article that we recently published.[1] Thus, we will just highlight a few key aspects relevant for this study here:

a.) Endotypes can be Measured: Using a validated custom algorithm modeling ventilatory drive from ventilation data, it is possible to quantify endotypes from routine polysomnography data.[2]

b.) Single-Drug Manipulation of Endotypes Partially Improves OSA: Several single-intervention studies have demonstrated the feasibility and efficacy of manipulating non-anatomical traits pharmacologically:

- **Arousal Threshold:** Following an airway obstruction, build-up of respiratory stimuli usually results in gradual recruitment of pharyngeal muscles restoring airway patency and thus stable sleep and breathing, unless premature awakening occurs. Consequently, in a small cross-over randomized placebo-controlled trial the hypnotic **eszopiclone** 3mg increased the arousal threshold (sleeping deeper) by 29% and improved the AHI by 23% in unselected OSA patients.[3]

- **Pharyngeal muscle recruitment:** Augmentation of pharyngeal muscle tone via an implanted hypoglossal nerve stimulator improves OSA severity by about 70%, demonstrating the importance of this endotype. Recent pharmaceutical attempts to augment upper airway tone primarily aimed to increase norepinephrine levels. E.g. in one small study of the noradrenergic tricyclic antidepressant desipramine improved pharyngeal muscle recruitment but simultaneously lowered (i.e. worsened) the arousal threshold (waking up easier) thus resulting in near zero net-effect with regards to OSA severity. We found similar results when testing the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine 50mg vs placebo in a recently completed trial (IRB#141272; manuscript in peer review). Importantly, results from our study

suggest that venlafaxine combined with a drug that increases the arousal threshold (e.g. eszopiclone) may improve the AHI by ~19%.

- Unstable ventilatory control (high loop gain, LG): In high LG conditions such as central or complex sleep apnea ventilatory instability may result in frank periodic breathing; in OSA, loop gain primarily amplifies the effect of respiratory disruptions caused by other traits by delaying the return to stable breathing. For example, an apnea due to compromised upper airway anatomy may be followed by periods of excessive respiratory effort that may lead to arousals from sleep. Consequently, in a small cross-over randomized trial acetazolamide significantly reduced loop gain (-41%) and improved OSA severity by ~50% in unselected OSA patients.[4]

Summary of Background & Significance

Novel, patient-acceptable therapies are urgently needed to reduce the large fraction of untreated OSA patients – drug therapy promises to be the answer but so far has remained elusive. Results from single-intervention therapies informed by recent insights in OSA pathophysiology have been promising, but on average provided only partial relief. To achieve full resolution the next frontier in pharmacological OSA research is multi-drug therapy. This study will address the following scientific gaps:

1.) Theoretically and based on limited data, the combination of drugs targeting different underlying mechanisms/endotypes of OSA should be additive/synergistic. This study will test this concept and will be the first study assessing the efficacy of combination therapy with acetazolamide+eszopiclone for OSA.
2.) It is largely unknown what proportion of subjects could be treated with single vs dual vs triple therapy, and if baseline endotypes (i.e. quantified from the placebo night) can predict response to these different regimens (i.e. help personalize treatment).

8. PROGRESS REPORT

N/A

9. RESEARCH DESIGN AND METHODS

We propose a phase II trial: all drugs are FDA approved and the dosages in the study are prescribed clinically. Phase I trials using the doses of Acetazolamide (AZM), Venlafaxine (VFX), and Eszopiclone (ESZ) we intend to use have been successfully completed.[5-7]

AIM 1: Determine the Efficacy of Dual-Drug Therapy for OSA

Rationale: In most cases, single-drug therapy with acetazolamide or eszopiclone improves, but does not resolve OSA. The goal of this aim is to assess the efficacy of combination therapy with acetazolamide+eszopiclone, two drugs that each target a different underlying mechanism.

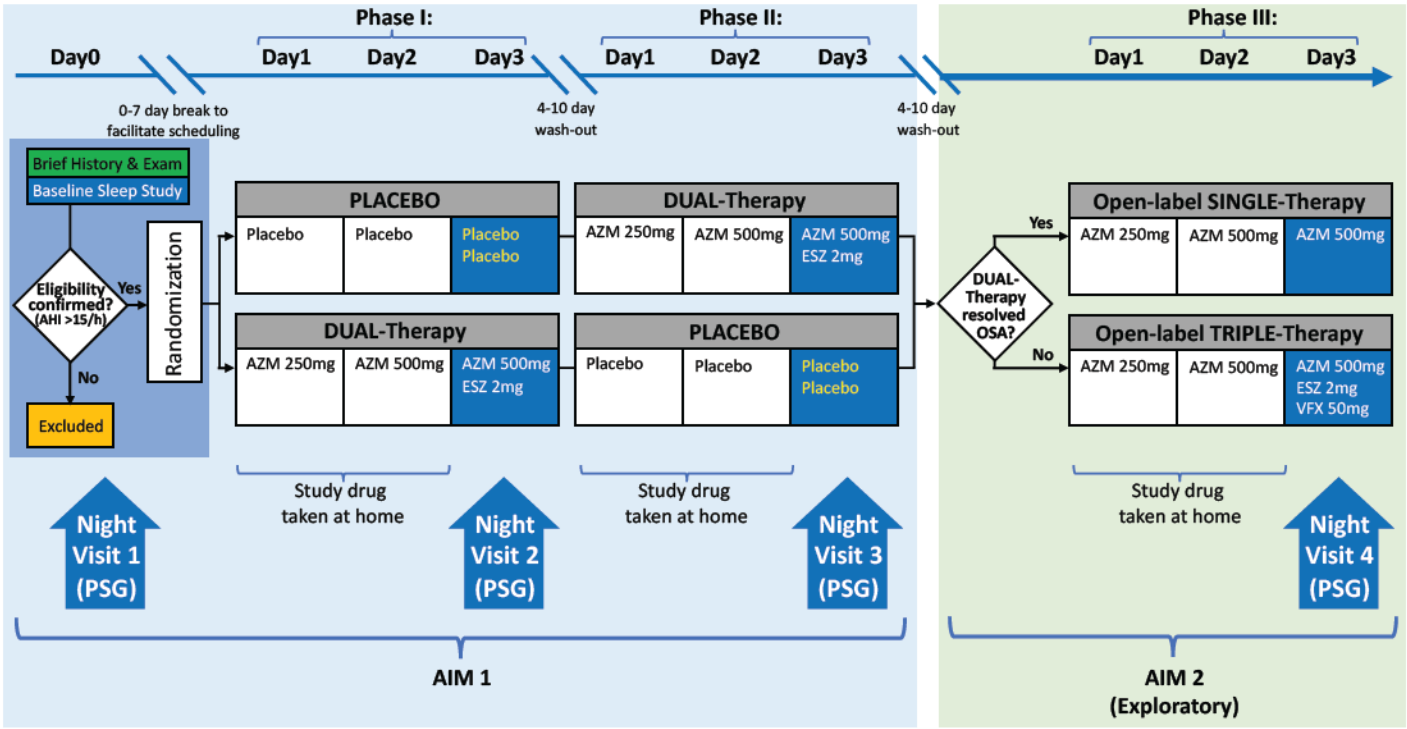

Figure 1. Study Design & Timeline. AZM Acetazolamide, VFX Venlafaxine, ESZ Eszopiclone, PSG Polysomnography. Drugs will be administered 30minutes before bedtime on the days shown. For more details see text.

