SPONSOR SIGNATURE PAGE

STUDY TITLES:

AIR001-CS05 - A Phase 2, Multi-Center, Open-label, Randomized, Parallel-Dose Study to Determine the Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension

AIR002-CS06 - A Phase 2, Multi-Center, Open-label Study to Evaluate the Intermediate/Long-Term Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension

Consolidated Synoptic Report for Studies: AIR001-CS05 and AIR001-CS06

Development Phase: 2

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the studies.

Name of Sponsor Signatory:	Edwin L. Parsley, D.O.
Title of Sponsor Signatory:	Chief Medical Officer, Aires Pharmaceuticals, Inc., a wholly owned subsidiary of Mast Therapeutics, Inc.
Signature:	
Date:	14 May 2015

INVESTIGATOR SIGNATURE PAGE

STUDY TITLES:

AIR001-CS05 - A Phase 2, Multi-Center, Open-label, Randomized, Parallel-Dose Study to Determine the Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension

AIR002-CS06 - A Phase 2, Multi-Center, Open-label Study to Evaluate the Intermediate/Long-Term Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension

I have read this report and confirm that to the best of my knowledge Study AIR001-CS05 and Study AIR001-CS06 were carried out as described in this Report.

Name of Investigator:	Adaani E. Frost, MD
Affiliation:	Baylor College of Medicine, Houston, Texas, USA
Signature of Investigator:	
Date:	May 13 / 2015

Information Type: Consolidated Synoptic Clinical Study Report
Control: Dose-response without placebo

Titles:	AIR001-CS05 - A Phase 2, Multi-Center, Open-label, Randomized, Parallel-Dose Study to Determine the Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension AIR002-CS06 - A Phase 2, Multi-Center, Open-label Study to Evaluate the Intermediate/Long-Term Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension

Phase:	2
Compound Number:	AIR001
Effective Date of Report:	12-MAY-2015

Author(s): Blackman, Andy; Emery, Laura; Knight, Colin; Layton, Gary; Oakes, Mike; Parsley, Ed; Stanley, Jennifer

Study Initiation Date:	30-JAN-2013
Early Termination Date:	31-MAR-2014

Sponsor Signatory: (and Medical Officer)
Edwin L. Parsley, D.O.
Chief Medical Officer,
Aires Pharmaceuticals, Inc.,
a wholly owned subsidiary of
Mast Therapeutics, Inc.

This study was performed in compliance with Good Clinical Practices and the Sponsor's Standard Operating Procedures for all processes involved, including the archiving of essential documents. This study complies with US 21 CFR 312.120.

ABBREVIATIONS

6MWD	Six Minute Walk Distance
95% CI	95% Confidence Interval
AE	Adverse Event
BSA	Body Surface Area
CFR	Code of Federal Regulations
CI	Cardiac Index
CO	Cardiac Output
CTD	Connective Tissue Disease
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECHO	Echocardiogram
ED	Erectile Dysfunction
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
ETRA	Endothelin Receptor Antagonist
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPAH	Heritable Pulmonary Arterial Hypertension
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPAH	Idiopathic Pulmonary Arterial Hypertension
IRB	Institutional Review Board
ITT	Intent-to-treat
LVEDP	Left Ventricular End Diastolic Pressure
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean Pulmonary Arterial Pressure
mRAP	Mean Right Atrial Pressure
MUGA	Multigated Acquisition
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
PCWP	Pulmonary Capillary Wedge Pressure
PDE-5i	Phosphodiesterase-5 Inhibitor
PFT	Pulmonary Function Test
PP	Per Protocol
PVR	Pulmonary Vascular Resistance
PVRI	Pulmonary Vascular Resistance Index
QD	Once Daily
QID	Four Times Daily
QOL	Quality of Life

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SVO_2	Mixed Venous Oxygen Saturation
SVR	Systemic Vascular Resistance
TTCW	Time to Clinical Worsening
V/Q	Ventilation-Perfusion
WHO	World Health Organization

ETHICS AND GOOD CLINICAL PRACTICE

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or independent ethics committee (IEC) or institutional review board (IRB), in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of IECs. Independent ethics committee and IRB approvals are maintained in the Sponsor's study file.

This study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and, the ethical principles that are outlined in the Declaration of Helsinki 2008. The study was monitored in accordance with ICH E6 guidelines.

Investigators were trained to conduct the study in accordance with GCPs and the study protocol as defined in the ICH E3 guidance. Written commitments were obtained from investigators to comply with GCP and to conduct the study in accordance with the protocol.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. The informed consent was signed and dated by the study subject and by the person who conducted the informed consent discussion. Subject data was recorded on electronic case report forms (eCRF).

Synopsis

Name of company: Aires Pharmaceuticals, Inc.

Name of finished product: AIR001 (Sodium Nitrite) Inhalation Solution

Name of active substance: AIR001 (Sodium Nitrite)

Study Number: Study AIR001-CS05, and its extension study AIR001-CS06, are summarized in this report.

Title: A Phase 2, Multi-Center, Open-label, Randomized, Parallel-Dose Study to Determine the Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension (AIR001-CS05)

A Phase 2, Multi-Center, Open-label Study to Evaluate the Intermediate/Long-Term Safety and Efficacy of AIR001 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension (AIR001-CS06)

Investigator(s): AIR001-CS05 and AIR001-CS06 were multi-center studies.

Study center(s): Subjects were enrolled at 17 sites in 5 countries (Australia, Germany, Hungary, Poland, and the United States).

Publication(s): None at the time of this report.

Study Period: 30 January 2013 to 31 March 2014

Phase of Development: 2

Objectives:

Primary Objectives

The primary objective of study AIR001-CS05 was to evaluate the efficacy of inhaled nebulized AIR001 administered for 16 weeks, according to 3 treatment arms (80 mg once daily [QD], 46 mg 4 times daily [QID], or 80 mg QID) in subjects with World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), as determined by change in Pulmonary Vascular Resistance (PVR) from Baseline to Week 16 measured post completion of AIR001 nebulization.

The primary objective of the extension study AIR001-CS06 was to evaluate the intermediate/long-term safety of inhaled nebulized AIR001 in subjects with WHO Group 1 PAH who completed the 16-week AIR001-CS05 study and continued therapy in AIR001-CS06.

Secondary Objectives

The secondary objectives of study AIR001-CS05 were:

- To evaluate the effect of inhaled nebulized AIR001 administered according to 3 treatment arms (80 mg QD, 46 mg QID, or 80 mg QID) in subjects with WHO Group 1 PAH for 16 weeks, as determined by time to the first morbidity/mortality event as defined in Time to Clinical Worsening (TTCW) assessments.

