RESEARCH PARTICIPANT CONSENT FORM

TITLE: Open-Label 4-Period Dose-Escalation Safety and Efficacy Study of AD313 in Participants With Obstructive Sleep Apnea

(SEED Study)

PROTOCOL NO.: SEED
IRB Protocol #20213629

SPONSOR: Apnimed, Inc.

<<CF-Main Header Block - Investigator>>
INVESTIGATOR: Name
Address
City, State Zip
Country

STUDY-RELATED PHONE NUMBER(S): <<CF-Main User Defined #1>>
Phone Number
Phone Number (24 hours)
[24 hour number is required]

RESEARCH CONSENT SUMMARY

You are being asked for your consent to take part in a research study. This document provides a concise summary of this research. It describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document will provide all relevant details.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

How long will I be in this research?

We expect that your taking part in this research will last up to 9 weeks from the time of screening to the last phone call.

Why is this research being done?

You are being asked to participate in this research study because you have been diagnosed with or have obstructive sleep apnea (OSA). The purpose of this research study is to assess the safety and efficacy of two commercially available medications utilizing 3 increasing dose combinations of atomoxetine with dronabinol, compared to baseline and to atomoxetine alone. The use of atomoxetine with dronabinol or atomoxetine alone for the treatment of sleep apnea is investigational in the study.

What happens to me if I agree to take part in this research?

If you decide to take part in this research study, you will have a sleep study and lab tests to determine if you qualify for the study. If you qualify, you will receive increasing dose combinations of two commercially available medications over a 4-week period. Three sleep studies and office visits will be performed while taking the medication to assess their safety and efficacy.

Could being in this research hurt me?

The most important risks or discomforts that you may expect from taking part in this research include risks of the medications being taken (you will receive medication fact sheets), and any discomforts from the sleep study.

Will being in this research benefit me?

Since these two drugs have not been studied very much alone or together to treat OSA, there are no guaranteed benefits to you for participating in this research study. There is a possibility that these medications could assist your study doctor in the treatment of your OSA. In addition, other patients who suffer from the same condition could benefit from your participation in this research study.

What other choices do I have besides taking part in this research?

Taking part in this research study is voluntary. You don't have to participate and you can stop at any time. If you decide not to take part in this study, you will continue to receive normal standard of care treatment.

What else should I know about this research?

Other information that may be important for you to consider so you can decide whether to take part in this research is the schedule of events. We ask that you make your best effort to attend each visit. Please also review the detailed consent for guidance on sexually active participants of childbearing potential and considerations regarding food and alcohol intake.

DETAILED RESEARCH CONSENT

You are being invited to take part in a research study. A person who takes part in a research study is called a subject, research participant.

In this consent form "you" generally refers to the research participant.

Why is this research being done?

You are being asked to participate in this research study because you have been diagnosed with or have moderate to severe obstructive sleep apnea (OSA) and you may qualify for this study to evaluate the treatment option of two commercially available medications for your OSA.

OSA is a common and serious sleep disorder and it affects approximately 20 million people in the United States. OSA is the repetitive collapse or "obstruction" of the airway during sleep, creating repetitive episodes of hypopnea (shallow breathing) or apnea (paused breathing). These episodes of shallow or paused breathing may lead to waking up from sleep, interrupted sleep, excessive daytime sleepiness and/or psychological disturbance. Long-term OSA is associated with increased risk of death and several adverse health consequences (e.g., heart disease, brain health, metabolism, functioning throughout the day).

Treatment for OSA has changed little over the past 40 years. While common treatments such as CPAP and related therapies are effective in improving sleep characteristics and providing more oxygen, many patients find these devices uncomfortable or intolerable. Efforts to develop pharmacological therapies (drugs) for the treatment of OSA have been ongoing for at least 20 years, with no success thus far.

Selective norepinephrine reuptake inhibitors (SNRIs) such as atomoxetine are thought to improve OSA by increasing the stiffness and responsiveness of the airway muscles. Cannabinoids, such as dronabinol, have shown potential for reduction of OSA severity. The sponsor of this study (Apnimed) believes that the combination of dronabinol and atomoxetine may have an improved efficacy profile in patients with OSA compared to either option taken by itself.

About 15 participants will take part in this research at up to 3 selected sites in the United States.

What happens to me if I agree to take part in this research?

If you agree to take part in this research study, a health screening will be conducted in order to confirm that you are eligible for the study. The screening visit will be conducted at your study doctor's office. The following assessments are not experimental, however will be performed solely for the purpose of this research study.