Approach: This is a randomized, double-blind, placebo-controlled cross-over trial.

Details of the study design are shown in Figure 1. As described in section 10 & 11 we will identify eligible subjects from various sources. One of the key inclusion criteria is a prior diagnosis of OSA with an AHI>15/h. Subjects who screen positive but in whom the current AHI is unclear (e.g. weight loss since prior sleep study) will be offered a home sleep test (optional) to confirm eligibility prior to the in-lab baseline assessment described next.

Subjects who screen positive will be invited for a baseline assessment (Figure 1, "night visit 1") to further confirm final eligibility: after written informed consent has been obtained, the subjects who screened positive will undergo a baseline history, exam and sleep study in our sleep research laboratory. If eligibility is confirmed (e.g. apnea-hypopnea index, $AHI_{NREM,supine}$>15/h) subjects will be included in the trial, else subjects will be excluded from further study. Subjects who are included in the trial, will undergo two phases (acetazolamide+eszopiclone [AZM+ESZ] vs placebo) in random order. In between phases there will be a wash-out period of 4-10 days. Of note, eszopiclone will only be taken during the in-lab overnight sleep study. Thirty minutes before bed, a sleep technologist will provide eszopiclone to the study participant and observe them take it. During the placebo phase subjects will receive an equal number of identical appearing pills. On days 1&2 of each phase subjects will take the assigned study drug (AZM vs placebo) at bedtime at home; on day 3 of each phase subjects will be given the study drugs (AZM+ESZ vs placebo) under supervision and be observed overnight in the sleep laboratory. UCSD ACTRI Investigational Drug Service will manufacture, store and dispense all study drugs, Active Drug and Matching Placebo for this study. Study drugs and Matching Placebo will be stored following USP-797 standards or packaging label accordingly. When the subject has been randomized, the ACTRI drug service will release the study drugs to our research group. All drugs will be stored in a locker/safe, which will then be placed in the PI's locked cabinet.

The following procedures will be undertaken:

Daytime Visit #1 (45 minutes; only if a home sleep apnea test is needed for screening)

Subjects who have not had a sleep study in the past 3 months or in whom a previous clinical sleep study is not available will be instructed on the use of a Home Sleep Test (HST) device. An HST is a small non-invasive diagnostic device worn for one night at home, with a nasal cannula to monitor airflow, an elastic chest band to monitor breathing effort, and a finger probe to monitor oxygen saturation and heart rate. The HST will be returned in person 1-2 days after it is completed. The results of the HST will be scored. If the subject's AHI is ≥ 15/h, the subject will be scheduled for overnight visit 1. This screening HST serves to avoid unnecessary baseline studies in the sleep lab.

Overnight Visit #1 (10-12h)

1. *Anthropomorphic & medical history (30-45min):* After signing written informed consent, baseline demographics and health status (OSA symptoms, medical problems, medications, allergies, social history) will be obtained. A basic exam, including height, weight, neck, hip, and waist circumference, blood pressure, and oxygen saturation will be obtained.

   Polysomnography: Monitoring for standard clinical polysomnography study will be applied to the subject, as follows: The subject will have EEG, EMG, EOG, and ECG electrodes, an adhesive body position sensor placed in standard locations. Pulse oximetry sensor will be attached either to a finger or ear lobe and secured by tape. The following parameters will be measured during sleep: electroencephalogram, eye movement, electrocardiogram, electromyogram, leg movement, snoring sounds, nasal pressure, and nasal-oral airflow by thermistor, respiratory effort and body position by piezo-electric bands of the thorax and abdomen or magnetometers, position sensors, and pulse oximetry. This equipment is standard for diagnostic polysomnography and should not be uncomfortable. Once all of this equipment has been comfortably and securely fastened, the subject will be allowed to fall asleep and data recording will begin. Subjects will be asked to remain in the supine position as much as possible. All data will be acquired on a Nihon Kohden. The study will end at approximately 6 AM, at which time the monitoring equipment will be removed. However, if the subject is still sleepy, they will be allowed to sleep until they feel rested.
2. *Sleepiness Measurement:* In the morning, 30-minutes after the final awakening, subjects will be given the following standard sleep questionnaires prior to caffeine to assess sleepiness: Stanford Sleepiness Scale (SSS), Karolinska Sleepiness Scale (KSS), Promis Sleep Disturbance SF 8.
3. *PVT:* Objective assessment of brain function will be done using 10-minute psychomotor vigilance test (PVT). In this computerized reaction assessment, the subject will be asked to quickly press the spacebar every instance a red dot appears on the screen.
4. *Blood Pressure:* The technician will obtain blood pressure following standard procedures.
5. *Randomization/Study drugs:* **The overnight study will be scored in real-time during the study, thus at the latest within one hour of its completion we will know if a subject meets eligibility criteria for inclusion into the randomized trial**: Ineligible subjects will receive their remuneration but will be excluded from further studies. Eligible subjects will be randomized and receive their assigned study drug (AZM vs placebo) to be taken at bedtime at home for 2 days. Subjects will be instructed on what day to start taking the study drug and when to return to the ACTRI sleep laboratory for administration of the 3rd dose of the assigned study regimen.

Weekly Phone Calls

After each wash out period is completed, subjects will be called to be reminded when to begin taking their study medication.

Overnight Visit #2 (10-12h)

Subjects will arrive to the research sleep laboratory at approximately 8PM and undergo the following procedures:

1. *Vitals and Pill Count:* The technician will obtain blood pressure, and oxygen saturation. They will also verify that the study drug was taken according to the instructions provided.
2. *Medications:* Thirty minutes before sleep, subjects will be provided with either AZM+ESZ or placebo.
3. *Polysomnography:* Monitoring for standard clinical polysomnography study will be applied to the subject, as follows: The subject will have EEG, EMG, EOG, and ECG electrodes, an adhesive body position sensor placed in standard locations. Pulse oximetry sensor will be attached either to a finger or ear lobe and secured by tape. The following parameters will be measured during sleep: electroencephalogram, eye movement, electrocardiogram, electromyogram, leg movement, snoring sounds, nasal pressure, and nasal-oral airflow by thermistor, respiratory effort and body position by piezo-electric bands of the thorax and abdomen or magnetometers, position sensors, and pulse oximetry. This equipment is standard for diagnostic polysomnography and should not be uncomfortable. Once all of this equipment has been comfortably and securely fastened, the subject will be allowed to fall asleep and data recording will begin. Subjects will be asked to remain in the supine position as much as possible. All data will be acquired on a Nihon Kohden. The study will end at approximately 6 AM, at which time the monitoring equipment will be removed. However, if the subject is still sleepy, they will be allowed to sleep until they feel rested.
4. *Sleepiness Measurement:* In the morning, 30-minutes after the final awakening, subjects will be given the following standard sleep questionnaires prior to caffeine to assess sleepiness: Stanford Sleepiness Scale (SSS), Karolinska Sleepiness Scale (KSS), Promis Sleep Disturbance SF 8.
5. *PVT:* Objective assessment of brain function will be done using 10-minute psychomotor vigilance test (PVT). In this computerized reaction assessment, the subject will be asked to quickly press the spacebar every instance a red dot appears on the screen.
6. *Blood Pressure:* The technician will obtain blood pressure following standard procedures.
7. *Phlebotomy*: Venipuncture will be performed by a certified research staff or physician using standard techniques and appropriate blood borne pathogen precautions. Approximately 15-20 cc of blood will be drawn in the evening or morning at wake into serum separator, plasma separator and EDTA tubes. Serum samples will be immediately processed to separate serum, which will be stored in darkness at -70°C to preserve until analysis can be conducted. EDTA tubes will be processed and refrigerated for use within 24 hours. DNA will be isolated from the buffy coat in the EDTA tubes to examine entire genome sequence, targeted sequence, or select genetic markers to search for genotype-phenotype relationships. Blood will also be collected to measure bicarbonate, high sensitivity C Reactive Protein (hsCRP), insulin, glucose (to calculate HOMA-IR), and cytokines such as IL-6 and TNF-alpha. Leukocytes from whole blood will be isolated for transcriptomic analysis. We will also store plasma for other potential markers, to explore other interactions, such as markers of liver disease like ALT and AST. Total RNA, including microRNAs, will be used to assess changes in gene expression. Fluids collected may be stored indefinitely and/or used in additional research to be conducted by sleep research study investigators conducting IRB approved research. Samples and data collected in the course of the study will be banked and may be sent to other research scientists anonymously (without identification).
8. *Study Drugs:* Before leaving, subjects will receive the study drugs for the second study phase.