- Change from Baseline to Week 16 in the following:

  - Pulmonary Vascular Resistance Index (PVRI)
  - N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP)
  - 6-Minute Walk Distance (6MWD) assessed immediately post completion of AIR001 nebulization (peak) but no more than 40 minutes after completion of AIR001 nebulization
  - 6MWD assessed prior to AIR001 nebulization (trough)
  - Cardiac Output (CO), Cardiac Index (CI)
  - Mean Right Atrial Pressure (mRAP)
  - WHO/New York Heart Association (NYHA) Functional Class
  - Quality of Life (QOL) as measured by Short-Form 36 (SF-36®) health survey instrument
  - Borg Dyspnea Index
  - Mean pulmonary artery pressure (mPAP)
  - PVR measured at greater than 5 hours after last AIR001 nebulization (trough)
  - PVR/systemic vascular resistance (SVR) ratio at greater than 5 hours after the last AIR001 nebulization (trough) and immediately post completion of AIR001 nebulization (peak)

- To evaluate the safety and tolerability of AIR001 in subjects with WHO Group 1 PAH.

The secondary objectives of extension study AIR001-CS06 were to evaluate the effect of inhaled nebulized AIR001 in subjects with WHO Group 1 PAH who completed the 16-week AIR001-CS05 study. Change from Baseline in AIR001-CS05 to the completion (40th week) or end of treatment in AIR001-CS06 in the following parameters were assessed:

- Time to the first morbidity/mortality event as defined in TTCW assessments

- Change 6MWD assessed immediately post completion of AIR001 nebulization (peak) but no more than 40-minutes after completion of AIR001 nebulization

- Change from Baseline in the following:

  - WHO/ NYHA functional class
  - QOL as measured by SF-36® health survey instrument
  - Borg Dyspnea Index
  - 6MWD assessed prior to AIR001 nebulization (trough)

Methodology: Study AIR001-CS05 was a Phase 2, multi-center, open-label, randomized (1:1:1), parallel-dose study to determine the safety and efficacy of inhaled nebulized AIR001 in subjects with WHO Group 1 PAH. AIR001 was delivered by the I-Neb AAD System nebulizer (I-Neb). A separate sub-study at selected sites was also planned to evaluate peak and trough hemodynamic catheterization parameters and pharmacokinetics (PK).

A screening evaluation was conducted over a period of 30 days prior to baseline/Day 1 to confirm the PAH diagnosis, assess the disease state, and determine the eligibility of each potential subject. The screening period began when the subject signed the

informed consent. All screening procedures were to be completed within 30 days prior to Baseline/Day 1. Screening documents for all subjects who were potentially eligible for randomization were reviewed by the Sponsor. Subjects approved by the Sponsor for randomization were centrally randomized to 1 of 3 dose groups: 80 mg QID, 46 mg QID, or 80 mg QD. A dynamic balancing randomization program was used in an attempt to maintain balance across treatment groups with respect to the following stratification factors:

- Inclusion in PK sub-study (Yes/No)
- Baseline PVR (≤800 and >800 dyn.sec/cm^5)
- Connective Tissue Disease (CTD) associated PAH vs. all other PAH classifications
- Baseline WHO functional class (Class II vs. III or IV)
- Baseline concomitant use of two disease-specific PAH therapies vs. concomitant use of one or none

The length of the treatment phase for all randomized subjects in study AIR001-CS05 was 16 weeks, unless the subject was prematurely discontinued from the study. All randomized subjects received 46 mg of nebulized AIR001 (either 1 or 4 times daily depending upon randomization) during the first 2 weeks of treatment (Run-in Period). Following the Run-in Period, subjects received their randomized dose during the remainder of the study (Targeted-Dose Period). Scheduled visits and assessments were performed according to the protocol as described in the AIR001-CS05 Schedule of Events Table (Table 11).

Subjects receiving 80 mg of nebulized AIR001 in the Targeted-Dose Period were permitted a one-time dose reduction to 46 mg, if hemodynamic intolerance was demonstrated or in the event of a dose-limiting adverse event (AE) (subject to approval by the Sponsor).

Subjects who completed the AIR001-CS05 study as planned (i.e., full 16-week study period) were eligible to enroll directly into the open-label extension study AIR001-CS06. Subjects continued to receive treatment in the extension study as assigned in AIR001-CS05. Subjects who prematurely discontinued from the AIR001-CS05 study were not eligible for AIR001-CS06.

The duration of treatment in the AIR001-CS06 study was at least 24 weeks, unless the subject was prematurely discontinued from the study. Scheduled visits and assessments were performed according to the protocol as described in the AIR001-CS06 Schedule of Events Table (Table 12). Subjects were to continue treatment in Study AIR001-CS06 until the last enrolled subject had completed the 24-week treatment period.

Number of subjects: 90 subjects (at least 27 per arm) were targeted for enrollment. A total of 29 subjects were randomized (10 subjects in the AIR001 80 mg QID group, 9 subjects in the AIR001 46 mg QID group, and 10 subjects in the AIR001 80 QD group). The study was terminated early by the Sponsor for administrative reasons. Three subjects were enrolled in the PK substudy at 1 site in the US (Source: Table 14.1.7).

Diagnosis and main criteria for inclusion:

Key Inclusion Criteria:

- Current diagnosis of symptomatic PAH classified by one of the following:

a. Idiopathic (IPAH) or heritable pulmonary arterial hypertension (HPAH); or

b. PAH associated with one of the following CTD:

i. Systemic sclerosis (scleroderma)
ii. Limited scleroderma
iii. Mixed connective tissue disease
iv. Systemic lupus erythematosus
v. Overlap syndrome

c. PAH associated with:

i. Human immunodeficiency virus (HIV) infection
ii. Simple, congenital systemic-to-pulmonary shunts at least one year post-surgical repair
iii. Exposure to legal drugs, chemicals and toxins, such as fenfluramine derivatives, other anorexigens, toxic rapeseed oil or L-tryptophan. Subjects with PAH associated with illegal drug use, such as methamphetamine, are excluded.

- Cardiac catheterization prior to screening consistent with the diagnosis of PAH that met all of the following criteria:

  a. mPAP ≥25 mmHg (at rest) and

  b. Pulmonary capillary wedge pressure (PCWP) ≤15 mmHg (Note: If PCWP was not available, then mean left atrial pressure (mLAP) or left ventricular-end diastolic pressure (LVEDP) ≤15 mmHg in the absence of left atrial obstruction was allowed.) and

  c. PVR >3 mmHg/L/min or 240 dyn.sec/cm^5.

- A qualification cardiac catheterization was required to confirm the persistence and severity of PAH, if the diagnostic catheterization was performed more than 1 month (30 days) prior to baseline/Day 1. This catheterization was used to provide baseline hemodynamic values for efficacy analyses. A cardiac catheterization performed within 1 month (30 days) prior to Baseline/Day 1, per the subject standard medical care (not for the purposes of this study) was allowed in lieu of repeating the test, if all the following criteria were met:

  a. Confirms diagnosis as per the required data points (PVR, CO, CI, mPAP, mRAP, PCWP, SVR, and mixed venous oxygen saturation [SVO2])

  b. PVR above 300 dyn.sec/cm^5 on the catheterization study used to qualify the subject for the study (to demonstrate the persistence and severity of PAH)

  c. No change in disease-specific PAH therapy since the catheterization used to qualify the subject for the study was performed.

