STUDY PROTOCOL

Auto-PAP for pulmonary hypertension treatment in decompensated heart failure patients with obstructive sleep apnea (ASAP-HF): A two center pilot study

Study Number: ASAP-HF

Version: Version 1.3 Final
Date: 30 May 2017

Principal Investigator:

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This protocol has been written in accordance with current applicable guidelines (IDE for USA) as well as all other relevant additional references, medical and legal.

PROTOCOL REVISION HISTORY

Version No. And Date	Section	Change	Rationale
Version 1.0 25/08/2016	10.4	Removal of Contrast Echocardiogram	Original Release/ Final Version
Version 1.1 Final 15/09/2016	3 6.2.5	Addition of exclusion "patients weighing less than 66 pounds(30kg)	Reflect device exclusion criteria
Version 1.2 Final 05/10/2016	8.3	Deleting section 'investigators are permitted to prescribe adjunctive medication per their medical discretion'	The attending physician will prescribe all medication related to the subject's medical conditions
Version: Version 1.3 Final Date: 30 May 2017	3 6.2.3	Up to 40 subjects overall will be randomized from in-patient clinical services to obtain endpoint data on 20 evaluable subjects (10 evaluable patients on each site). This accounts for the expected dropout rate (50%).	Increased number subjects enrolled, since a higher percentage are excluded after enrolled

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1. Responsibilities and addresses

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2. ABBREVIATIONS AND DEFINITIONS

6MWD	Six-minute walk distance
6MWT	Six-minute walk test
AE	Adverse Event
AHI	Apnea-Hypopnea Index
APAP	Auto-adjusting positive airway pressure
BNP	B-type natriuretic peptide
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous Positive Airway Pressure
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
E/e'	Ratio of early transmitral flow velocity to early diastolic mitral annular velocity
e/hr	Events per hour
EF	Ejection Fraction
EPAP	Expiratory Positive Airway Pressure
FDA	Food and Drug Administration
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LV	Left Ventricular
LVAD	Left ventricular assist device
LVEDP	Left ventricular end diastolic pressure
LVEF	Left ventricular ejection fraction
NT pro-BNP	N-terminal prohormone of b-type natriuretic protein
NYHA	New York Heart Association
OSA	Obstructive Sleep Apnea
PA	Pulmonary arterial
PAP	Positive Airway Pressure
PV	Pulmonary ventricular
RA	Right arterial
SAE	Serious Adverse Event
SDB	Sleep-Disordered Breathing
SOP	Standard Operation Procedures
UADE	Unanticipated adverse device effect

3. PROTOCOL SUMMARY

Objectives	The objective of the study is to evaluate the effect of continuous positive airway pressure (PAP) therapy on pulmonary arterial (PA) pressures in acute decompensated heart failure (HF) patients with obstructive sleep apnea (OSA). The study will also assess changes in functional parameters, biomarkers, and echocardiographic parameters.
Study Design	This study is a randomized, unblinded, two-center trial with parallel group design, with subjects randomized to either control (no PAP therapy) or active treatment (PAP therapy) in a 1:1 ratio.
Number of Subjects	Up to 40 subjects overall will be randomized from in-patient clinical services to obtain endpoint data on 20 evaluable subjects (10 evaluable patients on each site). This accounts for the expected dropout rate (50%).
Selection criteria	**Inclusion criteria for the study are:** 1. Age 18 years or more 2. Decompensated CHF with systolic PA pressures of ≥50 mmHg (including RA pressure) 3. Prior clinical diagnosis of heart failure (HFrEF or HFpEF) 4. Moderate to Severe predominately obstructive SDB documented by polygraphy with AHI ≥20e/h and 5% of the time spent <90% O_2 Sat (minimum 2hr recording time) 5. Patient is able to fully understand study information and sign informed consent **Exclusion criteria for the study are:** 1. Chronic renal insufficiency (HD or serum creatinine > 2) 2. Hemodynamically significant valvular disease 3. Severe arthritis or inability to complete 6MWT 4. LVAD/ heart transplant or hemodynamically unstable 5. Patient taking any Pulmonary vasodilators, including home oxygen. 6. Known diagnosis of OSA and on active therapy 7. 80% of the respiratory events being central/Cheyne-Stokes breathing (SERVE-HF criteria) 8. Recent cardiac surgery (within 30 days of admission) 9. Recent stroke (within 30 days of admission or with persistent neurological deficits) 10. Severe COPD defined as FEV_1 < 50% 11. Chronic renal failure on hemodialysis