After a 4-10 day wash-out period, the study drug (AZM vs placebo) is to be taken daily at home for 2 days. Subjects will be instructed on what day to start taking the study drug and when to return to the ACTRI sleep laboratory for the second overnight visit.

Overnight Visit #3 (10-12h)

Subjects will return to the sleep laboratory at 8PM for another overnight study and undergo the same procedures as during overnight visit #1:

1. *Vitals and Pill Count:* The technician will obtain blood pressure, and oxygen saturation. They will also verify that the study drug was taken according to the instructions provided.
2. *Medications:* Thirty minutes before sleep, subjects will be provided with either AZM+ESZ or placebo.
3. *Polysomnography:* Monitoring for standard clinical polysomnography study will be applied to the subject, as follows: The subject will have EEG, EMG, EOG, and ECG electrodes, an adhesive body position sensor placed in standard locations. Pulse oximetry sensor will be attached either to a finger or ear lobe and secured by tape. The following parameters will be measured during sleep: electroencephalogram, eye movement, electrocardiogram, electromyogram, leg movement, snoring sounds, nasal pressure, and nasal-oral airflow by thermistor, respiratory effort and body position by piezo-electric bands of the thorax and abdomen or magnetometers, position sensors, and pulse oximetry. This equipment is standard for diagnostic polysomnography and should not be uncomfortable. Once all of this equipment has been comfortably and securely fastened, the subject will be allowed to fall asleep and data recording will begin. Subjects will be asked to remain in the supine position as much as possible. All data will be acquired on Nihon Kohden. The study will end at approximately 6 AM, at which time the monitoring equipment will be removed. However, if the subject is still sleepy, they will be allowed to sleep until they feel rested.
4. *Sleepiness Measurement:* In the morning, 30-minutes after the final awakening, subjects will be given the following standard sleep questionnaires prior to caffeine to assess sleepiness: Stanford Sleepiness Scale (SSS), Karolinska Sleepiness Scale (KSS), Promis Sleep Disturbance SF 8.
5. *PVT:* Objective assessment of brain function will be done using 10-minute psychomotor vigilance test (PVT). In this computerized reaction assessment, the subject will be asked to quickly press the spacebar every instance a red dot appears on the screen.
6. *Blood Pressure:* The technician will obtain blood pressure following standard procedures.
7. *Phlebotomy*: Venipuncture will be performed by a certified research staff or physician using standard techniques and appropriate blood borne pathogen precautions. Approximately 15-20 cc of blood will be drawn in the evening or morning at wake into serum separator, plasma separator and EDTA tubes. Serum samples will be immediately processed to separate serum, which will be stored in darkness at -70°C to preserve until analysis can be conducted. EDTA tubes will be processed and refrigerated for use within 24 hours. DNA will be isolated from the buffy coat in the EDTA tubes to examine entire genome sequence, targeted sequence, or select genetic markers to search for genotype-phenotype relationships. Blood will also be collected to measure bicarbonate, high sensitivity C Reactive Protein (hsCRP), insulin, glucose (to calculate HOMA-IR), and cytokines such as IL-6 and TNF-alpha. Leukocytes from whole blood will be isolated for transcriptomic analysis. We will also store plasma for other potential markers, to explore other interactions, such as markers of liver disease like ALT and AST. Total RNA, including microRNAs, will be used to assess changes in gene expression. Fluids collected may be stored indefinitely and/or used in additional research to be conducted by sleep research study investigators conducting IRB approved research. Samples and data collected in the course of the study will be banked and may be sent to other research scientists anonymously (without identification)

Data Analysis: Primary outcome will be the change in AHI (during supine non-rapid eye movement

[NREM] sleep) from baseline to dual-therapy vs placebo which will be compared using a paired t-test (i.e. AZM&ESZ-baseline vs placebo-baseline). Secondary outcomes will be compared similarly and include other measures of OSA severity (e.g. SpO_2 nadir), measures of sleep quality, blood pressure, sleepiness and vigilance. Further we will determine the proportion (+95% confidence interval) of subjects who fully responded (drop in AHI>50% to <10/h). Non-parametric alternatives will be considered, if parametric assumptions fail. Furthermore, we will test if endotypes or changes in serum bicarbonate predict response using linear/logistic regression.

Sample size: 20 patients will give a power of >0.8 to detect a 50% (±75%) reduction in $AHI_{NREM,supine}$ (primary outcome; equivalent to a reduction by 15 ± 22.5/h from 30/h) with an alpha level of 0.05 (pwr.t.test, R). To account for attrition we plan to enroll up to 40 subjects.

AIM 2 Explore the Efficacy of Single and Triple-Drug Therapy for OSA

Rationale: Based on the response of subjects in aim 1, this aim will explore if

a.) subjects **who responded** to dual-therapy (AZM+ESZ) could also be treated with single-drug therapy (i.e. AZM alone);

b.) subjects **who did not respond** to dual-therapy (AZM+ESZ) could be "rescued" by addition of venlafaxine (VFX), a drug targeting a third mechanism (i.e. triple therapy with AZM+ESZ+VFX).

