Title Page

Protocol Title: The Effect on Subjective Comfort of a Device Providing Positive Airway Pressure (PAP) Drops During Inspiration (TPAP) Compared to Continuous Positive Airway Pressure (CPAP) in Obstructive Sleep Apnea Patients

Protocol Name: TheraPAP Comfort

Sponsor Protocol #: Office 0001

Version Number: 0.6

Compound Number: TheraPAP

Short Title: TPAP for Comfort in OSA

Sponsor Name and Legal Registered Address:

SleepRes

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Murfreesboro, TN 37129

United States

Regulatory Agency Identifying Number: Exempt

Approval Date: February 23, 2024

Protocol Number: WCG IRB Protocol #: 20240612

Sponsor Signatory:

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Date

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1 Protocol Summary

1.1 Synopsis

Protocol Title: The Effect on Subjective Comfort of a Device Providing Positive Airway Pressure (PAP) Drops During Inspiration (TPAP) Compared to Continuous Positive Airway Pressure (CPAP) in Obstructive Sleep Apnea Patients

Protocol Name/Number: TheraPAP Comfort

Phase: NA

Sponsor: SleepRes, LLC

Rationale: TheraPAP is a prototype device (with full documented electrical and isolation safety) being developed by SleepRes, LLC for the treatment of obstructive sleep apnea (OSA) that can deliver either standard CPAP at a set pressure or what is called TPAP[1]. TPAP is a pressure control algorithm that lowers the pressure from the set pressure at the beginning of inspiration and does not return the pressure to the full set level until about halfway through expiration. The present study, TheraPAP Comfort, aims at assessing whether TPAP improves patient comfort vs. CPAP during supine wakefulness.

Overall Design:

The TheraPAP Comfort Study is an in-office study to assess comfort of TPAP vs. CPAP in CPAP-naïve patients with OSA during supine wakefulness. Patients will be recruited after routine outpatient visits. They will be asked to breath normally for approximately 1 minute in supine wakefulness while being administered 2 different pressure therapies for comparison. For TPAP therapies, each baseline pressure (9 or 13 cmH_2O) will consider 3 separate settings, TPAP A,TPAP B and TPAP C for 9, then TPAP D,TPAP E and TPAP F for 13.

At the first baseline pressure, patients will be asked to choose their preference between CPAP and TPAP A. This will be the primary endpoint. If TPAP A is chosen, testing will move on to the second baseline pressure. If CPAP is preferred, CPAP will then be compared to TPAP B. If TPAP B is chosen, testing will move on to the second baseline pressure. If CPAP is again chosen as preferred, it will be lastly compared to TPAP C, the latter two comparisons being secondary endpoints.

[1] TPAP will be used herein to refer to the actual modified PAP delivery.

At the second baseline pressure, patients will be asked to choose their preference between CPAP and TPAP D. This will be the primary endpoint. If TPAP D is chosen, testing will move on to the second baseline pressure. If CPAP is preferred, CPAP will then be compared to TPAP E. If TPAP E is chosen, testing will move on to the second baseline pressure. If CPAP is again chosen as preferred, it will be lastly compared to TPAP F, the latter two comparisons being secondary endpoints.

Baseline CPAP (cmH_2O)	TPAP Setting	Pressure Drop 1 (cmH_2O)	Pressure Drop 2 (cmH_2O)
9	TPAP A	2	2
	TPAP B	1	2
	TPAP C	1	1
13	TPAP D	2	3
	TPAP E	2	2
	TPAP F	1	2

Table 1. Pressure Drops 1 and 2 refer to the first and the second drops in pressure that occur during inspiration and are maintained until about halfway through expiration. The overall pressure drops consist of Drop 1+ Drop 2. CPAP, continuous positive airway pressure.

Number of Participants:

A total of 384 participants will be enrolled.

Study Duration:

The overall study duration for each participant will be up to a half hour including recruitment screening and testing.

1.2 Schedule of Activities (SoA)

Procedures	In-office study
Informed consent	X
Demographics	X
Height	X
Weight	X
Randomization	X
In-office procedure	X
AE/SAE monitoring	X

Table 2. Schedule of Activities for the TheraPAP Comfort Study.

Abbreviations: AE = adverse event; SAE = serious adverse event;

2 Introduction

2.1 Study Rationale

A therapy able to provide lower positive airway pressure (PAP) during inspiration than during expiration, designated TPAP, is being developed by SleepRes, LLC, for the treatment of obstructive sleep apnea (OSA). TPAP, as well as normal CPAP, are available on the SleepRes TheraPAP prototype device. In prior studies, the administration of higher inspiratory than expiratory PAP did not substantially increase treatment efficacy or adherence to continuous PAP (CPAP), which remains low. In our recent investigation, we demonstrated that the addition of a resistor to the CPAP circuit to reduce inspiratory PAP increased subjective comfort. The present study, TheraPAP Comfort, is an in-office study designed to examine whether TPAP at two different levels of pressure relief provides more subjective comfort than CPAP in awake supine participants.