	12. Participation in a randomized controlled pharmaceutical or treatment-related cardiac or pulmonary clinical study within 1 month prior to randomization. 13. Patient weighing less than 66 pounds(30kg)
Primary Endpoints	Reduction in PA systolic pressure as measured by Echocardiogram over 48 hrs.
Secondary Endpoints	1. Change in functional parameters as measured by 6-minute walk test (6MWT) 2. Change in neurohumoral activation as measured by N-terminal pro b-type natriuretic peptide (NT pro-BNP) 3. Change in blood oxygenation as measured by arterial blood gas analysis 4. Heart failure symptoms as assessed by the New York Heart Association scale (NYHA) classification 5. Change in fluid retention as measured by weight 6. Echocardiographic parameters, including E/e' as assumption of LVEDP and PV acceleration time 7. Length of hospital stay
Scheduled follow up	For evaluation of the primary endpoint, subjects will be followed for a period of 48 hours while in hospital. Polygraphy, including pulse oximetry (ApneaLink Air) will be performed at screening. The following tests will be performed at baseline and at 48hrs: • Cardiac exam (including NYHA class and weight measurement) • Echocardiography • Functional capacity testing (6MWD) • Blood collection • Blood gas analysis

4. INTRODUCTION

4.1. Background Information

Pulmonary hypertension (PH) in the setting of congestive heart failure (CHF) is common, a marker of poor prognosis, and associated with accelerated mortality[1,2,3]. Currently available treatments targeted at secondary PH in CHF have not yielded positive results, which still leaves these patients with no productive therapy option today. Obstructive sleep apnea (OSA) is highly prevalent and still largely under-diagnosed in CHF patients[4]. OSA is believed to have significant hemodynamic impact, which may play a role in development of pulmonary hypertension. Prior studies have shown that pulmonary pressures increase during sleep even in normal subjects[5]. In patients with OSA the PA pressures increase over different stages with a further spike in REM stage with opposite effect on alveolar ventilation[6]. The pathophysiology of pulmonary hypertension due to OSA is believed to be due to generation of significant intra-pleural negative pressures due to glottic closure and intermittent hypoxia causing pulmonary vasoconstriction[6,7,8,9,10,11] leading to increased pulmonary pressures[6]. Treatment with tracheostomy and continuous positive airway pressure therapy has shown to improve pulmonary artery pressures[6,12,13]. Our preliminary data from a retrospective review of heart failure service revealed significant reduction in PA pressures in patients compliant with positive airway pressure therapy[13]. Therefore, it is reasonable to hypothesize that therapy with Automatic positive airway pressure (APAP) with fixed lower EPAP pressures may have a salutary effect on the PA pressures in the acute setting .

We hypothesize that acute inpatient intervention with auto-adjusting positive airway pressure therapy (APAP) in patients with decompensated CHF and OSA may significantly reduce PA pressures, and also reduce length of stay (LOS) and NT-proBNP levels leading to improved patient outcome. With this approach APAP may offer a novel therapy option for these comorbid patients, desperately seeking for improvements in symptoms.

4.2. Intended Use

The AirSense™ 10 AutoSet™ device is cleared for use by the US FDA with the following indication: The AirSense 10 AutoSet self-adjusting device is indicated for the treatment of obstructive sleep apnea (OSA) in patients weighing more than 66 lb (30 kg). It is intended for home and hospital use. The humidifier is intended for single patient use in the home environment and re-use in a hospital/institutional environment.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of this pilot study is to evaluate the effect of continuous positive airway pressure (PAP) therapy on pulmonary arterial (PA) pressures in acute decompensated heart failure

(HF) patients with severe obstructive sleep apnea (OSA). The study will also assess changes in functional parameters, biomarkers, and echocardiographic parameters.

5.2. Primary Efficacy Endpoint Measurement

The primary endpoint is reduction in PA pressures after 48 hrs, with a minimum 8hrs APAP therapy.

5.3. Secondary Objectives

1. To compare changes in functional parameters (6MWD) from baseline to 48hrs
2. To compare changes in NT pro-BNP from baseline to 48hrs
3. To compare changes in blood oxygenation from baseline to 48hrs
4. To compare changes in heart failure symptoms from baseline to 48hrs
5. To compare changes in fluid retention from baseline to 48hrs
6. To compare changes in echocardiographic parameters, including E/e' as assumption of LVEDP and PV acceleration time from baseline to 48hrs
7. To compare hospital length of stay between groups

5.4. Secondary Endpoint Measurements

1. Change in functional parameters as measured by 6-minute walk test (6MWT)
2. Change in neurohumoral activation as measured by N-terminal pro b-type natriuretic peptide (NT pro-BNP)
3. Change in blood oxygenation as measured by blood gas analysis
4. Heart failure symptoms as assessed by the New York Heart Association scale (NYHA) classification
5. Change in fluid retention as measured by weight
6. Echocardiographic parameters, including E/e' as assumption of LVEDP and PV acceleration time
7. Difference in length of stay between study groups

6. DESIGN

The ASAP-HF study is a prospective, randomized, controlled, two-center, study with a parallel group design, with subjects randomized to either control (no APAP) or active treatment (APAP) in a 1:1 ratio.

This study will be conducted in one center in the US and one center in Germany.

6.1. Enrollment

Subjects will be recruited from in-patient clinical services. If a subject is willing to participate in the ASAP-HF study, a written informed consent for the study must be obtained prior to any study related procedure. Before randomization, all eligibility criteria must be confirmed.