- Your study doctor will assess your eligibility to participate in this study. You will be asked about your symptoms, your demographics, your medical history and any medicine that you are taking.

- You will have a brief physical exam and your vital signs (temperature, respiratory rate, blood pressure and heart rate) will be assessed.
- Females of child-bearing potential, who are pre-menopausal and have not had a hysterectomy (uterus removed), you will have a blood pregnancy test.
- You will complete clinical laboratory testing (blood and urine tests).
- You will have a 12-Lead Electrocardiogram (EKG) to measure the electrical and muscular functions of your heart.
- You will have a sleep study, unless you've already had one that qualifies for screening within the last three months that you can provide.
- You will also perform the following questionnaires on an iPad or similar tablet:
    - Patient Global Impression of Severity of OSA (PGI-S)
    - Patient Reported Outcomes Measurement Information System (PROMIS) sleep impairment
    - PROMIS sleep disturbance
    - PROMIS fatigue
    - Digit Symbol Substitution Test (DSST)
    - Psychomotor Vigilance Test (PVT)

If you qualify for the study, you will receive increasing dose combinations of atomoxetine and dronabinol. The weekly dose schedule is as follows:

- Week 1: atomoxetine 40 mg x 4 days, then 80 mg x 3 days
- Week 2: atomoxetine 40 mg/dronabinol 2.5 mg
- Week 3: atomoxetine 80 mg/dronabinol 5 mg
- Week 4: atomoxetine 80 mg/dronabinol 10 mg

Dose escalation (increase) will be based on safety and tolerability, as assessed at weekly clinic visits and by telephone contact. If you do not tolerate dose escalation, you will be discontinued from the study.

You will be asked to come to the study doctor's office for office visits and additional sleep studies during the course of the study as follows:

Activities	**Screening** (May be performed over 1-2 visits)	**Baseline**	**Week 1** (1-7 days +/- 1)	**Week 2** (8-14 days +/- 2)	**Week 3** (15-21 days +/- 2)	**Week 4** (21-28 days +/- 2_	**Week 6** (42 days +/- 2)
Screening (Demographics, Exam, Labs, ECG)	X						
Sleep Study (performed at the end of the week, Weeks 1-4 when applicable)		X	X		X	X	
Office Visit				X			
Phone Call							X
Vital Signs		X	X	X	X	X	
Drug Receipt/Return		X	X	X			

Activities	**Screening** (May be performed over 1-2 visits)	**Baseline**	**Week 1** (1-7 days +/- 1)	**Week 2** (8-14 days +/- 2)	**Week 3** (15-21 days +/- 2)	**Week 4** (21-28 days +/- 2_	**Week 6** (42 days +/- 2)
Questionnaires		X	X		X	X	

Description of Medications:

Atomoxetine (STRATTERA®):

Atomoxetine (STRATTERA®) has been FDA approved for over 18 years (approved in 2002) for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) but not approved for your condition. The daily dose of atomoxetine that will be studied will be within the range typically recommended for adults, per the current U.S. prescribing information. Your study doctor will review this medication with you in detail and will answer any questions you may have.

Dosing instructions: 1 capsule given by mouth with up to 240 mL (about 1 cup) of water.

Dronabinol (Marinol®):

Dronabinol (Marinol®) was initially approved by FDA in 1985 in adults for the treatment of: Anorexia associated with weight loss in patients with AIDS, Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments but not approved for your condition. The daily dose of dronabinol that will be studied will be within the range typically recommended for adults, per the current U.S. prescribing information. Your study doctor will review this medication with you in detail and will answer any questions you may have.

Dosing instructions: 1 capsule given by mouth with up to 240 mL (about 1 cup) of water.

You will be instructed to keep a daily diary of the time at which you took your medications each day.

What are my responsibilities if I take part in this research?

If you take part in this research, your general responsibilities include:

- Follow the instructions of the study doctor and the research staff.
- Follow all your doctor and study doctor's prescribed medication routine throughout the study period. If you have any questions, please contact your Study doctor or research staff.
- If you have any kind of allergy to medications, please notify the study doctor and the research staff right away.
- If you believe you are pregnant, please notify the study doctor and research staff.
- Keep all of your study appointments. If you need to reschedule your missed research appointment, please contact the research staff to reschedule your visit as soon as you know that you will miss your originally scheduled appointment.

- Tell the study doctor or research study staff about any side effects, doctor visits and/or hospitalizations that you experience through the entire study period.
- Ask questions as you think of them.
- Tell the study doctor or research staff if you change your mind about staying in the study.