- Newly diagnosed PAH on no disease-specific PAH therapy or previously diagnosed with PAH on stable (i.e., 3 months [90 days] prior to the baseline qualification cardiac catheterization) oral disease-specific PAH therapy with either an endothelin receptor antagonist (ETRA) and/or phosphodiesterase-5 inhibitor (PDE-5i). Doses of these

agents were to remain stable throughout the study. The use of PDE-5i as needed for erectile dysfunction (ED) was permitted as long as the subject did not take a dose within 48 hours of any baseline or study-related efficacy assessment. Subjects were not allowed to take more than 8 sildenafil tablets, 6 vardenafil tablets, or 4 tadalafil tablets per month for ED.

- Subjects were required to have pulmonary function tests (PFTs) within 6 months (180 days) prior to Baseline/Day 1 with no evidence of significant parenchymal lung disease. Parenchymal lung disease was defined as:
    - Forced expiratory volume in 1 second (FEV_1) ≤70% (predicted) (pre-bronchodilators)
    - Forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC) ≤70% (pre-bronchodilators) or
    - Total lung capacity <70% (predicted).
- WHO/NYHA functional class II - IV symptomatology.
- Male or female ≥18 and ≤75 years of age at screening.
- Body weight ≥40 kg at screening.
- Subjects were required to have a 6MWT distance of ≥50 meters at screening. If the distance walked was not within the required range, a 2nd assessment (conducted on a separate day) was allowed. The distance walked during the 2nd assessment must have been ≥50 meters and within 15% of the first distance walked.
- Subjects were required to have a ventilation-perfusion (V/Q) lung scan or pulmonary angiogram prior to screening that showed no evidence of thromboembolic disease (i.e., noted as “normal” or “low probability” for pulmonary embolism). V/Q scanning was preferred, but if unavailable, spiral/helical/electron beam computed tomography (CT) angiography was considered acceptable in subjects with NO history of venous thromboembolic disease. If V/Q scan was unavailable and subject had a prior history of venous thromboembolic disease, then selective pulmonary angiography was required to exclude chronic thromboembolic disease. If a V/Q scan was abnormal (i.e., anything other than “normal” or “low probability”), then a selective pulmonary angiography must have been conducted to exclude chronic thromboembolic disease. All tests were required to be performed prior to screening.
- Subjects receiving any of the following therapies that may affect PAH were required to be on a stable dose for at least 1 month (30 days) prior to baseline/Day 1 and the dosage maintained throughout the study: vasodilators (including calcium channel blockers), digoxin, spironolactone, or L-Arginine supplementation.
- Subjects receiving corticosteroids must have been on a stable dose of ≤20 mg/day of prednisone (or equivalent dose, if other corticosteroid) for at least 1 month (30 days) prior to study baseline/Day 1. If any other drug treatment was received for CTD, doses were to remain stable for the duration of the study.

- Women of childbearing potential were required to use at least one form of medically acceptable contraception or two barrier methods during the study. Negative pregnancy tests were required at screening and baseline/Day 1. Women who were surgically sterile or post-menopausal for at least 2 years were not considered to be of childbearing potential. Men who were not sterile (i.e., did not have a vasectomy) were also required to use contraception during the study.

Key Exclusion Criteria:

- Participant in a device or other interventional clinical study
- Participant in a cardio-pulmonary rehabilitation program based upon exercise within 1 month (30 days) prior to baseline/Day 1 and/or during study participation.
- Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (SBP) >160 millimeters of mercury (mmHg) or sitting diastolic blood pressure (DBP) >100 mmHg during screening.
- Sitting SBP <90 mmHg at screening or baseline/Day 1.
- History of orthostatic hypotension or demonstrated orthostatic hypotension at screening, defined as a drop in SBP by ≥20 mmHg or DBP of ≥10 mmHg or the development of significant postural symptoms (e.g., syncope, near syncope, lightheadedness, or vertigo) when going from the supine to the standing position.
- History of left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    - Aortic or mitral valve disease (stenosis or regurgitation) defined as greater than mild aortic insufficiency;
    - Pericardial constriction;
    - Restrictive or congestive cardiomyopathy;
    - Left ventricular ejection fraction <40% by multiple gated acquisition scan (MUGA), angiography or echocardiography (ECHO) prior to screening;
    - Left ventricular shortening fraction <22% by ECHO prior to screening;
    - Symptomatic coronary disease.
    - Significant (2+ for regurgitation) valvular disease other than tricuspid or pulmonary regurgitation.
    - Acutely decompensated heart failure within 1 month (30 days) prior to baseline/Day 1.
- History of atrial septostomy within 6 months (180 days) prior to baseline/Day 1.
- History of obstructive sleep apnea (treated, untreated or resolved).
- Moderate to severe hepatic impairment classified as a Child-Pugh Class B or C at screening.
- Chronic renal insufficiency as defined by serum creatinine >2.5 mg/dL or an estimated Glomerular Filtration Rate (eGFR) <30 mL/min at screening, or subjects who required dialytic support.

- Hemoglobin (Hgb) concentration <8.5 g/dL at screening.

- For subjects with HIV-associated PAH, any of the following:

    - Concomitant active opportunistic infections within 6 months (180 days) prior to screening;
    - Detectable viral load within 3 months (90 days) of screening;
    - Cluster designation (CD4+) T-cell count < 200 mm^3 within 3 months (90 days) of screening;
    - Changes in antiretroviral regimen within 3 months (90 days) of screening;
    - Using inhaled pentamidine.

Subjects receiving any prohibited concomitant medications according to the protocol were also excluded.

Treatment administration: All subjects in the study received nebulized AIR001 at 1 of 3 randomized doses: 80 mg QID, 46 mg QID, or 80 mg QD.

Batch numbers for study drug used during the trial are available upon request.

Criteria for evaluation:

Efficacy Assessments: Hemodynamic evaluations were completed via cardiac catheterization, according to the detailed instructions in the AIR001-CS05 study protocol. Blood samples for analysis of NT-proBNP were collected at designated intervals throughout the studies. 6MWTs were performed to assess subjects' sub-maximal aerobic capacity, followed immediately by an evaluation of dyspnea using the Borg Dyspnea Index (conducted at peak and trough). Functional assessments using WHO/NYHA functional class scales were performed at designated intervals throughout the studies. A detailed definition of clinical worsening was provided in the study protocols. Hemodynamics were only evaluated at Baseline and pre- and post-dose at Week 16 (or End of Treatment visit) in AIR001-CS05. Other efficacy assessments were performed during the studies according to the Schedule of Events Tables in each protocol.

Safety Assessments: Safety assessments included monitoring and recording all AEs and serious AEs (SAEs), evaluation of laboratory parameters (hematology and chemistry), collection of vital signs, electrocardiogram (ECG) assessments, and evaluation of pulmonary function tests. Laboratory samples were analyzed using a central laboratory. Investigators were responsible for appropriate medical care of subjects during the study and for the detection, documentation, and reporting of all events that met the definition of an AE or SAE according to the study protocols. Adverse events were collected after the first dose of study drug until completion of study participation or early termination. Serious AEs were collected from the time informed consent was signed until 14 days after the last dose of study drug. Safety assessments were performed according to the Schedule of Events Table for each study. A Data Safety Monitoring Board (DSMB) was established to independently monitor the safety of subjects throughout the study.