6.2. Selection of subjects

6.2.1. Informed Consent

The consent form is written in accordance with applicable data privacy acts and FDA Regulations and approved by the responsible Institutional Review board (IRB)/Ethics Committee (EC).

The investigator or responsible staff will explain the nature, purpose and risks associated with the study. The patient will be given sufficient time to consider the study's implications before deciding whether to participate. Information materials created by the investigators must be approved by the responsible IRB/EC prior to use.

A signed, IRB/EC-approved consent form must be obtained from the patient prior to the performance of any protocol-related testing or treatment procedures. The consent process must be performed by a designated clinical study team member authorized by the IRB/EC to consent patients and listed on the Delegation of Authority Log as having privileges to consent patients. A signed copy of the consent form must be maintained in the study files and a copy provided to the patient. The patient's permanent medical records should indicate study participation.

6.2.2. Study Population and Randomization

Enrolled subjects who fulfill the inclusion criteria and none of the exclusion criteria for the ASAP-HF study and who sign the consent form(s) are considered as potential candidates for randomization to either control or active treatment arm in a ratio of 1:1.

Subjects will be randomized to one of the treatment options, Group A (active): standard medical therapy plus treatment with continuous APAP for 48hrs, or Group B (control): standard medical therapy only.

6.2.3. Number of Subjects

Up to 40 subjects will be randomized in order to achieve 20 evaluable subjects (10 per arm and 10 per site).

6.2.4. Subject Inclusion Criteria

1. Age 18 years or more
2. Decompensated CHF with systolic PA pressures of ≥50 mmHg (including RA pressure)

3. Prior clinical diagnosis of heart failure (HFrEF or HFpEF)
4. Moderate to Severe predominately obstructive SDB documented by polygraphy with AHI ≥20e/h and 5% of the time spent <90% O2 Sat (minimum 2hr recording time)
5. Patient is able to fully understand study information and sign informed

6.2.5. Subject Exclusion Criteria

1. Chronic renal insufficiency (HD or serum creatinine > 2)
2. Hemodynamically significant valvular disease
3. Severe arthritis or inability to complete 6MWT
4. LVAD/ heart transplant or hemodynamically unstable
5. Patient taking any Pulmonary vasodilators, including home oxygen.
6. Known diagnosis of OSA and on active therapy
7. 80% of the respiratory events being central/Cheyne-Stokes breathing (SERVE-HF criteria)
8. Recent cardiac surgery (within 30 days of admission)
9. Recent stroke (within 30 days of admission or with persistent neurological deficits)
10. Severe COPD defined as FEV1 < 50%
11. Chronic renal failure on hemodialysis
12. Participation in a randomized controlled pharmaceutical or treatment-related cardiac or pulmonary clinical study within 1 month prior to randomization.
13. Patient weighing less than 66 pounds(30kg)

7. STUDY DEVICES

7.1. AirSense 10 AutoSet

The AirSense 10 AutoSet (“AutoSet”) is a market-released device that has been FDA-cleared (K140124) in the US and CE-marked in Germany (EC149) to provide non-invasive ventilatory support to treat patients weighing more than 66 lbs (30 kg). The device is intended for home and hospital use.

The treatment pressure required by the patient may vary due to changes in sleep state, body position and airway resistance. In AutoSet mode, the device provides only that amount of pressure required to maintain upper airway patency.

The device analyzes the state of the patient’s upper airway on a breath-by-breath basis and delivers pressure within the allowed range according to the degree of obstruction. The AutoSet

algorithm adjusts treatment pressure as a function of three parameters: inspiratory flow limitation, snore, and apnea.

Ancillary equipment includes the humidifier, air delivery hose, mask, and headgear. The AirSense 10 AutoSet provides a minimum and maximum pressure within the range of 4-20 cm H_2O.

See AirSense 10 AutoSet Clinician's Manual for details.

7.2. ApneaLink Air

The ApneaLink Air is a market-released polygraphy device that has been FDA-cleared (K143272) for use by Health Care Professionals, where it may aid in the diagnosis of sleep disordered breathing for adult patients. ApneaLink Air records the following data: patient respiratory nasal airflow, snoring, blood oxygen saturation, pulse, and respiratory effort during sleep. ApneaLink Air uses these recordings to produce a report that may aid in the diagnosis of sleep disordered breathing or for further clinical investigation. The ApneaLink Air may be used with an optional dual-lumen cannula in cases where the patient cannot be taken off oxygen for the duration of the test.

The ApneaLink Air recorder is a 3-channel battery-powered respiratory pressure sensor and oximetry system. The ApneaLink Air recorder and the respiratory effort sensor must be fastened with the re-usable belt on the patient's chest. All relevant respiratory information during sleep will be collected via nasal cannula, pulse oximetry adapter and respiratory effort sensor. The disposable plastic nasal cannula is connected to the ApneaLink Air recorder and fixed at the patient's nose. The oximetry sensor is connected to the patient's finger. The respiratory effort sensor is connected to the ApneaLink recorder and held in place by the belt. With the ApneaLink Air Software installed on a personal computer, the physician can generate a report with the recorded and analyzed data. The default settings for the ApneaLink Air includes a flow reduction of 30% combined with a desaturation of 4% to automatically score a hypopnea and a respiratory effort sensor to differentiate between central, obstructive and mixed apneas.