Approach: As shown in Figure 1, for this exploratory aim, subjects whose OSA resolved (AHI reduction by >50% and AHI<10/h) will undergo a third, open-label phase of single-therapy (AZM); conversely, subjects whose OSA did not resolve with dual-therapy will undergo a third, open-label phase of triple therapy (AZM+ESZ+VFX). As in aim 1, AZM will be administered for 2 days at home, and on the 3rd day subjects will receive the final dose of AZM or AZM+ESZ+VFX in the ACTRI sleep lab where a fourth overnight study will be performed with the following procedures:

Overnight Visit #4 (10-12h)

1. *Vitals and Pill Count:* The technician will obtain blood pressure, and oxygen saturation. They will also verify that the study drug was taken according to the instructions provided.
2. *Medications:* Thirty minutes before sleep, subjects will be provided with either AZM or AZM+ESZ+VFX.
3. *Polysomnography:* Monitoring for standard clinical polysomnography study will be applied to the subject, as follows: The subject will have EEG, EMG, EOG, and ECG electrodes, an adhesive body position sensor placed in standard locations. Pulse oximetry sensor will be attached either to a finger or ear lobe and secured by tape. The following parameters will be measured during sleep: electroencephalogram, eye movement, electrocardiogram, electromyogram, leg movement, snoring sounds, nasal pressure, and nasal-oral airflow by thermistor, respiratory effort and body position by piezo-electric bands of the thorax and abdomen or magnetometers, position sensors, and pulse oximetry. This equipment is standard for diagnostic polysomnography and should not be uncomfortable. Once all of this equipment has been comfortably and securely fastened, the subject will be allowed to fall asleep and data recording will begin. Subjects will be asked to remain in the supine position as much as possible. All data will be acquired on Nihon Kohden. The study will end at approximately 6 AM, at which time the monitoring equipment will be removed. However, if the subject is still sleepy, they will be allowed to sleep until they feel rested.
4. *Sleepiness Measurement:* In the morning, 30-minutes after the final awakening, subjects will be given the following standard sleep questionnaires prior to caffeine to assess sleepiness: Stanford Sleepiness Scale (SSS), Karolinska Sleepiness Scale (KSS), Promis Sleep Disturbance SF 8.
5. *PVT:* Objective assessment of brain function will be done using 10-minute psychomotor vigilance test

(PVT). In this computerized reaction assessment, the subject will be asked to quickly press the spacebar every instance a red dot appears on the screen.

6. *Blood Pressure:* The technician will obtain blood pressure following standard procedures.
7. *Phlebotomy*: Venipuncture will be performed by a certified research staff or physician using standard techniques and appropriate blood borne pathogen precautions. Approximately 15-20 cc of blood will be drawn in the evening or morning at wake into serum separator, plasma separator and EDTA tubes. Serum samples will be immediately processed to separate serum, which will be stored in darkness at -70°C to preserve until analysis can be conducted. Tubes will be processed and refrigerated for use within 24 hours. DNA will be isolated from the buffy coat in the EDTA tubes to examine entire genome sequence, targeted sequence, or select genetic markers to search for genotype-phenotype relationships. Blood will also be collected to measure bicarbonate, high sensitivity C Reactive Protein (hsCRP), insulin, glucose (to calculate HOMA-IR), and cytokines such as IL-6 and TNF-alpha. Leukocytes from whole blood will be isolated for transcriptomic analysis. We will also store plasma for other potential markers, to explore other interactions, such as markers of liver disease like ALT and AST. Total RNA, including microRNAs, will be used to assess changes in gene expression. Fluids collected may be stored indefinitely and/or used in additional research to be conducted by sleep research study investigators conducting IRB approved research. Samples and data collected in the course of the study will be banked and may be sent to other UCSD research scientists. The blood samples will not be shared with other researchers/institutions outside of University of California, San Diego.

Data Analysis: Primary outcomes will be the change in $AHI_{NREM,supine}$ from baseline to single or triple therapy vs placebo, respectively, which will be compared using a paired t-test. Secondary outcomes will be compared similarly and include other measures of OSA severity (e.g. SpO_2 nadir), measures of sleep quality, blood pressure, sleepiness and vigilance. Further we will determine the proportion (+95% confidence interval) of subjects who fully responded (drop in AHI>50% to <10/h). Non-parametric alternatives will be considered, if parametric assumptions fail. Furthermore, we will test if endotypes or changes in serum bicarbonate predict response using linear/logistic regression. Moreover, we will determine the proportion (+95% confidence interval) of subjects who fully responded (drop in AHI>50% to <10/h) to single or triple therapy, and use linear/logistic regression to test if endotypes predict response to the different combinations.

Sample Size: Since aim 2 is an exploratory aim no separate sample size calculation has been performed.

IND Exemption

For this trial we will administer acetazolamide 500mg PO and/or venlafaxine 50mg PO and/or eszopiclone 2mg PO. All three drugs are commonly used (PO) and safe. Further, we carefully chose dosages and eligibility criteria to minimize associated risks. FDA approved indications include glaucoma, epilepsy, high and altitude sickness for acetazolamide, insomnia for eszopiclone, and depression and anxiety for venlafaxine. Patients with sleep apnea were not excluded from the pivotal trials leading to these indications, and in clinical practice OSA patients do often get treated with these medications for comorbid conditions. In fact, there have been small trials demonstrating that acetazolamide[4], eszopiclone[3] and venlafaxine[IRB#141272; in peer review] improve obstructive sleep apnea in patients with similar characteristics as will be enrolled in the RESCUE-Drug trial. Thus, we believe that the proposed RESCUE-Drug trial qualifies for an IND exemption. Specifically:

(i) This investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drugs.

(ii) The drugs that are undergoing investigation are lawfully marketed as prescription drug products, but the investigation is not intended to support a significant change in the advertising for the products.

(iii) This investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug products.

(iv) This investigation will be conducted in compliance with the requirements for institutional review set forth in 21 CFR Part 56 and with the requirements for informed consent set forth in part 50.

(v) This investigation will be conducted in compliance with the requirements of 21 CFR 312.7.

The FDA has provided a letter confirming that this study meets criteria for an IND exemption.

10. HUMAN SUBJECTS

We will recruit up to 40 adult OSA patients who are untreated and meet the following eligibility criteria:

Inclusion Criteria:

- Age 18-65 years
- BMI 18-40 kg/m^2
- Untreated Moderate or Severe OSA ($AHI_{NREM,supine}$>15/h) with a fraction of hypopneas >25% of all events

Exclusion Criteria:

- Pregnancy
- Breastfeeding
- Prisoners
- Adherent with effective therapy for OSA
- Other known untreated sleep fragmenting disorder, such as periodic limb movement disorder, or narcolepsy
- Inability to sleep supine for overnight sleep studies
- Circadian rhythm disorder
- Unrevascularized coronary artery disease, angina, prior heart attack or stroke, congestive heart failure
- Uncontrolled hypertension (SBP >160, DBP >95)
- Presence of tracheostomy
- Hospitalization within the past 90 days
- Prior peptic ulcer disease, esophageal varicies, or gastrointestinal bleeding (< 5 years)
- Prior gastric bypass surgery
- Chronic liver disease or end-stage kidney disease
- Active illicit substance use or >1.2 oz daily alcohol use (i.e. >2 12 oz bottles of beers, >2 5 oz glasses of wine, >2 1.5 oz glasses of hard liquor (spirits, gin, whiskey, etc.)
- Psychiatric disease, other than well controlled depression/anxiety
- Cognitive impairment, inability to provide consent, or inability to complete research procedures (e.g. questionnaires that are only available/validated in English)
- Chronically using study drugs or drugs with similar pharmacodynamic effects (acetazolamide - carbonic anhydrase inhibitors, eszopiclone – benzodiazepine receptor agonists, venlafaxine – serotonin/norepinephrine reuptake inhibitors and other antidepressants)
- Regular use of medications known to affect control of breathing (opioids, benzodiazepines, theophylline)
- Contraindications to taking study drugs, including allergies to any of the drugs or sulfa allergy; concomitant use of antidepressants, opioids, sedatives/hypnotics, thiazide diuretics or angiotensin-receptor blockers; or severe nocturnal hypoxia (SpO_2 nadir <70% on diagnostic sleep study).