Statistical methods:

Sample Size Determination: With at least 27 subjects per treatment group, testing the change from baseline to Week 16 in PVR (measured immediately post completion of

AIR001 nebulization) at the 10% level of significance (1-tailed) and assuming a standard deviation of 300 dyn.sec/cm^5, within group comparisons had at least 80% power to obtain a statistically significant result, if the true effect size was a reduction of 125 dyn.sec/cm^5.

The within group comparison when the 2 QID doses were pooled would have had at least 96% power of demonstrating statistical significance. The between group test comparing the combined QID groups with the QD group would have had at least 68% power to obtain a statistically significant difference.

Analysis Populations: The intent-to-treat (ITT) population, which was used in all analyses of efficacy, included all subjects who were randomized to study treatment and received at least 1 dose of study drug. The safety population, which was used in all safety analyses, included all randomized subjects who received at least 1 dose of study drug and was identical to the ITT population. A per-protocol (PP) population was defined in the statistical analysis plan (SAP) for the PVR and 6MWD efficacy endpoints; however, the PP analyses were not performed due to the reduced sample size with early termination of the study.

Efficacy: Statistical methods for the primary, all secondary efficacy analyses, and exploratory efficacy analyses that were to be conducted are described in detail in the AIR001-CS05 and AIR001-CS06 SAPs. For the primary efficacy analysis of change from baseline in PVR, missing scores were to be imputed using the technique of multiple imputation, under the assumption that scores were missing at random (MAR). The small sample size entailed by the early termination of the study resulted in the covariates employed in the imputation model being reduced to treatment group, baseline PVR, baseline 6MWD, baseline WHO functional class, body surface area (BSA), etiology (CTD vs. Non-CTD subjects) and concomitant use, at randomization, of two disease-specific PAH therapies vs. concomitant use of one or none as covariates. Furthermore, in order to achieve model convergence, the data was log-transformed prior to analysis. Overall changes from baseline in PVR were assessed by one-way analysis of variance with treatment as the factor.

Safety: All safety endpoints were reported in summary tables and listings, including AEs, SAEs, AEs leading to discontinuation, changes and shifts from baseline in hematology and clinical chemistry laboratory parameters, changes in vital sign and ECG parameters, changes in pulmonary function tests, and study drug dose reductions. Any deaths during the study were to be listed. Presentations were by randomized treatment group, and summaries within each treatment group were grouped by actual dose at the time of the event (i.e., occurred during Run-in Period, during Targeted-dose Period, or after any down-titration). No statistical significance testing was performed on any safety results.

Summary:

Subject Disposition: The AIR001-CS05 study enrolled 29 subjects in 5 countries (10 subjects in the AIR001 80 mg QID group, 9 subjects in the AIR001 46 mg QID group, and 10 subjects in the AIR001 80 QD group) (Source: Table 14.1.1). All 29 randomized subjects were included in the ITT and safety populations. Study AIR001-CS05 and study AIR001-CS06 were terminated by the Sponsor due to administrative reasons on 31 March 2014. A total of 22 subjects (76%) completed participation in study AIR001-CS05 (Source: Table 14.1.1). Five of the 7 subjects who

prematurely discontinued study treatment did so due to AEs. Four subjects discontinued study treatment due to AEs as reported on the study termination page (Subject 131002, Subject 105002, Subject 115001, and Subject 108001) (Source: Listing 16.2.1), and 1 additional subject (Subject 118002) discontinued study treatment due to an AE according to the AE log (Source: Listing 16.2.4.3). The majority of withdrawal AEs were severe (Subjects 131002, 105002, 108001, and 118002), but all were considered unrelated to study treatment. The fatigue and cough in Subject 115001 were reported as moderate and considered related to study treatment by the investigator.

Seventeen of the 22 subjects who completed study AIR001-CS05 agreed to participate in study AIR001-CS06. The majority of these subjects (n=16; 94%) were still receiving study drug at the time of study termination. Most randomized subjects (n=25; 86%) received at least 12 weeks of study treatment prior to study closure (Source: Table 14.1.4).

Demographics and Baseline Characteristics: All randomized subjects were White, and most were female (Table 1). The mean age was 50.3 years across the treatment groups, with slightly older subjects randomized into the AIR001 46 mg QID arm. Approximately half (48%) of the randomized subjects had IPAH or HPAH (Table 2). Of note, fewer subjects with this etiology were randomized into the 80 mg QID arm compared with the other 2 treatment arms. Of the remaining subjects, 28% had PAH due to CTD (primarily systemic scleroderma or lupus erythematosus). All subjects were WHO Class II (59%) or III (41%) at study entry. The majority of randomized subjects (90%) were receiving standard of care concomitant therapy for PAH, including monotherapy with a PDE-5i or ETRA or dual therapy with both agents. Most subjects were diagnosed and initiated standard of care PAH treatment >24 months prior to study entry (Source: Table 14.1.9.2). Ten percent of randomized subjects were treatment naïve (Table 2). Baseline hemodynamic values were consistent with those expected for the target PAH population.

Table 1 Subject Demographics

	AIR001 80 mg QD (N=10)	AIR001 46 mg QID (N=9)	AIR001 80 mg QID (N=10)	Overall (N=29)
Age, yrs				
Mean (95% CI)	49.5 (41.3, 57.7)	57.9 (51.8, 64.0)	44.3 (36.5, 52.1)	50.3 (46.0, 54.7)
Median	46.0	59.0	41.5	49.0
Minimum	38	47	27	27
Maximum	67	73	62	73
Gender, n (%)				
Male	3 (30)	1 (11)	3 (30)	7 (24)
Female	7 (70)	8 (89)	7 (70)	22 (76)
Race, n (%)				
White	10 (100)	9 (100)	10 (100)	29 (100)
Hispanic	0	1 (11)	2 (20)	3 (10)
Non-Hispanic	10 (100)	8 (89)	8 (80)	26 (90)
Weight, kg				
Median	73.0	69.6	68.5	71.1
Minimum	57.7	52.3	54.0	52.3
Maximum	110.0	122.5	108.0	122.5
Body mass index, kg/m^2				
Median	26.8	27.2	24.7	26.7
Minimum	22.5	20.9	21.8	20.9
Maximum	39.4	44.9	31.4	44.9