See ApneaLink Air Clinician's Manual in study Manual of Procedures for details.

7.3. Device Accountability

An accurate and current accounting of the dispensing of ResMed devices (AirSense 10 AutoSet, ApneaLink Air) will be maintained on an on-going basis by a qualified member of the study site using a “Device Disposition Log”. Devices will be made available to the investigator by ResMed. If a replacement device is dispensed, it will be documented per device accountability procedure.

7.4. Labeling

The label contains the information as required by relevant regulatory requirements:

a) Manufacturer name and address

b) Serial number to identify the individual device

c) Instruction For Use

7.5. Packaging

The AirSense 10 AutoSet and ApneaLink Air study devices are FDA 510(k) cleared in the US and are CE marked according to the European Declaration of Conformity. The devices will be used with the standard packaging.

7.6. Instruction for Use

The devices will be used as specified in the relevant Instructions for Use.

8. THERAPY

8.1. Treatment with AutoSet PAP (AirSense 10 AutoSet)

The AirSense 10 AutoSet device will be used in the hospital. Although the AutoSet device has two therapy modes, CPAP and AutoSet, only the AutoSet mode will be used for this study. The device will be used continuously for 48hrs while the subject is in hospital except when eating, using the bathroom, or going for a test. Subjects who are not able to use the device for at least 5hrs in a 24hr period or 8hrs over the 48hr period will be excluded from analysis.

8.2. Set up of AirSense 10 AutoSet

For initiation of therapy, the AutoSet device will be set to a minimum expiratory PAP (EPAP) of 8 cmH_20, a maximum EPAP of 15 cmH_2O. EPAP may be lowered to up to 6 cm if patient unable to tolerate higher EPAP.All subjects will be provided humidifiers and ClimateLine tubing to address any instance of upper airway dryness or other forms of discomfort with the airflow of the device during the initiation or during therapy with the device. For the initiation of therapy, a ResMed full face mask is recommended, but if this mask is unsuitable for the subject another type of mask such as a nasal mask will be tried. Subjects who are unable to tolerate EPAP of 8 cm of H_2O pressure will be given an acclimation trial over 2 hours at lower pressures. If despite the acclimation trial the subject is unable to tolerate the pressure, they will be discharged from the study.

8.3. Usual Medical Therapy

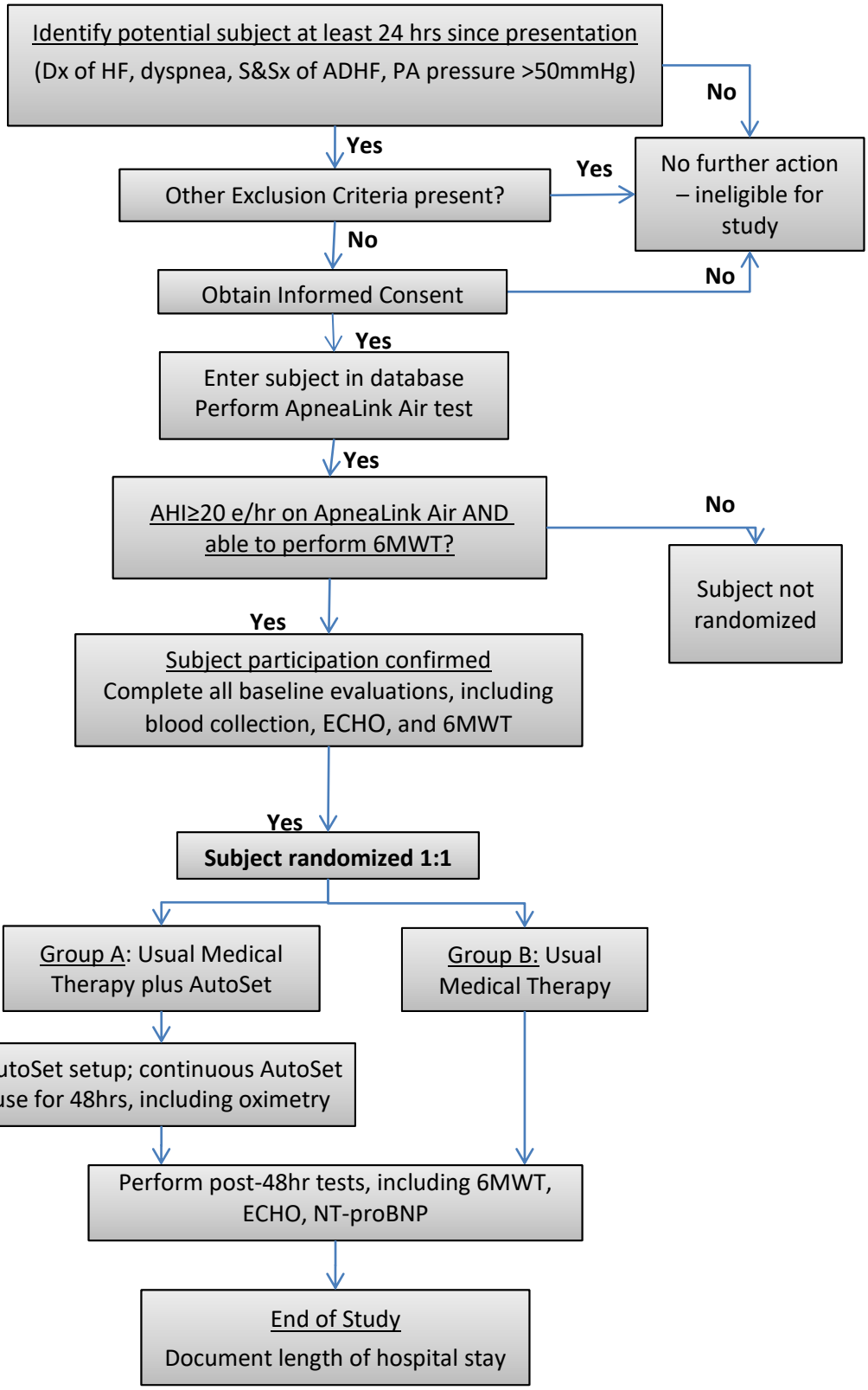
All subjects should be treated with usual therapy for heart failure in accordance to the applicable guidelines, particularly with reference to medication. Other guideline-recommended therapies should be encouraged. All medications will be documented.