For male participants:

If you are sexually active with female partner(s) of childbearing potential, from Study Day 1 through 1 week after the last dose of study drug, the participant must agree to ONE of the following during the protocol-defined time frame:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a contraceptive method with a failure rate of less than 1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study treatment.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or to use a male condom during each episode of penile penetration during the protocol-defined time frame.

For female participants:

If you are a female of childbearing potential, from Study Day 1 through 1 week after the last dose of study drug, you are eligible to participate if you agree to use a highly effective method of contraception consistently and correctly as described in the table below. All females of childbearing potential must have a negative result of a blood (serum) pregnancy test performed at screening. If you become pregnant during this time, you will no longer be able to participate in the study, and the study doctor will ask to collect information about the pregnancy and its outcome.

Highly Effective Contraceptive Methods That Are User Dependent*   *Failure rate of less than 1% per year when used consistently and correctly.*
Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation: Oral (e.g., birth control pill)   Intravaginal (e.g., NuvaRing)   Transdermal (e.g., birth control patch)
Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral (e.g., birth control pill)   Injectable (e.g., Depo-Provera)

Highly Effective Contraceptive Methods That Are User Independent*

Implantable progestogen-only hormonal contraception associated with inhibition of ovulation IUD (e.g., copper IUD, ParaGard, or similar) Intrauterine hormone-releasing system (IUS) (e.g., Mirena, or similar) Bilateral tubal occlusion or ligation (e.g., "tubes tied")

Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception from the above list should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from (not having) heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

*Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Meals and Dietary Restrictions:

- Participants should not eat or drink anything containing the following foods within 72 hours before the first dose of study drug and during the study: grapefruit or grapefruit juice, pomelo juice, star fruit, pomegranate, and Seville or Moro (blood) orange products.
- You should not start any new diet programs during the study.

Caffeine, Alcohol and Tobacco:

- During the study, participants should not drink more than 2 standard units per day of alcohol for men or 1 unit/day for women (for example, 1 beer, 1 4 oz. glass of wine, or 1 mixed drink), consumed no less than 3 hours prior to bedtime. You should not drink any alcohol the day of a sleep study.
- Caffeinated beverages (such as soda, energy drinks or coffee), containing up to a total of 400 mg caffeine per day is permitted during the study period. Please do not drink them within 3 hours of bedtime.

Physical Activity:

- You should not start any new exercise programs during the study.

Could being in this research hurt me?

As with taking any type of medications, there are known potential risks with taking medications like these two, as well as potential risks that may be unknown. Please review the medication fact sheets for more information.

Risks of atomoxetine: Constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation.

Risks of dronabinol: abdominal pain, dizziness, euphoria, nausea, paranoid reaction, somnolence, thinking abnormal and vomiting.

Precautions to be taken for atomoxetine and dronabinol:

- Effects on heart rate and blood pressure; pulse and blood pressure will be measured at baseline and following dose increases.
- Emergent psychiatric adverse events; do not to operate motor vehicles or other dangerous machinery until you are reasonably certain that mental or physical abilities are not impaired.
- Nausea and vomiting; consult with the study doctor to consider discontinuation if symptoms continue or worsen
- Dizziness, drowsiness; tolerance often develops to CNS adverse effects, and are less with nighttime dosing.
- Rash; may be a symptom of hypersensitivity reaction, serious allergic reactions are rare but have been reported.

Consult your study doctor if you experience any of these symptoms.

In addition to these risks, taking part in this research may harm you in unknown ways. It is possible that your condition may not improve and could worsen if you take part in this study.

Taking part in this study may hurt a pregnancy or fetus in unknown ways.

Non-Experimental Study Procedures

Risks of Blood Draws: You may experience swelling, bruising, bleeding where the needle enters the body. There is a risk of fainting, please let the study team know if this has happened to you in the past.

Risks of Blood Pressure Measurements: The blood pressure cuff may cause some mild discomfort, bruising, or red spots on the arm. If this happens, it usually goes away shortly after the blood pressure cuff has been removed.

Risks of Electrocardiogram (EKG) and Sleep Study: Skin irritation from the EKG and other sleep study electrode pads or pain when removing the pads can occur. If this happens, it is usually temporary. Difficulty sleeping in the study center may also occur.

For more information about risks and side effects, ask the study research staff or doctor <<Investigator Full Name-Title>>[PI Name].

Will it cost me money to take part in this research?

Taking part in this research may lead to added costs to you, such as travel costs, and time away from work. You will be compensated fairly to cover these costs, see below. The sponsor, Apnimed, Inc. will be paying for the services related to research, such as your office visits, sleep studies, and the study medication.

Will I be paid for taking part in this research?