Source: Table 14.1.5

Table 2 Baseline Characteristics

	AIR001 80 mg QD (N=10)	AIR001 46 mg QID (N=9)	AIR001 80 mg QID (N=10)	Overall (N=29)
PAH Etiology, n (%)				
IPAH or HPAH	5 (50)	6 (67)	3 (30)	14 (48)
Associated with CTD	3 (30)	2 (22)	3 (30)	8 (28)
Systemic scleroderma[a]	1 (33)	2 (100)	0	3 (38)
Limited scleroderma[a]	0	0	1 (33)	1 (13)
Mixed connective tissue disease[a]	1 (33)	0	0	1 (13)
Systemic lupus erythematosus[a]	1 (33)	0	2 (67)	3 (38)
Associated with Other	2 (20)	1 (11)	4 (40)	7 (24)
HIV infection[b]	0	0	1 (25)	1 (14)
Simple, congenital systemic-to-pulmonary shunts[b]	1 (50)	1 (100)	2 (50)	4 (57)
Drugs and toxins[b]	1 (50)	0	1 (25)	2 (29)
PAH Disease Specific Therapy, n (%)				
Naïve	0	3 (33)	0	3 (10)
Monotherapy	4 (40)	3 (33)	6 (60)	13 (45)
PDE-5i[c]	3 (75)	1 (33)	3 (50)	7 (54)
ETRA[c]	1 (25)	2 (67)	3 (50)	6 (46)
Dual therapy (PDE-5i and ETRA)	6 (60)	3 (33)	4 (40)	13 (45)
Pulmonary Vascular Resistance (PVR), dyn.sec/cm^5				
Mean (95% CI)	648.9 (439.0, 858.9)	541.3 (344.4, 738.2)	797.4 (426.2, 1168.6)	666.7 (522.3, 811.2)
Median	568.1	458.0	675.7	567.2
Minimum	349.0	314.8	370.8	314.8

	AIR001 80 mg QD (N=10)	AIR001 46 mg QID (N=9)	AIR001 80 mg QID (N=10)	Overall (N=29)
Maximum	1168.2	1036.5	2160.0	2160.0
Pulmonary Vascular Resistance Index (PVRI), dyn.sec.m^2/cm^5				
Mean (95% CI)	1190.2 (815.7, 1564.7)	944.6 (569.2, 1320.0)	1437.9 (755.9, 2119.8)	1190.9 (934.9, 1446.8)
Median	1120.0	805.2	1237.0	996.8
Minimum	569.7	535.2	704.5	535.2
Maximum	1863.7	1944.3	3626.7	3626.7
Mean Arterial Pressure (MAP), mmHg				
Mean (95% CI)	95.4 (83.7, 107.2)	93.8 (82.4, 105.2)	87.9 (78.6, 97.2)	92.3 (86.8, 97.9)
Median	95.0	92.0	85.2	92.0
Minimum	67.3	75.3	66.0	66.0
Maximum	124.0	126.3	105.0	126.3
Mean Pulmonary Artery Pressure (mPAP), mmHg				
Mean (95% CI)	45.8 (40.4, 51.3)	39.9 (33.0, 46.8)	48.0 (38.4, 57.5)	44.7 (40.7, 48.7)
Median	46.0	39.0	45.0	43.0
Minimum	35.0	29.0	37.0	29.0
Maximum	55.0	52.0	80.0	80.0
Mean Right Atrial Pressure (mRAP), mmHg				
Mean (95% CI)	8.2 (6.2, 10.2)	5.3 (2.8, 7.8)	6.2 (3.1, 9.3)	6.6 (5.2, 8.0)
Median	8.0	5.0	4.5	6.0
Minimum	5.0	2.0	0	0
Maximum	13.0	13.0	15.0	15.0
Cardiac Output (CO), L/min				
Mean (95% CI)	4.7 (3.9, 5.4)	5.1 (4.1, 6.1)	4.6 (3.5, 5.8)	4.8 (4.3, 5.3)
Median	4.6	4.9	4.3	4.7
Minimum	3.2	3.0	2.5	2.5
Maximum	6.6	6.8	7.5	7.5
6MWD, meters				
Mean (95% CI)	460.5 (392.8, 528.2)	375.2 (252.7, 497.7)	444.3 (352.8, 535.8)	428.4 (379.2, 477.7)
Median	480.5	456.0	459.5	461.0
Minimum	303.0	148.0	237.0	148.0
Maximum	591.0	517.0	600.0	600.0
Concomitant Therapy Use at Randomization, n (%)				
2 disease-specific PAH therapies	6 (60)	3 (33)	6 (60)	13 (45)
1 or no disease-specific PAH therapies	4 (40)	6 (67)	4 (40)	16 (55)
WHO Functional Class, n (%)				
Class I	0	0	0	0
Class II	5 (50)	5 (56)	7 (70)	17 (59)
Class III	5 (50)	4 (44)	3 (30)	12 (41)

Source: Table 14.1.6, Table 14.1.7

a. Denominator is number of subjects with PAH associated with CTD in each treatment group.

b. Denominator is number of subjects with PAH associated with Other in each treatment group.

c. Denominator is number of subjects receiving monotherapy in each treatment group.

Efficacy: Overall, median peak PVR was reduced by 12.6 dyn.sec/cm^5 compared with baseline values in the End of Treatment Analysis (Table 3). The largest decrease in median PVR was observed in the AIR001 80 mg QD arm (-69.0 dyn.sec/cm^5). Reductions in median PVR were also noted in the 46 mg QID and 80 mg QID dose groups. In contrast, *mean* PVR increased slightly in the study population overall in this analysis (Table 3). Reductions in mean PVR were observed in the 80 mg QD (-8.4 dyn.sec/cm^5) and 46 mg QID dose groups (-6.5 dyn.sec/cm^5), subjects in the 80 mg QID arm experienced an increase in mean PVR at the end of treatment (33.5 dyn.sec/cm^5) compared with baseline values. However, given the small sample size, outliers greatly affected results.

There was little change in peak PVR in the primary multiple imputation analysis (Table 4). Given the small sample size in each group, multiple imputation analyses may be considered somewhat unreliable, as changes in PVR in each dose group were inconsistent with results overall when multiple imputation was used (Source: Table 14.2.1.2.1).

Table 3 Summary of Change from Baseline in PVR (Peak) at End of Treatment

	Overall (N=29)		
	Baseline	**End of Treatment Value**	**Change from Baseline**
n	20	20	20
Mean PVR (95% CI), dyn.sec/cm^5	658.2 (455.2, 861.3)	672.8 (473.4, 872.3)	14.6 (-48.3, 77.6)
Median	508.8	611.1	-12.6
Minimum	315	252	-169
Maximum	2160	2158	285
Geometric LS Mean (95% CI)[a]	1.01 (0.90, 1.14)		
p-value	0.796		
	AIR001 80 mg QD (N=10)		
	Baseline	**End of Treatment Value**	**Change from Baseline**
n	9	9	9
Mean PVR (95% CI), dyn.sec/cm^5	682.2 (458.6, 905.9)	673.8 (455.2, 892.5)	-8.4 (-121.5, 104.6)
Median	642.1	662.0	-69.0
Minimum	349	280	-169
Maximum	1169	1080	237
	AIR001 46 mg QID (N=9)		
	Baseline	**End of Treatment Value**	**Change from Baseline**
n	5	5	5
Mean PVR (95% CI), dyn.sec/cm^5	388.9 (248.4, 529.5)	382.4 (167.8, 596.9)	-6.5 (-122.4, 109.4)
Median	351.0	289.0	-36.6
Minimum	315	252	-115
Maximum	588	667	102

	Overall (N=29)		
	Baseline	**End of Treatment Value**	**Change from Baseline**
	AIR001 80 mg QID (N=10)		
	Baseline	**End of Treatment Value**	**Change from Baseline**
n	6	6	6
Mean PVR (95% CI), dyn.sec/cm5	638.5 (277.4, 999.7)	672.0 (316.4, 1027.6)	33.5 (-52.0, 119.0)
Median	399.0	600.0	-1.8
Minimum	315	252	-125
Maximum	2160	2158	285

Source: Table 14.2.1.1.1, Table 14.2.1.1.2
Note: Table includes only subjects with available end of treatment assessments.
a. Analysis of variance (ANOVA) model includes treatment as a factor.