9. STUDY SCHEDULE

9.1. Study Entry

A patient meets eligibility criteria of the study if all of the inclusion criteria and none of the exclusion criteria are met.

9.2. Study Flow



9.3. Follow-Up, Procedures at the visits

The clinical study plan of the ASAP-HF study includes monitoring the subject while in hospital, and evaluations after 48hrs relative to the time of randomization.

At the end of the study, for subjects in both arms of the study, there will be a discussion regarding management of the subject's sleep-disordered breathing.

See **Section** 10 for description of specific study procedures.

9.4. Screening Procedures

Patients who have been admitted to the hospital with symptoms of acute decompensated heart failure will first be evaluated for eligibility for the study based on chart review. Permission to review records will be requested to conduct preliminary chart review and interview. Review the patient's records to ensure the following:

1. The patient is hospitalized and has signs and symptoms of acute decompensated HF as determined by dyspnea and elevated BNP as listed in inclusion criteria.
2. The patient is able to perform the 6MWT (i.e., is not wheelchair-bound).
3. The patient has PA pressures of ≥50mmHg

If the patient appears to be eligible based on the initial cardiology-related entry criteria, they may be approached about study participation and consent obtained.

NOTE: All subjects who sign a consent form must be entered in the data management system, whether or not they are randomized into the study.

1. Document demographics and eligibility criteria data
2. Arrange for AHI measurement using the ApneaLink Air overnight (see Section **10.2**). Subject is <u>not</u> eligible for study entry if AHI<20 e/hr from ApneaLink Air.
3. If ApneaLink Air results show AHI≥20 e/hr with at least 2hr recording time and 5% of time <90% O_2Sat and other entry criteria are met, then subject is considered enrolled in the study.

9.5. Detailed Visit Schedule

The following visit schedule applies to subjects who met all eligibility criteria, and are enrolled in the ASAP-HF study. Document the following in the subject's medical record (source documentation).

9.5.1. Baseline	Treatment Group	
	A	B
Perform cardiac exam (including NYHA) and record vitals (including weight)	X	X
Document all medications		
Perform echocardiography	X	X
Conduct exercise capacity testing (6MWT)	X	X
Draw blood for NT-proBNP testing.	X	X

9.5.2. Randomization	Treatment Group	
	A	B
When all baseline assessment have been completed, the subject will be randomized to **Group A** (Usual Medical Treatment + continuous AutoSet therapy) or **Group B** (Usual Medical Treatment alone). ***Subjects randomized to Group A should begin using the AutoSet device immediately***.		
Mask fitting and AutoSet device set up	X	
Assess for issues with mask or AutoSet device	X	
Begin continuous AutoSet therapy while awake and asleep	X	

9.5.3. 48hrs post-randomization	Treatment Group	
	A	B
Stop AutoSet therapy; download device data	X	
Perform cardiac exam (including NYHA) and record vitals (including weight)	X	X
Document all medications	X	X
Perform echocardiography	X	X
Conduct exercise capacity testing (6MWT)	X	X
Draw blood for NT-proBNP testing	X	X
Assess for issues with mask or AutoSet device	X	

9.5.4. End of Study	Treatment Group	
	A	B
Discuss options for management of SDB	X	X
Assess for issues with mask or AutoSet device	X	
Assess for issues with sleep hygiene	X	X

Document length of hospital stay	X	X

9.6. Overview of procedures

	Screening	Baseline	48hrs	End of Study
Visit Location:	In Hospital	In Hospital	In Hospital	In Hospital
Review of HF history, signs & symptoms	X			
ApneaLink Air test	X			
Cardiovascular examination (includes ECG and NYHA)		X	X	
Echocardiography		X	X	
Exercise capacity testing (6MWT)		X	X	
Initiation of continuous AutoSet Therapy[1]		X		
AutoSet Device download[1]			X	
AE monitoring		X	X	X
Assess mask or AutoSet issues[1]		X	X	X
Labs (NT pro-BNP)		X	X	
Post study SDB management plan				X

[1] Group A only.