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Subjects will be recruited from the following sources: 1) IRB-approved flyers or advertisements, with prospective subjects initiating contact with the research staff, 2) Persons who have participated in prior research studies from our laboratory or affiliated laboratories who have indicated that they would like to be contacted to hear about potential research studies, 3) Patients from the UCSD Pulmonary and Sleep Center who have indicated that they are interested in hearing about research opportunities, and 4) Persons who have been identified via SlicerDicer.

Identifying Eligible Subjects with Partial HIPAA Waiver

A temporary waiver of consent and partial waiver of HIPAA authorization is requested for this study in order to: 1) Pre-screen persons (from sources 2 and 3 above) who meet the inclusion and exclusion criteria, and 2) Perform telephone or in-person interviews with potential subjects for screening of inclusion and exclusion criteria prior to obtaining consent. The following points justify the waiver of consent: 1) Private information that will be reviewed is non-sensitive, and anyone pre-screened will have previously agreed to contact for research, 2) No research procedures will be performed without consent, so there should be minimal possibility of adverse effect on potential subjects, 3) Adequate enrollment could not be achieved without accessing this information, since specific medical conditions are being investigated, 4) All persons contacted will be provided with information about our screening procedures. For the partial HIPAA authorization: 1) Any PHI accessed for screening will be kept by research staff until either consent is obtained, or it will be destroyed immediately if consent and HIPAA authorization is not obtained, 2) Identifying potential subjects and then contacting/approaching them to discuss the research will require accessing PHI, 3) Minimal necessary PHI will be accessed and kept only temporarily while that subject is being screened, as above, 4) PHI will only be accessed by members of the research team included in the IRB, and will include name, date of birth, medical record number, contact information, diagnoses and dates of diagnostic tests.

SlicerDicer

Slicer Dicer will be used to identify both Summary & Patient Level Requests:
Researchers plan to use UC San Diego Health's Epic SlicerDicer, a self-service cohort discovery tool. Researchers will have access to direct summary and patient level data. Using SlicerDicer, researchers will: Review the charts at a patient level to identify potential patients for recruitment. We will be identifying patients based on the inclusion/exclusion study criteria. We will create a call list with the patient's name, phone number, and email address. This call list will be stored digitally under password protection on a UCSD secured drive shared between the research team. Once identified, an investigator of the study team will contact the patient to ask if he/she is interested in hearing about sleep medicine research study opportunities. If yes, the study team member will provide full details about the study. If no, the patient will be removed from our call list. MRNs of uninterested patients will be retained on a no-call list. All Epic Slicer Dicer users will have access and security provided by UCSD's Epic access team.

If a potential subject does not answer their phone, we will leave a voicemail stating the name of the researcher calling, ask if they may be interested in participating in a sleep research study, and provide our call back number and email address to reach us, if interested.

Prospective subjects will also be recruited from the community after individuals have initiated contact with the research staff. Permission to distribute IRB approved messages and flyers is being requested for the following sites and locations:

UCSD Listserve, UCSD Hospital Bulletin Board, Facebook, Craigslist, UCSD CTRI REDCap Survey
IRB approved flyers will be digitally posted on the UCSD Listserv, Facebook, and Craigslist. The flyers will also be placed on UCSD Hospital Bulletin Boards by the Community Engagement Manager for the Clinical Transitional Research Institute (CTRI).

Facebook Page Welcome Message
We are requesting permission to have this message posted on a Facebook page created for recruitment purposes:

> Welcome to the UCSD Pulmonary and Sleep Medicine Research group's Facebook page. We have ongoing research studies, primarily investigating obstructive sleep apnea. If you or someone you know has obstructive sleep apnea, please see our IRB approved flyers below. Occasionally, we are looking for healthy individuals without sleep disorders. Please regularly check our page for flyers describing these research opportunities.

Research Match
ResearchMatch will be used to contact prospective subjects with an IRB approved recruitment message. The message will be submitted for approval in an amendment if it is not already included with the initial project submission.

Research Group Website
The UCSD Pulmonary and Sleep Medicine Research group has a webpage hosted by UCSD health sciences. Wording from IRB approved flyers will be posted there.

UCSD CTRI REDCap Survey
Prospective subjects can voluntarily choose to fill out a UCSD CTRI REDCap Survey for this protocol. Information will be securely collected and stored via REDCap and will be used to determine if the prospective subject is eligible for the study.

12. INFORMED CONSENT

The research coordinator will screen the subjects over the telephone (or in person for clinic patients, time and patient preference allowing) following the screening script. A waiver of documented consent will be requested and once oral consent by the subject is obtained this consent will be used for the sole purpose of discussing the study with the subjects over the phone and performing the screening process as needed. The reason for this is because the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Individuals interested in participating in this study will be given detailed explanation of the procedures, potential benefits, risks and discomforts of the study by the study researchers listed in the IRB application. All study staff are CITI certified and the importance of following GCP and HIPAA rules has been impressed upon them by the PI. Staff obtaining consent will have sufficient knowledge of the study to answer any questions that might arise during the consent process.

A copy of the consent form will be given to the potential subject by email a minimum of 48 hours in advance of any planned baseline visit. If the individual agrees to participate, they will meet with research staff in person prior to any data collection to obtain written informed consent. Subjects who have given a written consent will be given a copy of the signed consent form. The original consent and HIPAA authorization will be kept in the subject's research file in a locked cabinet. No research procedures will be performed prior to obtaining informed consent.

English will be used in all discussions during the consent process. The patient will be excluded from the study if their preferred language is one other than English or if they do not understand English. The information being communicated will not include any exculpatory language through which the potential subject will waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the University or its agents from liability for negligence. Subjects unable to give their own consent will not be included in the study.

13. ALTERNATIVES TO STUDY PARTICIPATION

This study aims to test if certain investigational interventions can improve OSA severity in patients who declined or are not adherent with standard therapies.

Thus, the alternative to study participation is continued follow up with his/her healthcare provider.

14. POTENTIAL RISKS

Overall, we believe there are few risks to participants in this study. In the following is a list of all the study procedures, their associated risks and the risk mitigation strategies:

1. *Screening* will be based on a query and review of the electronic medical records. Further eligibility assessment will be based on a conversation with subjects who screened positive, either over the phone or in person. The main risk is breach of privacy which will be mitigated by ensuring conversations are private (i.e. no one can overhear it) and storing any resultant data in the secure REDCap database. Our research team undergoes extensive CITI and other training modules on an annual basis; further, we are well versed with this process and the critical importance of maintaining privacy.
2. *Standard home sleep apnea test:* Select subjects who screen positive, but in whom the OSA diagnosis is unclear will undergo a home sleep apnea test as part of the screening process. The nasal cannula, respiratory belts, and oximeter used to monitor sleep and breathing may be mildly uncomfortable and could interfere with normal sleep. Thousands of routine home sleep studies are conducted every night across the country without incident.
3. Subjects who are eligible based on screening will undergo a in-person visit to sign consent..
4. *Anthropomorphic & medical history:* Baseline demographics and health status (OSA symptoms, medical problems, medications, allergies, social history) will be obtained. A basic exam, including height, weight, neck, hip, and waist circumference, blood pressure, and oxygen saturation will be obtained. Assessment will occur in a private space in the research clinic and data will be directly entered into the REDCap database via eCFRs by staff to minimize any risk of privacy breach. Other potential risks include mild inconvenience, frustration, boredom, and fatigue from completing these assessments.
5. Following this baseline assessment, subjects will undergo a baseline overnight sleep study to confirm eligibility. *Standard Polysomnography:* The nasal cannula, respiratory belts, electroencephalography, ECG and oximeter used to monitor sleep and breathing may be mildly uncomfortable and could interfere with normal sleep. Thousands of routine sleep studies are conducted every night across the country without incident.