2.2 Baseline

2.2.1 Obstructive Sleep Apnea

The National Commission on Sleep Disorders Research identified sleep disorders as a major public health burden. OSA is the most common of the more serious sleep disorders and affects approximately 20 million people in the United States (US), with approximately 13% of men and 6% of women affected (1). OSA is characterized by repetitive collapse or 'obstruction' of the pharyngeal airway during sleep, manifesting as repetitive episodes of hypopnea (i.e., shallow breathing) or apnea (i.e., paused breathing). These episodes of hypopnea or apnea may lead to hypoxemia, arousal from sleep, sleep fragmentation, excessive daytime sleepiness, and/or neuropsychological impairment.

Long-term, OSA is associated with increased mortality and a number of adverse cardiovascular, neurocognitive, metabolic, and daytime functioning consequences (2-11).

2.2.2 Unmet Medical Need

The large majority of OSA patients are treated with positive airway pressure, the most common of which is CPAP, provided by a machine that mechanically maintains an open airway. However, long-term adherence to therapy remains a challenge for many patients (12, 13). Common complaints include inconvenience, lack of perceived benefit, discomfort related to improper fitting of the interface, and difficulty expiring against positive pressure (14, 15).

As many patients cannot use CPAP because they find it intolerable, this represents a significant health concern, as OSA is associated with numerous adverse health outcomes and increased mortality. Strategies to improve tolerance of CPAP, and subsequently adherence, are needed.

2.2.3 Biological Rationale

TPAP is an innovative device/algorithm designed to deliver a lower inspiratory than expiratory PAP. The drop in inspiratory pressure can be modulated during the inspiratory phase. Previous research has shown that reducing inspiratory PAP by placing a resistor in the inspiratory line can enhance subjective comfort and decrease leaks when compared to CPAP, despite maintaining a similar residual apnea-hypopnea index (AHI). However, the resistor could only provide a fixed inspiratory PAP reduction based on existing PAP settings. TPAP addresses this limitation by allowing for adjustable drops in PAP throughout inspiration and part of expiration, offering a potentially more personalized and adaptive therapeutic approach.

3 Endpoints

	Endpoints
Primary	• CPAP vs. TPAP A at 9 cmH_2O • CPAP vs. TPAP D at 13 cmH_2O
Secondary	• CPAP vs. TPAP B at 9 cmH_2O • CPAP vs. TPAP C at 9 cmH_2O • CPAP vs. TPAP E at 9 cmH_2O • CPAP vs. TPAP F at 9 cmH_2O
Safety Endpoints	• Spontaneous adverse events

Table 3. Summary of TheraPAP Comfort Study endpoints.

4 Study Design

4.1 Overall Design

The TheraPAP Comfort Study is an in-office study to assess patient-level comfort on TPAP vs. CPAP. Pre-screening is conducted to establish potential eligibility with a previous sleep study showing an AHI>10 events/hr. Eligible participants will undergo an in-office study in which they will breathe in the supine position during wakefulness on CPAP and on TPAP. In cases where CPAP is preferred, TPAP will be dropped to different levels based on the baseline CPAP levels, according to Table 1. CPAP and TPAP will be administered in one and in the opposite order per patient following a randomized design, to simulate patient blinding to treatment.

4.2 Detailed Design

4.2.1 Recruitment

Individuals deemed potentially eligible for enrollment based on the assessment of their medical data during a scheduled outpatient visit will be recruited once they arrive at the clinic to collect their CPAP equipment. Participants selected for eligibility will be naïve CPAP OSA consistently with enrollment criteria.

4.2.2 In-office study

Individuals who agree to participate will be asked to sign an informed consent prior to commencement of study procedures upon their arrival at the clinic.

The following activities will also occur:

- Height and weight will be measured.
- Randomization of CPAP/TPAP order.

To begin the study, each participant will lay in a supine position on a reclining chair in the office and all therapy comparisons will be made in this orientation. Subsequently, each patient will be studied on two different baseline positive pressures: 9 and 13 cmH_2O. At either of the above pressures, each patient will assess CPAP against 2 different pressure drops in one-to-one comparisons.

For the baseline CPAP of 9 cmH_2O, TPAP will be set to:

- TPAP A
- Followed by TPAP B if CPAP was previously preferred
- Followed by TPAP C if CPAP was previously preferred

For the baseline CPAP of 13 cmH_2O, TPAP will be set to:

- TPAP D
- Followed by TPAP E if CPAP was previously preferred
- Followed by TPAP F if CPAP was previously preferred

Note that TPAP drops, designated as x/y, indicate first and second drop of PAP, starting during inspiration.