9.7. Duration of the study

An individual randomized subject's participation is expected to be 48hrs. The overall study duration is calculated to be approximately 6 months.

10. VISIT PROCEDURES

10.1. Cardiac Exam and Weight

The cardiovascular exam should include heart sounds, rhythm, pulses, breath sounds, as well as standardized blood pressure, heart rate, respiration rate, routine local lab tests, vitals (including weight) and ECG.

The New York Heart Association (NYHA) Functional Classification[14] provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and or angina pain:

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

NYHA Class determination should be performed by an independent assessor who is blinded to the subject's treatment group once the subject has been randomized.

10.2. Polygraphy

Every subject in the study will undergo polygraphy (including pulse oximetry) using ApneaLink Air at screening while in hospital. Data acquisition and analysis is described in the ApneaLink Systems Clinical Guide and data collection and the settings required for automatic scoring will be described in the Manual of Procedures. Completion of the test is defined as the time the report is generated.

10.3. AirSense 10 AutoSet Device Set-up

All subjects meeting eligibility criteria and randomized into Group A will be fitted with a mask and set up on the AirSense 10 AutoSet device. Subjects who are unable to tolerate EPAP of 8 cm H_2O pressure will be given an acclimation trial over 2 hours at lower pressures. If despite the acclimation trial the subject is unable to tolerate the pressure, they will be discharged from the study.

10.4. Echocardiography

Echocardiogram image acquisition protocols and procedures are provided in the Manual of Procedures. Resting transthoracic 2-D and Doppler echocardiograms will be performed in subjects at admission and at 48 hours post PAP therapy at the enrolling site for a comprehensive evaluation of systolic function, diastolic function and Doppler parameters. The primary echocardiographic endpoints are the change over time between treatment and control groups for the following parameters: Pulmonary artery systolic pressure (PASP), Right atrial pressures (RAP), Tricuspid regurgitation (TR) jet, left ventricular ejection fraction (LVEF), and left ventricular systolic volume index (LVSVI) for subjects with reduced EF (HFrEF, LVEF <45%), and the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity determinant of mean left atrial pressure (E/e‘) in subjects with preserved EF (HFpEF, LVEF≥45%). Echocardiograms should be performed at the time of discontinuation of PAP therapy.

10.5. Functional Capacity Testing (6MWT)

The 6-Minute Walk Test (6MWT) serves as an objective evaluation of the response to medical intervention. The distance walked in 6 minutes (6MWD) on a hard, flat surface is measured. The 6MWT will be performed according to standard operating procedures specified for this protocol (see Manual of Procedures). All subjects will be assessed for clinical stability immediately prior to

exercise and a physician will be in attendance during the test. Exercise will be performed on a level indoor surface following American Thoracic Society (ATS) guidelines in a way that minimizes variability. If there are any signs of medical instability, the attending physician will end the test before 6 minutes.

10.6. Biomarker testing and specimen storage

Blood will be collected and processed to obtain samples for NTpro-BNP. All samples will be sent to the site's local clinical laboratory for testing.

11. SAFETY

The investigator is responsible for monitoring the safety of subjects enrolled into the study at the study site. The investigator or qualified designee will enter the required initial and follow-up information regarding events on the appropriate eCRF within the EDC system. Investigators are responsible for following all serious adverse events (SAEs) until resolution, stabilization, or the event is otherwise explained, and to report serious adverse events as well as serious injury or death that were related to (caused by or contributed to) the AirSense 10 AutoSet study device in accordance with their local IRB/EC requirements. Investigators should follow usual clinical practice at their institutions for reporting serious events to the regulatory authorities.

11.1. Labeled Adverse Device Effects

Expected adverse device events are determined to be mild and are related to the interface (mask) between the AutoSet device and the subject. In this study any skin or eye irritation that is transient (ie, resolves within 24 hours following device use and requires no medical intervention), will not be classified as an adverse device effect.