Subjects who are found to be ineligible (e.g. AHI<15/h) will receive remuneration for this baseline assessment but will be excluded from further study. Subjects whose eligibility is confirmed, will be provided with a 2-day supply of the randomly assigned study drug (AZM vs placebo) to be taken at home, with clear instructions of how and when to use them. During this period subjects will be able to contact research staff at any time to seek clarifications and/or report any side effects. On the 3rd day subjects will receive either

AZM+ESZ or placebo just prior to an overnight sleep study. Furthermore, after completion of aim 1, subjects will undergo a third phase of open-label therapy with either single or triple therapy. Similar as for aim 1, subjects will be provided with a 2-day supply of acetazolamide with clear instructions of how and when to use it; on the 3rd day subjects will receive either AZM alone (single therapy) or AZM+ESZ+VFX (triple therapy) just prior to an overnight sleep study. For both aims, subjects will be monitored for at least 8h following the administration of the study drugs in the laboratory:

6. *Standard Polysomnography:* The nasal cannula, respiratory belts, electroencephalography, ECG and oximeter used to monitor sleep and breathing may be mildly uncomfortable and could interfere with normal sleep. Thousands of routine sleep studies are conducted every night across the country without incident.
7. *Sleepiness Measurement:* this assessment will include the psychomotor vigilance test (10 minute assessment of reaction speed on a laptop) and some more questionnaires (e.g. Stanford Sleepiness Score). Risks and mitigation strategies are the same as for the assessment of "*Anthropomorphic & medical history*" discussed above.
8. *Venipuncture:* Phlebotomy is a commonly performed procedure with no major risk apart from local discomfort, dizziness, bruising, hematoma and theoretically infection. There have not been observed major complications from this procedure in the context of our research studies.
9. *Study Drugs:* All drugs are generally safe and well-tolerated. The safety data for acetazolamide, venlafaxine, and eszopiclone are reviewed below. No significant adverse interactions between these three drugs are expected. The risk of severe adverse events is expected to be very low (<1%), and there are multiple safeguards in place ranging from careful dose selection and exclusion of patients with risk factors that could increase the risk of side effects, to close monitoring including 24/7 availability of research staff while subjects take acetazolamide vs placebo at home and overnight observation of subjects after ingestion of combination therapy (acetazolamide+venlafaxine+eszopiclone vs placebo).
    a) Acetazolamide (brand name Diamox) has been used for more than 60 years and is still commonly prescribed for various conditions such as prevention of high-altitude sickness. It is a carbonic anhydrase-inhibitor causing bicarbonate diuresis and thus mild metabolic acidosis with resultant increase of minute ventilation, which helps to stabilize ventilatory control (i.e. lowers loop gain). Acetazolamide up to 1000mg is generally well tolerated. Common side effects are paresthesias (tingling sensation in extremities), altered taste when drinking carbonated beverages, slightly increased urination, and fatigue. All of these side effects are fully reversible upon discontinuation of the drug; further, most of these side effects are dose-dependent and thus less likely with the low-dose (500mg) we plan to use. Severe adverse events are virtually limited to patients with certain characteristics that will be excluded from this study (e.g. patients taking thiazide diuretics or angiotensin-receptor blockers will be excluded due to risk of hypokalemia).
    a. Eszopiclone (brand name Lunesta) is a well-tolerated hypnotic which has been evaluated for insomnia in several large clinical trials in which >1000 patients were followed for 6 or more months, and has been used in sleep medicine practice for more than a decade. Note, that OSA frequently co-exists with insomnia (some studies report a co-prevalence up to 69%) and in the above cited trials there was no specific screening to identify and exclude patients with OSA, therefore the resultant safety data are generalizable to OSA patients. Common side effects include: metallic taste in the mouth, nausea and somnolence. With regards to somnolence it is important to note, that two independent RCTs including a total of 48 healthy volunteers showed that 6.5 to 9h after ingestion there was no measurable impairment of objective psychomotor function or driving-related skills. Thus, after eszopiclone administration subjects

will be required stay 8h overnight in the research lab. Further, before leaving subjects will have to confirm in writing that they are alert and safe enough to drive. Importantly, subjects will be offered *ad libitum* sleep prior to leaving as needed. Those who continue to feel sleepy and unsafe to drive will be given a cab voucher which could be used to go home.

b. Venlafaxine (brand name Effexor) is a serotonin and norepinephrine reuptake inhibitor (SNRI). Venlafaxine was approved by the U.S. FDA for the treatment of depression in 1993. It is also approved for treatment of generalized anxiety disorder, panic disorder and social anxiety disorder. In clinical practice venlafaxine is considered safe for -and often given to- OSA patients with co-morbid mood disorders, or to treat cataplexy in patients with co-morbid narcolepsy (off-label use). Furthermore, we recently completed a randomized trial (IRB#141272) comparing one dose of venlafaxine 50mg vs placebo in OSA patients with similar characteristics as in the proposed study and found that it was overall well tolerated: Two subjects reported mild nausea shortly after venlafaxine administration which resolved within 1h; in addition, one subject complained of nausea in the morning following placebo; no serious or unanticipated problems related to venlafaxine were observed during the study. In children, adolescents, and young adults (18 to 24 years of age) with major depressive disorder (MDD) and other psychiatric disorders, venlafaxine has a very small risk of suicidal thoughts and behavioral change. Therefore, we will exclude patients with MDD or other psychiatric disorders. Adverse reactions include headache, insomnia, dizziness, diaphoresis, weight loss, nausea, xerostomia, anorexia, abnormal ejaculation and weakness. In rare cases, subjects may develop "serotonin syndrome" when venlafaxine is used in combination with other similar classes of medications or supplements that may increase the serotonin level; these symptoms include agitation, restlessness, dilated pupils and in severe cases high fever and irregular heartbeat. We will exclude subjects who are taking medications, which increase serotonin levels, therefore the likelihood of serotonin-syndrome risks is extremely low. Other rare side effects include vasodilation, palpitations, edema, anxiety, tachycardia, agitation, hypertonia, twitching, anorgasmia, paresthesia. Venlafaxine has the following common side effects: nausea, dry mouth, headache, sweating. Of note, half-life of venlafaxine is short (about 11 hours) so any potential side effects from venlafaxine should dissipate within 1-2 days.

10. *Randomization:* For aim1, participants will be assigned to one of two allocation-sequences (AZM+ESZ followed by placebo, or vice versa) in random order. Randomization is based on chance rather than a medical decision made by the researchers. Participants will have a 1 in 2 chance of being assigned to one sequence or the other. During the placebo phase subjects will receive matching placebo (a sugar pill), which has no active ingredients. The placebo pill is intended to have no effect, however, rarely individuals may experience symptoms such as constipation, nausea, or headaches. These effects should last a short time and will resolve on their own.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

PROTECTIONS AGAINST RISK

To ensure privacy and confidentiality, at no time will subject identities be revealed in any manner, whether in presentation, description or publication of the research for scientific purposes. All data obtained with subject identifiers will be kept in locked file cabinets to ensure confidentiality, and all paper file contents will be shredded before disposal. All subjects will be assigned a unique study number for use in the computer database and all electronic data are kept in password-protected computer files on secured servers to ensure confidentiality.