<<CF-Main Payment for Part. Paragraph>>For taking part in this research, you may be paid up to a total of $[Amount]. Your compensation will be broken down as follows:

- Completion of screening, if you do not qualify for the study: $[Amount]
- Completion of screening and baseline, if you do qualify for the study: $[Amount]
- Each research related sleep study: $[Amount]
- Each office visit (without sleep study): $[Amount]

If you withdraw from the study, you will only be compensated for the study visits or procedures completed.
<<CF-Main Financial Disclosure>>

Will being in this research benefit me?

Since these two drugs have not been studied very much alone or together to treat OSA, there are no guaranteed benefits to you for participating in this research study. There is a possibility that these medications could assist your study doctor in the treatment of your OSA. In addition, other patients who suffer from the same condition could benefit from your participation in this research study.

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits to you could include improvement of your OSA.

We cannot promise any benefits to others from your taking part in this research. However, possible benefits to others include additional information on the use of these medications to treat OSA in the future.

What other choices do I have besides taking part in this research?

Your alternative is to not take part in the research. The other treatment options include use of continuous positive airway pressure (CPAP), pharyngeal surgery, mandibular advancement devices, and implantable nerve stimulators.

What happens to the information collected for this research?

Your private information and your medical record will be shared with individuals and organizations that conduct or watch over this research, including:

- The research sponsor
- Medical personnel associated with the study

- People who work with the research sponsor<<CF-Main SMO Company 1>><<CF-Main Affiliated IN Language 1>>
- Government agencies, such as the Food and Drug Administration (FDA)
- WCG IRB, the Institutional Review Board (IRB) that reviewed this research

We may publish the results of this research. However, we will keep your name and other identifying information private.

We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data collected in this research might be deidentified and used for future research or distributed to another investigator for future research without your consent.

If you join this study, you should understand that you will not own your biospecimens or data.

The information and biospecimens (samples of material such as urine, blood, etc.) obtained from this research study may be of commercial value, but you will not share in any potential profits from the commercialization of products developed from your participation in this study.

Who can answer my questions about this research?

If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page of this document.

This research is being overseen by WCG IRB. An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289 or researchquestions@wcgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research participant.

What if I am injured because of taking part in this research?

If you are injured or get sick because of being in this research, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance may be billed for this treatment. The sponsor will pay any charges that are not covered by your insurance policy or

the government, provided the injury was not due to your underlying illness or condition and was not caused by you or some other third party. No other payment is routinely available from the study doctor or sponsor.

If you are a Medicare patient and receive payment for medical expenses from a study-related injury, the sponsor will need to know some information about you like your name, date of birth and social security number or Medicare Health Insurance Claim Number. This is because the sponsor has to report any study-related injury claim payments to Medicare. The sponsor will not use this information for any other purpose. The Centers for Medicare and Medicaid Services (CMS) is the agency that administers the Medicare program. The sponsor (or its delegate) must have certain private information about you, such as:

- Your name
- Date of birth
- Social Security number
- Medicare claim number
- Date of injury
- A description of the injury

The sponsor normally would not receive such private information about you. However, the sponsor (or its delegate) has agreed to use this information only for the purposes described in this paragraph. The sponsor also agrees to use it as otherwise specified in the Authorization to Use and Disclose Protected Health Information section. This is included at the end of this consent document.

Can I be removed from this research without my approval?

The person in charge of this research can remove you from this research without your approval. Possible reasons for removal include:

- It is in your best interest
- You have a side effect that requires stopping the research
- You need a treatment not allowed in this research
- You become pregnant
- The research is canceled by the FDA or the sponsor
- You are unable to take the research medication
- You are unable to keep your scheduled appointments
- Other reasons we do not know at this time

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

What happens if I agree to be in this research, but I change my mind later?

Participation is voluntary. You may refuse to participate or discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to leave this research, contact the research team so that the investigator can describe the procedures for leaving the study early. This will include returning of any unused study medication.

Statement of Consent:

Your signature below documents your consent to take part in this research<<CF-Main California Bill of Rights>>.

Printed name of adult participant capable of consent	
Signature of adult participant capable of consent	Date
Signature of person obtaining consent <<CF-Main California HIPAA>>	Date

****For Sites in California****

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.

Who may use and give out information about you?
The study doctor and the study staff. [They may also share the research information with [enter SMO company name], an agent for the study doctor. delete if the site does not have an SMO]

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- The institution where the research is being done,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Institutional Review Board (IRB).

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
This permission will be good until December 31, 2070.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Authorization:
I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

AUTHORIZATION SIGNATURE:

Signature of Subject	**Date**