<u>Mask</u>

- Mild skin irritation around the nose and forehead from the mask
- Mild facial abrasions from ill-fitting mask interface
- Eye irritation, caused by leakage of air from the sides of the mask

<u>Flow Generator</u>

- Drying of the nose, mouth, or throat
- Nosebleed
- Bloating
- Ear or sinus discomfort
- Eye irritation
- Skin rashes

12. STATISTICAL ANALYSIS

Descriptive summaries including medians, 25th and 75th percentiles will be presented for continuous variables; the number and frequency of subjects in each category will be presented for nominal

variables. Statistical tests with a two-sided p-value <0.05 will be considered statistically significant, unless otherwise specified. Analyses will be performed using validated software. Appropriate statistical models will be used to examine the effect of continuous APAP treatment on both the primary and secondary outcomes in the study. For continuous response (endpoint) variables, conventional general linear models will be used. For endpoints where the response is dichotomous (binary), the logistic regression model will be used. For time-to-event endpoints, the Cox regression model will be used. Subject flow will be described using a CONSORT style diagram[15]. The primary analysis will be conducted on an intention-to-treat (ITT) basis. The ITT population includes all participants who are randomized.

12.1. Primary analysis

To be determined

12.2. Secondary analyses

Continuous secondary endpoints will be analyzed analogously, possibly log-transformed if appropriate. Categorical endpoints will be compared using a Fisher's exact test.

12.3. Justification of the Sample Size

Pilot study

13. STOPPING AND DISCONTINUATION CRITERIA

It is estimated that up to 22 subjects will be recruited to obtain the 20 evaluable subjects required for the primary endpoint.

13.1. Discontinuation Criteria Related to the Study

Discontinuation of the study may be decided due to safety events as determined by the Principal Investigators.

Each site investigator will oversee the patient safety at his/her site, including the review of all Serious Adverse Events (SAEs) and unanticipated adverse device effects (UADEs), ensuring that appropriate study data are communicated to the subject's physicians and the IRB/EC, and that appropriate referrals or interventions are initiated. Major unanticipated adverse events and unanticipated product problems will be reported to the IRB/EC.

13.2. Discontinuation Criteria related to the Subject

The subjects will be advised in the consent form that they have the right to withdraw from the study at any time without prejudice. In the event that a subject drops out of the study, the Study Termination CRF should be completed. In the Study Termination CRF the investigator should record the reason for the subject's termination. Once randomized, the subject stays within his/her group, and will be followed to the end of the study. Those subjects in whom protocol deviation or

violation is noticed will remain in the intention-to-treat group and will be followed according to protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data Collection

During the study, the investigator, sub-investigator(s), or study coordinator participating in the study will record progress notes to document all data required by the protocol.

Any changes to information in the study progress notes, or other source documents, must be initialed and dated on the date the change is made by a clinician authorized to make the change.

14.2. Study Documentation

Throughout the conduct of the study, all required data will be entered into the eCRF for each subject. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the eCRFs and in all required reports. Data entered into the eCRF must be consistent with source documents. Any change or correction to an eCRF will be captured in the EDC system audit trail.

The site PI or designee and the clinical monitor will review completed eCRFs for accuracy, discrepancies, and missing information.

14.3. Query Generation and Resolution

Queries will be generated based upon anomalous or missing data and will be tracked via the EDC System.

Once all queries are resolved, the database will be verified by ensuring all electronic files were completely and correctly loaded. In addition, as part of the routine site monitoring, source documentation should be reviewed against data entered into the EDC System.

14.4. Data Storage

Access to data maintained in the EDC System is strictly limited to authorized personnel.

14.5. Study Files and Record Retention

The investigator must maintain adequate and accurate records as specified in Essential Documents for the Conduct of a Clinical Trial (E6, Section 8 of the ICH Guideline for GCP) to enable the conduct of the study to be fully documented and the study data to subsequently be verified. These documents should be classified into two separate categories: (1) investigator’s study file and (2) subject clinical source documents.

Essential documents must be retained until at least 2 years after the investigations have been discontinued OR 2 years after the last approval of a marketing application.

14.6. Regulatory Documentation

Documents that must be maintained in the study files:

- Signed, dated current (within 2 years) curriculum vitae of Investigator and Sub-Investigator(s)
- Assurance that the IRB/EC complies with requirements set forth in Title 21 Part 56 of the Code of Federal Regulations. The required documentation consists of name and address of the IRB/EC, a current list of members including title, gender, occupation and any institutional affiliation of each member. A general assurance number from the Department of Health and Human Services may be substituted for this list.
- Written notification (copy) to the Investigator from the IRB/EC approving the protocol
- IRB/EC approved informed consent (copy) and any other adjunctive materials to be used in the study as required.

15. ETHICAL CONSIDERATIONS

15.1. Institutional Review Board (IRB)/Ethics Committee (EC)

The investigator must have written and dated approval from the IRB/EC for the protocol, consent form, subject recruitment materials/process (advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/EC with a copy of the product labeling information and any updates. The investigator will provide the IRB/EC with reports, updates, and other information (e.g., safety updates and protocol amendments) as required by regulations.

15.2. Protocol Deviations

An investigator is required to conduct this study in accordance with this Investigational Plan, applicable laws and FDA regulations, and any conditions of approval imposed by the reviewing IRB/EC and FDA. According to FDA regulation 21 CFR § 812.150(a)(4), an investigator shall notify the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred.