As above, subjects in this proposed study may not sleep well in the testing environment, and may be sleepy

the next morning after the overnight PSG. They will have the option of sleeping without equipment for as long as they would like (*ad libitum)* before leaving the sleep laboratory to avoid any risk of drowsy driving. If they do not feel rested and safe to drive home, they will be provided with a cab voucher. Participants will be encouraged to ask someone else to drive them to and from the studies, or use public transportation (which is easily available 1 block from the sleep laboratory). Subjects who drive themselves must state that they are able to drive and sign a statement to that effect prior to leaving from the testing center. If the research staff (sleep technician or physician) feel that the subject is not safe to drive home, the subject may continue to rest longer in the laboratory, or a cab voucher will be used. After taking study drugs in the lab (which may potentially include eszopiclone) subjects will be required to stay in the lab for 8 hours before driving.

It is expected that we will NOT find a new clinically relevant sleep problem given that subjects will have already undergone sleep testing and be diagnosed with OSA.

However, it may be that other abnormalities, such as a cardiac arrhythmia or very high blood pressure, are noted during the study. In that case, the investigators will go over the results with the subject as soon as possible, a copy of these results will be given to the subject and, if so requested, the subject's PCP.

In case of any potentially life-threatening findings during the study, e.g. chest pain concerning for a heart attack or symptoms concerning for a stroke etc, research staff will immediately contact PI Schmickl (or his mentors), who is board certified in internal and sleep medicine and who will evaluate the situation.

Any complications resulting from this study will be immediately reported to the UCSD HRPP. Each subject will be given 24-hour emergency contact information and will be able to contact the study PI and the study coordinator at any time regarding questions or complications.

DATA AND SAFETY MONITORING (DSM) PLAN

Given the relative low risk associated with the study, and that the majority of the interventions are commonly used in clinical practice in different contexts (e.g. eszopiclone for insomnia, and acetazolamide for central sleep apnea, venlafaxine for depression or cataplexy in narcolepsy patients), we believe that a DSM-Plan focusing on the PI (rather than a DSM-Board) to capture and promptly report abnormal clinically relevant data and adverse events is most adequate.

PI Schmickl will be responsible for overall trial monitoring and reporting to the UCSD HRPP. However, he will be assisted by his mentor team (Dr Malhotra and Dr Owens), who will help adjudicate any potential adverse event. The PI, and his mentor team will jointly review the safety data at least once annually; during these meetings all the data included in the DSM report (see below) will be reviewed.

Monitoring Procedures

We will adhere to the following definitions (based on OHRP) for categorizing and reporting events:

Adverse Event (AE): any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Events will be self-rated by subjects as mild, moderate or severe.

Serious adverse event (SAE): any adverse event that: (1) Results in death; (2) is life threatening, or places the subject at immediate risk of death from the event as it occurred; (3) Requires or prolongs hospitalization; (4) Causes persistent or significant disability or incapacity; (5) Results in congenital anomalies or birth defects; (6) is another condition which investigators judge to represent significant hazards.

Unanticipated Problem (UP): any incident, experience, or outcome that meets all of the following criteria: unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied; related or possibly related to participation in the

research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Events versus Unanticipated Problems: All adverse events are not necessarily unanticipated problems. All unanticipated problems are not necessarily adverse events. Some events may be both. Same applies to severe vs serious adverse events.

At each visit subjects will be asked about side effects in an open-ended manner. In addition, each subject will be given 24-hour emergency contact information and will be able to contact the study PI and the study coordinator at any time regarding questions or complications.

Any event noted by monitoring or reported by subjects will be captured on a separate electronic case report form (eCRF), which will be saved in the subject's record within the REDCap database and promptly brought to the PI's attention.

DSM Report

A data safety monitoring report will be prepared at least annually and included with reports to the UCSD HRPP (yearly continuing review) and the funding agency (yearly progress report). In addition to enrollment, it will track:

1) All adverse events in which abnormal testing results were conveyed to the subject.
2) All adverse events in which abnormal testing results were conveyed to a subject's designated physician. (A record of this communication will be kept in the patient's file)
3) Any other adverse events, serious adverse events, and unanticipated problems, all of which will be adjudicated and classified as study-related or unrelated to the study.
4) The report will also include amendments to the study protocol.

This yearly report will be comprehensive; however, more prompt reporting may be needed.

Adverse Event Reporting Mechanisms to the UCSD HRPP, plus Management of SAEs

Any SAE determined to be study related or any UP will be reported within 1 business day to the UCSD HRPP. Although we do not anticipate any serious adverse event arising specifically from the proposed research, any SAE will be tracked until resolution by the investigators. If subjects are injured as a direct result of participation in the research, the University of California will provide any medical care needed to treat those injuries. This information, and contact information for the UCSD HRPP, is included in the consent form. Subjects in the study who have an SAE, whether related to the study or not, will be reviewed by the PI in order to determine whether to continue with the study. For example, a subject who completes part of the study and then has a prolonged intercurrent illness may be withdrawn from the study.

HIPAA Compliance

Almost all data will be entered directly into electronic CRFs that are created and maintained in a HIPAA-compliant REDCap database, a secure web application designed for building and managing online surveys and databases. At UCSD, in order to access REDCap, users need to have a logon ID and password, which only allows viewing of the projects to which they are assigned. For instances where written records are needed (e.g. investigator's notes from overnight sleep studies) these records will only have the subject's anonymous study ID number and no personal health information (PHI). Additionally, the notes will be kept in a locked file cabinet in a locked room. As this study is being conducted solely at the University of California San Diego, we do not anticipate transmitting data outside of our institution.

Data Analysis
This is a randomized controlled trial testing the feasibility and efficacy of interventions targeting the underlying OSA mechanisms (endotypes) with regards to improve OSA severity. However, this is more of a pilot study, with a relatively small number of participants and short duration of interventions. Therefore, there are no formal plans for interim analyses and no stopping rules. Data will be analyzed according to the research plan under the rigorous guidance of Professor of Biostatistics Dr Sonia Jain.

Adverse Events and Blinding
We recognize that adverse events may provide a clue as to which study arm (active vs placebo) subjects have been assigned to. To maintain blinding during the analysis of efficacy data, it will be performed separately from the analysis of safety data.

Emergency Facilities
We do not anticipate any cardiopulmonary arrests, but all research staff undergo the UCSD basic resuscitation training (BART) at least biannually. The UCSD Jacobs Medical Center Emergency Room is right across the street from the sleep research laboratory which is located on the ground floor of the ACTRI building.

Adequacy of Resources
The UCSD sleep research laboratory is a state-of-the art facility. It is led by Dr Malhotra and Dr Owens who have almost two decades of experience with research studies including overnight endotyping studies, randomized controlled trials and drug investigations. Our team further includes two staff research assistants and two sleep technicians who have extensive experience with all aspects of this trial.