Table 4 Summary of Change from Baseline to Week 16 in PVR (Peak) Using Multiple Imputation (Primary Endpoint Analysis)

	Overall (N=29)		
	Baseline	**Week 16 Value**	**Change from Baseline**
n	29	29	29
Mean PVR (95% CI), dyn.sec/cm5	666.8 (522.3, 811.3)	710.8 (560.6, 860.9)	44.0 (-7.8, 95.8)
Median	567.2	639.2	21.9
Minimum	315	252	-169
Maximum	2160	2158	371
Geometric LS Mean (95% CI)[a]	1.03 (0.91, 1.16)		
p-value	0.654		

Source: Table 14.2.1.2.1, Table 14.2.1.2.2
a. Analysis of variance (ANOVA) model includes treatment as a factor.

Improvements in peak 6 MWD were observed during the study (Table 5). Overall, subjects with an available Week 16 assessment (n=15) experienced a 20.0 meter improvement in mean peak 6 MWD (median: 24 meters) compared with baseline. The most notable observation was an increase in mean peak 6 MWD of 33.5 meters in subjects in the 80 mg QID dose group at Week 16 compared with baseline values. Subjects in the 46 mg QID dose group had the smallest change in peak 6 MWD (mean: 2.4 meters; median: -6.0 meters). Improvements in peak 6 MWD were also observed in some treatment groups in the Week 16 LOCF analysis; although, the magnitude of change was generally lower (Table 6).

Table 5 Summary of Change from Baseline to Week 16 in 6 Minute Walk Distance (Peak)

	Overall (N=29)		
	Baseline	**Week 16 Value**	**Change from Baseline**
n	20	20	20
Mean (95% CI), meters	453.7 (398.7, 508.6)	471.3 (414.3, 528.3)	17.7 (2.3, 33.0)
Median	491.0	495.5	18.5
Minimum	175	165	-63
Maximum	600	658	67
	AIR001 80 mg QD (N=10)		
	Baseline	**Week 16 Value**	**Change from Baseline**
n	8	8	8
Mean (95% CI), meters	439.5 (360.1, 518.9)	466.3 (391.2, 541.3)	26.8 (2.8, 50.7)
Median	460.5	473.0	30.0
Minimum	303	324	-7
Maximum	586	585	67
	AIR001 46 mg QID (N=9)		
	Baseline	**Week 16 Value**	**Change from Baseline**
n	5	5	5
Mean (95% CI), meters	435.2 (249.8, 620.6)	437.6 (241.9, 633.3)	2.4 (-54.5, 59.3)
Median	487.0	485.0	-6.0
Minimum	175	165	-63
Maximum	548	546	55
	AIR001 80 mg QID (N=10)		
	Baseline	**Week 16 Value**	**Change from Baseline**
n	7	7	7
Mean (95% CI), meters	483.0 (363.6, 602.4)	501.1 (373.9, 628.4)	18.1 (-7.4, 43.7)
Median	528.0	544.0	16.0
Minimum	240	252	-30
Maximum	600	658	58

Source: Table 14.2.3.1.1
Note: Table includes only subjects with available Week 16 assessments.

Table 6 Summary of Change from Baseline to Week 16 in 6 Minute Walk Distance (Peak) - LOCF Analysis

	Overall (N=29)		
	Baseline	**Week 16 LOCF Value**	**Change from Baseline**
n	29	29	29
Mean (95% CI), meters	427.1 (378.3, 476.0)	437.8 (385.4, 490.2)	10.7 (-3.3, 24.6)
Median	461.0	485.0	8.0
Minimum	148	91	-63
Maximum	600	658	75
	AIR001 80 mg QD (N=10)		
	Baseline	**Week 16 LOCF Value**	**Change from Baseline**
n	10	10	10
Mean (95% CI), meters	456.3 (391.1, 521.5)	477.4 (417.9, 536.9)	21.1 (0.9, 41.3)
Median	478.0	495.5	14.0
Minimum	303	324	-10
Maximum	586	585	67

	Overall (N=29)		
	Baseline	**Week 16 LOCF Value**	**Change from Baseline**
	AIR001 46 mg QID (N=9)		
	Baseline	**Week 16 LOCF Value**	**Change from Baseline**
n	9	9	9
Mean (95% CI), meters	378.7 (253.3, 504.1)	371.4 (234.1, 508.8)	-7.2 (-37.1, 22.6)
Median	456.0	450.0	-6.0
Minimum	148	91	-63
Maximum	548	546	55
	AIR001 80 mg QID (N=10)		
	Baseline	**Week 16 LOCF Value**	**Change from Baseline**
n	10	10	10
Mean (95% CI), meters	441.6 (351.5, 531.7)	457.9 (364.1, 551.7)	16.3 (-12.3, 44.9)
Median	454.5	460.5	18.0
Minimum	240	252	-61
Maximum	600	658	75

Source: Table 14.2.3.1.1
Note: Table includes all randomized subjects by treatment group. For subjects without an available Week 16 assessment, the last available peak 6 MWD value was used in the analysis.
Abbreviation: LOCF=last observation carried forward.

Reductions in median mRAP (-1.0 mmHg) and median PCWP (-2.0 mmHg) were observed at the end of study treatment (Table 7). There were no important differences in these parameters noted between dose groups in the enrolled subject population.

Table 7 Summary of Changes from Baseline in mRAP and PCWP

Mean Right Atrial Pressure (mRAP)	**Overall (N=29)**	
	Baseline	**End of Treatment Change from Baseline**
n	29	20
Mean (95% CI), mmHg	6.6 (5.2, 8.0)	-0.9 (-1.8, 0.0)
Median	6.0	-1.0
Minimum	0	-4
Maximum	15	3
Pulmonary Capillary Wedge Pressure (PCWP)	**Overall (N=29)**	
	Baseline	**End of Treatment Change from Baseline**
n	29	20
Mean (95% CI), mmHg	9.0 (7.8, 10.2)	-1.3 (-2.7, 0.1)
Median	9.0	-2.0
Minimum	3	-5
Maximum	15	7

Source: Table 14.2.32, Table 14.2.35

Results for all other secondary efficacy endpoints are provided in the appendices to this report.