A list of subjects with protocol deviations will be compiled based on entry criteria deviations as well as deviations from study conduct and assessments. Prior to data base lock, an evaluation of subjects with significant protocol deviations will be performed to assess the appropriateness of their inclusion in the analysis.

15.3. Risk Analysis and Confidentiality

15.3.1. Risk Determination of the Study

The AirSense 10 AutoSet device has been cleared (K140124) by FDA to provide self-adjusting treatment of obstructive sleep apnea (OSA) in patients weighing more than 66 lbs (30 kg). The device is intended for home and hospital use. The purpose of this study is to evaluate the effect of an adjunctive therapy on the hemodynamics of adult patients with acute decompensated heart failure and severe sleep apnea. Continuously treating the patient with the device over a short period of time is hypothesized to affect the pulmonary arterial pressure in these patients.

Clinical personnel will observe the subject on the fitting and use of the AutoSet device. They will monitor the subject's clinical parameters, which include hemodynamics and will intervene, if required.

This study is considered to be of minimal risk to the patients assigned to the AutoSet arm of the study. PAP therapy is the most widely accepted and effective form of treatment for SDB, and the risks associated with its use in this study are reasonable in terms of knowledge gained and potential benefits to patients. By its nature, use of PAP therapy may be associated with minor side effects. Side effects may cause minor discomfort, especially in a patient who has not previously used PAP therapy. In this study, these side effects will not be classified as adverse events unless they do not resolve within a reasonable period of time when PAP therapy is discontinued.

For patients diagnosed with severe sleep apnea and assigned to the usual medical therapy arm of the study, the risk of not providing treatment for their sleep apnea is deemed as clinically acceptable. Subjects enrolled into the study have been living with untreated sleep apnea, often for many years. The study duration (48hrs while in hospital) will not put these subjects at increased risk with regard to their sleep apnea; additionally, all subjects in the study will be counseled regarding treatment of their sleep apnea when they are discharged from the hospital.

Subjects should be encouraged to discuss any issues they are having with PAP therapy during the study. The investigator should assess for changes in the health or well-being of the subject in response to general, non-directed questioning. Side effects should be documented on the site's source documents. Any transient side effects, at a minimum, should be documented in the clinic record.

15.3.2. Subject Data Confidentiality

All information and data collected for the ASAP-HF study concerning subjects or their participation in this investigation will be considered confidential. Only authorized personnel will have access to these confidential files. All data will be handled in accordance with applicable local laws. Authorized FDA personnel or Regulatory Authorities have the right to inspect and copy all records pertinent to this investigation. All data used in the analysis and reporting of this investigation will be without identifiable reference to specific subject name.

16. QUALITY CONTROL AND QUALITY ASSURANCE

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

16.1. Site Selection

The sites should have previously participated in clinical studies and must have adequate experience, time, staff, and facilities to perform all required duties. Sites must permit clinical trial related monitoring, audits, IRB/EC review, and regulatory inspections, providing direct access to source data/documents, as appropriate.

16.2. Polygraphy Data

Each participating site will be trained and follow the clinical guide for use of the ApneaLink Air device and interpretation of data produced in the report.

16.3. Six-Minute Walk Test

Each site must demonstrate the ability to follow a standardized protocol for performance of the test, including acceptable coaching phrases according to methods described in 6MWT SOP.

16.4. Echocardiograhpy

Each site should have access to an experienced sonographer and imaging services in order to ensure image acquisition quality.

16.5. Training

Each site will be trained on the clinical protocol, study manual, ApneaLink Air and AutoSet Instructions for Use, as required. In addition, training on the Data Management System will be conducted. If new study staff members are employed at the site after the initiation, experienced site personnel must train new employees as noted above and document the training.

16.6. Site Monitoring

Each site will have an internal monitor to review the flow of the study and make sure that all procedures are being performed in a timely manner. The monitor will verify that standards of Good Clinical Practice (GCP) are being followed.

16.7. Audits and Inspections

FDA and any other regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with Federal regulations.

17. RESPONSIBILITIES

17.1. Clinical Investigator Responsibilities

With the approval of their institution's IRB/EC, qualified investigators will conduct the CAT-HF clinical investigation in accordance with the Declaration of Helsinki: "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects". Each site principal investigator and their co-investigators are responsible for the following:

- Completion of all required agreements
- Screening and evaluation of subjects
- Strict adherence to the Clinical Protocol, Study Manual of Procedures and all Federal Regulations
- Supervising investigational device use and return
- Obtaining informed consent prior to study related procedures and the collection of data during study and follow-up examinations in a timely manner
- Timely reporting of all SAEs and UADEs

It is acceptable for the site principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the site principal investigator remains responsible for proper conduct of the clinical investigation. The investigation is non-transferable to other centers attended by the investigator unless prior approval is obtained from the appropriate IRB/EC.

18. STUDY REPORTS AND PUBLICATIONS

The Principal Investigator is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

19. REFERENCES

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