This study will be performed as part of a foundation grant obtained by the PI Schmickl who has an MD/PhD background. Dr Schmickl completed clinical training in internal medicine and sleep medicine (Harvard Combined Program) and several years of research experience including hands-on experience as a research fellow in clinical ICU-research at Mayo Clinic and formal training in epidemiology/biostatistics at Harvard School of Public Health. Currently Dr Schmickl has a dual appointment as Assistant Physician and as a T32 fellow in the UCSD PCCSM Division/Department of Medicine. Contingent upon a career-development award Dr Schmickl will be proposed for a faculty position as Assistant Professor.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

All data will be collected and recorded for research purposes. Sources of data include:

- The UCSD electronic medical record, which will only be accessed by the investigators in the manner approved by the UCSD Human Research Protections Program
- Questionnaires (e.g. sleepiness scores) completed by the subjects
- Physiological measurements made by the investigators, such as the values measured during the overnight sleep studies

All data collected in this study will be maintained in a secure REDCap database on an internal server at UCSD. Information in the study database (not the screening database) will be stored for an indefinite period of time to allow for subsequent data analysis and future reference. All study documents that may be linked to a study subject will be shredded at completion of the study. Nearly all data will be collected from direct assessments and entered directly into the secure study database via electronic case report forms (eCRFs) either directly by subjects (in the case of questionnaires) or by research staff. Access to the REDCap database will be secured by two layers of passwords: first the staff must access the UCSD intranet via a password to access the link to the database, which can only be entered via another password. The UCSD intranet is

maintained by Next Generation Network (NGN), which provides and maintains all resources for access to the database and provides network security. Importantly, only members of the research team who are "invited" by the PI to have access to the research record can access the data.

Blood samples will be processed and securely stored by ACTRI Clinic staff. Serum and plasma blood samples will be labelled with the subject's unique de-identified code. De-identified DNA/RNA from each subject will be stored and may be utilized in future analysis as new discoveries related to genetic or physiological aspects of the study are made, i.e. to assess whether newly discovered genetic factors relate to phenotypes collected in this study. The research group may choose to share stored DNA/RNA samples and associated physiological information with other investigators with the purpose of further answering research questions related to the same theme; however, any shared information will be de-identified and without behavioral data.

It is not reasonably foreseeable that the study will have access to or collect information that Federal, State, and/or local laws/regulations requires or may require to be reported to other officials or ethically requires actions.

17. POTENTIAL BENEFITS

Subjects enrolled in this trial have un(der)treated moderate-severe OSA and are thus at risk of adverse health outcomes related to OSA. Therefore, subjects may benefit from participation temporarily in that their OSA and associated symptoms may temporarily improve. Additionally, we may uncover other important health information, such as hypertension, that may speed diagnosis and treatment. Thus, given the minor risks from the proposed research, we believe that the benefits of participation in this study outweigh the risks.

More broadly, we expect that the findings of this study will be relevant for the large fraction of un(der)treated OSA patients in general, for whom this study may reveal a feasible strategy to provide alternative therapies.

18. RISK/BENEFIT RATIO

The investigators feel risks associated with these studies are outweighed by the benefits.

19. EXPENSE TO PARTICIPANT

There will be no cost to the subject for participating in this study. All of the tests and procedures that will be done for this research will be paid for by study funds. We will pay for any sleep studies done for research purposes.

20. COMPENSATION FOR PARTICIPATION

Subjects will be remunerated after completing each portion of the study, as outlined below:

- Daytime Visit #1: $25 (if needed)
- Overnight Visit 1: PSG: $100
- Overnight Visit 2: PSG: $100
- Overnight Visit 3: PSG: $100
- Overnight Visit 4: $100
- Weekly Phone Calls: $20/each

- Completion of All Visits: $100

Subjects will be remunerated a total $560.00 for completion of all the study visits (with exception to the daytime visit). If the daytime visit is needed, the subject will be compensated $585.00
If an additional daytime visit is needed for data collection: $25

If data is inconclusive and an additional polysomnogram night is required, they will be paid $100.

Parking will be available free of charge and participants will also be reimbursed for minor out of pocket expenses including meal vouchers, public transportation or taxi vouchers. If the subject terminates the study early, they will receive an amount based on the visits that have been completed. If any of the visits are missed, the subject will not be remunerated for those visits.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Christopher Schmickl MD, PhD is a T32 postdoctoral fellow and assistant physician with medical privileges at UCSD Medical Centers who will manage all day-to-day activities with close support from the mentor team and associated research assistance/sleep technicians. Thus, Dr Schmickl will be involved in all aspects of the clinical trial including screening, recruitment, data collection including overnight research studies, analysis, coordinate adverse event reporting and other safety reports during the conduct of the trial, and dissemination of findings via articles and presentations at conferences.

Atul Malhotra PhD is a tenured Professor of Medicine and Vice Chair of Research in the Pulmonary, Critical Care and Sleep Medicine Division with medical privileges at UCSD Medical Centers who is an international expert on OSA mechanisms and has substantial experience with the design and conduct of both single center and multicenter clinical trials. Dr Malhotra will serve as Dr Schmickl's primary mentor and provide guidance on all aspects of the trial.

Robert Owens MD is a tenured Associated Professor in the Pulmonary, Critical Care and Sleep Medicine Division with medical privileges at UCSD Medical Centers who has co-developed the techniques used to measure the underlying OSA mechanisms (endotypes) and has also substantial experiences with clinical trials. He will serve as co-mentor and provide primarily hands-on support with design of the REDCap database, IRB relations, overnight research studies and analysis of resultant data using custom algorithms programmed in MATLAB.

Jeremy Orr MD is an Assistant Professor in the Pulmonary, Critical Care and Sleep Medicine Division with medical privileges at UCSD Medical Centers. He has significant experience with overnight endotyping studies and analysis of such data and will provide help in this regard.

Mathew Light MD is a physician in the Pulmonary, Critical Care and Sleep Medicine Division with medical privileges at UCSD Medical Centers. He will serve as a Co-Investigator.

Sonia Jain PhD is a tenured Professor in Biostatistics and Bioinformatics who has helped design the studies, and who will provide support with statistical analysis on an as-needed basis.

Tatum Simonson PhD is a tenured Assistant Professor in Physiology at UCSD. As a Co-Investigator, she will provide her expertise in genomics and lead DNA-based analyses of blood specimen.

Dillon Gilbertson MS and Rebbecca Brena RPSGT, BS are experienced sleep technicians who will help with recruitment, and be responsible for overnight data acquisition, assessment of baseline characteristics and secondary outcomes (sleepiness measurements, blood pressure etc.).

Janelle Fine BS is a research assistant who will be responsible for recruitment and data collection.

Pamela DeYoung BS RPSGT is a registered sleep technologist with long experience in clinical trials who will perform clinical scoring of sleep studies and will support Dillon Gilbertson with subject recruitment as needed. DeYoung will serve as the IRB contact.

Naa-Oye Bosompra BA is an experienced research assistant who will help with recruitment and data collection. Bosompra will serve as the IRB administrative contact.

Shannon Wright will serve as the Fiscal Contact for this protocol.

Sultan Al Azzawi and **Lana McGinnis** are UCSD volunteer research assistants who will help with data collection and data analysis.

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23. FUNDING SUPPORT FOR THIS STUDY

The PI was awarded an unrestricted ATS grant ($40,000) for the proposed study, which is pending IRB approval. Costs related to this study exceeding the amount of the awarded grant, will be covered by the Malhotra/Owens sleep research laboratories.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

N/A

26. IMPACT ON STAFF

N/A

27. CONFLICT OF INTEREST

N/A

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