Safety: The overall median duration of treatment with AIR001 was 18.4 weeks (range: 5.1 to 57 weeks) when exposures in Study AIR001-CS05 and Study AIR001-CS06 were

combined (Source: Table 14.1.4). All subjects in the AIR001 46 mg QID treatment arm received their randomized dose throughout the study (Source: Table 14.3.4.9 and Table 14.3.1.1). A total of 5 subjects (1 in the AIR001 80 mg QD arm and 4 in the AIR001 80 mg QID arm) were dose-reduced during the study (Source: Table 14.3.1.1). Three of these 5 subjects (1 in 80 mg QD arm and 2 in 80 mg QID arm) were dose-reduced due to AEs (throat pain and numbness in lips/mouth in Subject 108002; near syncope in Subject 118002; and cough in Subject 131002). One subject (Subject 108001) was not up-titrated from 46 mg QID after the Run-in Phase (due to fear of exacerbation of migraine headaches) and 1 subject (Subject 128001) was down-titrated at the end of the study to wean off of study drug. Of note, this down titration was not specified in the protocol and was performed without sponsor approval.

The majority (93%) of randomized subjects experienced at least 1 AE during study participation (Table 8). Most AEs were mild to moderate in severity. Adverse events leading to treatment discontinuation were low (5 subjects). Twenty four percent of subjects had SAEs during study participation. There were no fatal AEs during the study.

The most frequently reported AE overall was cough, which occurred in approximately half (52%) of the randomized subjects (Table 9). Cough was reported at a similar incidence (44-60%) in each of the individual dose groups (Source: Table 14.3.1.2). Most subjects who experienced cough had events that were considered to be related to study treatment by the investigator (Table 10). One subject in the AIR001 80 mg QD arm had a cough that was reported as severe and 1 subject in the AIR001 46 mg QID arm had a cough reported as moderate (Source: Listing 16.2.4.3). All other events of cough were reported as mild.

Other frequently reported AEs (>15%) in subjects overall included headache, dizziness, and upper respiratory tract infection (Table 9). Frequently reported treatment-related AEs (>10%) (in addition to cough) included dizziness and nausea (Table 10). There were no notable differences in the distribution of AEs observed across the AIR001 dose groups (Source: Table 14.3.1.2 and Table 14.3.1.3).

Table 8 Overview of Treatment-Emergent Adverse Events

	Overall, n (%)			
	Run-in (N=29)	**Targeted Dose Period (N=29)**	**Down-titration (N=5)**	**Overall (N=29)**
Any AE	19 (66)	27 (93)	5 (100)	27 (93)
Severe AEs	0	4 (14)	3 (60)	7 (24)
Related AEs	19 (66)	22 (76)	4 (80)	23 (79)
Any SAE	0	5 (17)	2 (40)	7 (24)
AEs leading to discontinuation of study drug	0	2 (7)	2 (40)	4 (14)[a]
AEs leading to study drug dose reduction or interruption	1 (3)	3 (10)	2 (40)	3 (10)
Deaths[b]	0	0	0	0

Source: Table 14.3.1.1, Listing 14.3.3

a. Subject 105002, Subject 115001, Subject 108001, and Subject 118002 had AEs that resulted in withdrawal of study drug according to the AE log. An additional subject (Subject 131002) was reported to have discontinued study treatment due to an AE in the study disposition summary.

b. There were no fatal AEs during the study. Subject 105002 died of progressive disease on 25 August 2013, >28 days after study drug discontinuation, despite initiation of prostacyclin therapy.

Table 9 Summary of Treatment-Emergent Adverse Events Reported in at Least 10% of Subjects Overall (All Causality)

Preferred Term	Overall, n (%)			
	Run-in (N=29)	Targeted Dose Period (N=29)	Down-titration (N=5)	Overall (N=29)
Any AE	19 (66)	27 (93)	5 (100)	27 (93)
Cough	14 (48)	15 (52)	4 (80)	15 (52)
Headache	4 (14)	2 (7)	3 (60)	5 (17)
Dizziness	2 (7)	4 (14)	0	5 (17)
Upper respiratory tract infection	1 (3)	5 (17)	0	5 (17)
Nausea	2 (7)	1 (3)	2 (40)	4 (14)
Dyspnoea	0	3 (10)	0	3 (10)
Presyncope	0	3 (10)	2 (40)	3 (10)
Tachycardia	2 (7)	2 (7)	0	3 (10)
Throat irritation	3 (10)	2 (7)	1 (20)	3 (10)
Wheezing	1 (3)	3 (10)	0	3 (10)

Source: Table 14.3.1.2

Table 10 Summary of Related Treatment-Emergent Adverse Events Reported in at Least 10% of Subjects Overall

Preferred Term	Overall, n (%)			
	Run-in (N=29)	Targeted Dose Period (N=29)	Down-titration (N=5)	Overall (N=29)
Any Related AE	19 (66)	22 (76)	4 (80)	23 (79)
Cough	13 (45)	14 (48)	3 (60)	14 (48)
Dizziness	2 (7)	3 (10)	0	4 (14)
Nausea	2 (7)	1 (3)	2 (40)	4 (14)
Headache	3 (10)	1 (3)	1 (20)	3 (10)
Presyncope	0	3 (10)	2 (40)	3 (10)
Throat irritation	3 (10)	2 (7)	1 (20)	3 (10)

Data Source: Table 14.3.1.3

Serious AEs were reported in 7 of the 29 randomized subjects (24%) (Table 8). There were no individual SAEs reported in more than 1 subject (Source: Table 14.3.1.4). Reported preferred terms were:

- AIR001 80 mg QD arm (1 subject): urinary calculus (Subject 132001)
- AIR001 46 mg QID arm (3 subjects):, right ventricular failure (Subject 105002); hyponatremia, complete atrioventricular block, acute cardiac failure, and second degree atrioventricular block (Subject 105003); and respiratory acidosis (Subject 113001)
- AIR001 80 mg QID arm (3 subjects): pulmonary arterial hypertension (Subject 141001); pulmonary hypertension (Subject 118002); and abnormal behavior (Subject 108001)

All SAEs were considered to be unrelated or not likely to be related to study drug by the investigators (Source: Listing 16.2.4.3). Case narratives for all subjects with SAEs are provided in this report.

A total of 5 subjects (17%) had AEs that led to discontinuation of study treatment (Source: Listing 16.2.1 and Listing 16.2.4.3). Two subjects in the AIR001 46 mg QID arm (right ventricular failure in Subject 105002; cough and fatigue in Subject 115001), 2 subjects in the AIR001 80 mg QID arm (abnormal behavior in Subject 108001; pulmonary hypertension in Subject 118002) and 1 subject in the 80 mg QD arm (cough in Subject 131002) experienced AEs that led to discontinuation of study drug. Both subjects in the AIR001 80 mg QID arm experienced the withdrawal AEs while on a reduced dose of AIR001 (i.e., 46 mg QID) (Source: Table 14.3.1.5). The AEs of cough and fatigue in Subject 115001 and cough in Subject 131002 were considered related to study treatment by the investigator.

There were no clinically significant abnormalities in hematology (Source: Table 14.3.4.1.1 and Table 14.3.4.1.2) or clinical chemistry (Source: Table 14.3.4.2.1 and Table 14.3.4.2.2) laboratory parameters noted during the study.