Assessment of comfort will be made by comparing one-to-one TPAP against each other or against CPAP by having the patient breathe on the pressure for one minute (or more as needed based on the judgment of the Study Coordinator) and then indicating which is more comfortable

by voice or hand sign. The indicated choice will be recorded by the Study Coordinator. The patient will be able to ask to repeat settings as often as needed to make the most informed choice.

4.2.2.1 Risk-benefit Analysis

The procedures involved in the studies include minimal risk, i.e., related to very short-term TPAP or CPAP administration (e.g., uncomfortable breathing, claustrophobia, lightheadedness, etc.). Upon experiencing any discomfort by the participant, the procedures will be interrupted.

There is no direct benefit or treatment to the participants, however the results of the study can potentially yield future benefit to the participants in terms of wider treatment alternatives for their OSA.

4.3 End of Study Definition

A participant is considered to have completed the study if they have completed all TPAP and CPAP administration.

5 Study Population

Eligible participants will be recruited from the existing clinic population at the study site. Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Age and Sex

1. Between 18 to 70 years of age, inclusive.

OSA Measures

2. AHI > 10 on a previous HST.
3. CPAP naïve individuals

Weight

4. BMI above 18 kg/m^2, inclusive.

Informed Consent

5. Participant voluntarily agrees to participate in this study and signs an Institutional Review Board (IRB)-approved informed consent prior to performing any of the study-related procedures.
6. Participant must be able to understand the nature of the study and must have the opportunity to have any questions answered.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Any non-previously mentioned vulnerable population.
2. Any condition that in the investigator's opinion would present an unreasonable risk to the participant, or which would interfere with their participation in the study or confound study interpretation.
3. Any chronic lung diseases.
4. Patients with hypoglossal nerve stimulation implant.
5. Chronic oxygen therapy.
6. A serious illness or infection in the past 30 days as determined by investigator.

5.3 Screen Failures

By definition, patients that do not meet the inclusion/exclusion criteria at the outpatient screening visit, will not be invited to or further contacted to participate in the study.

5.4 Preparation/Handling/Storage/Accountability

Prototype TheraPAP devices will be provided by the sponsor and will be kept in locked location when not in use. These devices will be used only for approved study purposes as designated by the office coordinator who will oversee their use in the office.

5.5 Measures to Minimize Bias

The order of CPAP tested first or second for each of the comparative tests for each baseline pressure will be randomized per patient, although the order of baseline pressure will be maintained for each patient starting with 9 cmH_2O, then moving to 13 cmH_2O.

5.6 Concomitant Therapy

Usual therapy is allowed as per the participants' physicians' indications, except for oxygen therapy that constitutes an exclusion criterion.

5.7 Discontinuation of Study Treatment

If a clinically significant finding is identified, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an adverse event (AE).

5.8 Stopping Criteria

5.8.1 Individual Participant Stopping Criteria

Participants reporting any SAE considered possibly related or related to study device will be withdrawn from the study.

Any other AE that in the judgment of the Investigator necessitates the participant stopping to protect participant safety, will result in early withdrawal from the study.

5.9 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.

If the participant withdraws consent, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

All participants who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.

Participation may be terminated before completing the study and the reason recorded as follows:

- Withdrawal due to AE
- Participant withdrew consent at own request (e.g., due to intolerance to study procedures)
- At the discretion of the Investigator for safety, behavioral, or administrative reasons.
- Other

5.10 Participant compensation

Participants will be compensated for their time and participation with a free V̇-Com™ (approximately $30 value) upon full completion of the study.

6 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1 In-office study set-up

- Methods: Participants will be connected to the TheraPAP circuit through a CPAP mask (which will be the same that they will be given for their at-home treatment) and two 22 mm hoses to prevent cross contamination. A panoramic of the setup in the patient room is shown in Figure 1.

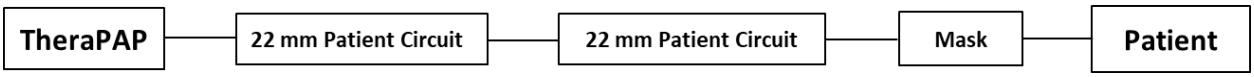

Figure 1. Continuous positive airway pressure (PAP)/TheraPAP circuit. TPAP, TheraPAP device.

6.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Safety assessments will include monitoring and recording of AEs, SAEs, and recording of study discontinuations.

6.3 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group (or designee) may wish to carry out source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to

data protection and medical confidentiality. The Investigator assures the Sponsor and affiliates or designees (such as a CRO) of the necessary support at all times.

Appendix 3.

Adverse events will be reported by the participant.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study device or the study, or that caused the participant to discontinue the study.

6.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the start until the end of the study.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group (or designee) may wish to carry out source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor and affiliates or designees (such as a CRO) of the necessary support at all times.

Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group (or designee) may wish to carry out source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor and affiliates or designees (such as a CRO) of the necessary support at all times.

Appendix 3.

6.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

6.3.3 Follow-up of AEs and SAEs

Ongoing AEs and SAEs will be followed until resolution or stability as determined by the Investigator.

6.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification (within 24 hours, see Regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group (or designee) may wish to carry out source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor and affiliates or designees (such as a CRO) of the necessary support at all times.

Appendix 3) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

7 Statistical Considerations

7.1 Sample Size Determination

A score of 1 and 2 will be combined for a preference of Pressure 1 and a score of 4 and 5 will be combined for a preference of Pressure 2. A score of 3 indicates no preference. In a 2x2 Williams

Cross over design with 2 treatments, where the endpoint is a proportion, (i.e., the proportion that prefer one pressure over another) the sample size per sequence that is needed to achieve 80% power, based on a two-sided 5% significance level, with a total of 6 comparisons results in a total number of participants of 384.

7.2 Randomization

All comparisons for each baseline pressure level (9 and 13 cmH_2O) will be randomized separately for either baseline pressure per patient by using CPAP first in one case then CPAP second in the other. However, the baseline pressure order will not be randomized so that PAP-naïve patients can acclimate to PAP first at the lower pressure.

7.3 Populations for Analyses

For the purposes of analysis, the following analysis sets are defined:

Set	Description
Randomized	All participants who were randomized.
Modified Intent to Treat (mITT) Set	The mITT set comprises all participants who are randomized, undergo at least 1 pair of PAPs comparison (e.g., CPAP 9 cmH_2O vs. TPAP), and have at least 1 measurement on the primary endpoint ().
Safety Set	The mITT set comprises all participants who are randomized, undergo at least 1 minute breathing on any TPAP setting.
Per Protocol (PP) Set	The PP Population consists of all participants without any major protocol violations that could influence efficacy assessment.

7.4 Interim Analyses

No interim analysis is planned.

8 Supporting Documentation and Operational Considerations

8.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

8.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAE or other significant safety findings as required by IRB procedures.
- Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB guidelines, and all other applicable local regulations.

8.1.2 Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

8.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must consent to the most current version of the ICF(s) during their participation in the study.

A copy of the signed ICF(s) must be provided to the participant.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all participants subsequently enrolled in the study.

8.1.4 Data Protection

Participants will be assigned a unique identifier by the study site. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

8.1.5 Data Quality Assurance

All participant data relating to the study will be recorded on electronic reports and spreadsheets. Any study data will be de-identified. The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the study records.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the study records.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All data generated by the site personnel will be captured and stored in an internal password-protected system.

8.1.6 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site.

8.1.7 Publication Policy

The Sponsor will support publication upon review of the manuscript.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors' authorship requirements.

A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinTrials.gov).

8.1.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IR/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions. Any deviations from the protocol will be reported to the Sponsor as Protocol Deviations.

8.1.9 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by medical steps taken in the course of the study.

8.1.9.1 Access to Source Data

Regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group (or designee) may wish to carry out source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor and affiliates or designees (such as a CRO) of the necessary support at all times.

8.2 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the device product. • NOTE: An AE can therefore be any unfavorable and unintended sign, symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal safety assessments (e.g., vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that:
Results in death
Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Recording and Follow-up of AE and SAE

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the CRF. It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities. Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The Investigator will also consult the Instructions for Use and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAE to Sponsor

SAE Reporting to the Sponsor
The Investigator must report any SAEs to the Sponsor within 24 hours of becoming aware of the event. The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference documents. Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone. Contacts for SAE reporting can be found in the Study Reference Manual.

All SAEs will be recorded from randomization until the end of the study. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally-related to study treatment.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
Any AE that is serious, associated with the use of the study treatment, and unexpected (SUSAR) has additional reporting requirements, as described below. If the SUSAR is fatal or life-threatening, associated with study treatment, and unexpected, regulatory authorities will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study treatment, and unexpected, regulatory authorities and will be notified within 15 calendar days after the Sponsor learns of the event.

8.3 Appendix 5: List of Abbreviations

AE	adverse event
AHI	Apnea-hypopnea index
BMI	body mass index
CFR	Code of Federal Regulations
CPAP	continuous positive air pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EOS	end of study
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
OSA	obstructive sleep apnea
PAP	positive airway pressure
SAE	serious adverse event
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TPAP	TheraPAP algorithm
VAS	Visual analog scale
US	United States

9 References

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Declaration of the Investigator

Title: The Effect on Subjective Comfort of a Device Providing Positive Airway Pressure (PAP) Drops During Inspiration (TPAP) Compared to Continuous Positive Airway Pressure (CPAP) in Obstructive Sleep Apnea Patients

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Instructions for Use, and other scientific data.

The study will not commence without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number