Maximum methemoglobinemia was 0 to <1% in 16 subjects (55%) and 1% to <3% in 13 subjects (45%) during study participation (Source: Table 14.3.4.4.2). The maximum value reported in any subject was 1.4% (Source: Listing 16.2.6.14.3).

There were no clinically significant abnormalities in vital signs (Source: Table 14.3.4.5), ECG parameters (Source: Table 14.3.4.7), or pulmonary function test parameters (Source: Table 14.3.4.8) observed in any subject.

Two subjects (both in AIR001 80 mg QID arm) experienced orthostatic hypotension during the study (measured when subject moved from the supine to the standing position) (Source: Table 14.3.4.6). Based on additional information received from the investigator, both of these subjects should have been excluded from study participation, as there was evidence of orthostatic hypotension at Screening (Subject 101002: supine DBP 89 mmHg, standing DBP 71 mmHg; Subject 141001: supine DBP 80 mmHg, standing DBP 70 mmHg). Subject 141001 was retested prior to the first dose of study drug and orthostatic hypotension was absent (supine DBP 70 mmHg, standing DBP 70 mmHg) (Source: data on file).

The independent DSMB performed a review of all safety data just prior to the termination of the study by the Sponsor. There were no safety concerns noted by the DSMB during this review.

Conclusions:

A total of 29 out of the planned 90 subjects were randomized into the AIR001-CS05 study. Prior to the completion of enrolment, the AIR001-CS05 study, and its extension study AIR001-CS06, were terminated by the Sponsor for administrative reasons.

- Due to the early termination of enrolment, the primary endpoint of change from baseline in peak PVR was not achieved. There were changes in median peak PVR observed in the 80 mg QD and 46 mg QID dose groups. The small sample size made detection of a statistically significant reduction in PVR unlikely. Improvements in peak 6 MWD were observed in some treatment groups at Week 16.

- AIR001 was well tolerated in randomized subjects. The most frequently reported AE was cough. The incidence of severe (24%) or serious AEs (24%) was in the range expected for the defined subject population. Discontinuations of study drug due to AEs were infrequent, occurring in 5 of the 29 randomized subjects (17%). An independent DSMB reported no safety concerns following review of study data prior to the Sponsor's decision to terminate the study.

Post-text tables and figures

Table 11 Schedule of Events for Study AIR001-CS05

Week	Screening [1]	TREATMENT PHASE								Safety Follow-up Visit for Term Subjects	Survival Follow-up for Term Subjects and completed Subjects not entering AIR001-CS06
		RUN-IN PERIOD			TARGETED-DOSE PERIOD						
		Baseline[2]	Week 1 (Phone Contact)	Week 2	Unscheduled Dose Reduction	Week 4	Week 8	Week 12	Week 16 (EOS/ Term)[24]		
	Up to 30 days	Day 1	Day 7 (±2)	Day 14 (±2)	Anytime between Day 14 and Day 112	Day 28 (±2)	Day 56 (±2)	Day 84 (±2)	Day 112 (±2)	14 Days after last visit (Phone Contact)[25]	Yearly after Week 16 or originally anticipated Week 16 (Phone Contact)[27]
Informed consent	X										
Inclusion/exclusion screen	X										
Demography documentation	X										
Medical history [3]	X	X									
PFT [4,5]	X								X		
Cardiac Catheterization[6,7]	X								X		
Aires approval for randomization (upload of data) [8]	X										
Randomization allocation		X									
AE collection		X	X	X	X	X	X	X	X	X	
Concomitant medication collection	X	X		X	X	X	X	X	X	X	
Administration of study drug		X		X	X	X	X	X	X		
Dose Titration/Reduction				X	X						
Dispense study drug [9]		X			X	X	X	X			

Week	Screening [1]	TREATMENT PHASE								Safety Follow-up Visit for Term Subjects	Survival Follow-up for Term Subjects and completed Subjects not entering AIR001-CS06
		RUN-IN PERIOD			TARGETED-DOSE PERIOD						
		Baseline[2]	Week 1 (Phone Contact)	Week 2	Unscheduled Dose Reduction	Week 4	Week 8	Week 12	Week 16 (EOS/ Term)[24]		
	Up to 30 days	Day 1	Day 7 (±2)	Day 14 (±2)	Anytime between Day 14 and Day 112	Day 28 (±2)	Day 56 (±2)	Day 84 (±2)	Day 112 (±2)	14 Days after last visit (Phone Contact)[25]	Yearly after Week 16 or originally anticipated Week 16 (Phone Contact)[27]
Return study drug [9]						X	X	X	X		
Download adherence data from nebulizer device[10]				X	X	X	X	X	X		
Physical examination	X	X		X	X	X	X	X	X	X[26]	
Height	X										
Weight	X	X		X	X	X	X	X	X	X[26]	
Vital sign measurements [11]	X	X		X	X	X	X	X	X	X[26]	
WHO/NYHA FC	X	X		X	X	X	X	X	X		
12-lead electrocardiogram	X								X		
QOL (SF-36®)		X							X		
NT-proBNP blood sample [12]		X					X	X	X		
Clinical chemistry[13]	X								X		
CBC w/ platelets and diff.[13]	X								X		
Venous Methemoglobin [14]		X		X		X			X		
Serum/Urine pregnancy test[15]	X	X		X	X	X	X	X	X		
Coagulation [16]		X									
6-Minute Walk Test [17]	X	X				X	X	X	X		
Borg Dyspnea Index [17]	X	X				X	X	X	X		
CWE determination [18]				X	X	X	X	X	X		
Discontinuation in IWR[19]									X		

Week	Screening [1]	TREATMENT PHASE								Safety Follow-up Visit for Term Subjects	Survival Follow-up for Term Subjects and completed Subjects not entering AIR001-CS06
		RUN-IN PERIOD			TARGETED-DOSE PERIOD						
		Baseline[2]	Week 1 (Phone Contact)	Week 2	Unscheduled Dose Reduction	Week 4	Week 8	Week 12	Week 16 (EOS/ Term)[24]		
	Up to 30 days	Day 1	Day 7 (±2)	Day 14 (±2)	Anytime between Day 14 and Day 112	Day 28 (±2)	Day 56 (±2)	Day 84 (±2)	Day 112 (±2)	14 Days after last visit (Phone Contact)[25]	Yearly after Week 16 or originally anticipated Week 16 (Phone Contact)[27]
Survival Assessment											X
SUB-STUDY SITES/SUBJECTS ONLY[20]											
Sub-Study ICD[21]	X										
PK blood sample [22]		X							X		
Cardiac Catheterization [23]									X		
Endothelin-1 pre-dose sample[22]		X							X		

1. All screening procedures must be completed within 30 days prior to baseline/Day 1, inclusive of the CMO's review for potential randomization. See number 8 below.
2. All baseline/Day 1 procedures must be performed prior to the first dose of study medication, with the exception of the post dose 6MWT. All baseline/Day 1 procedures must be performed on the same day, with the exception of the cardiac catheterization.
3. Medical history should include any medical condition that is ongoing as of screening or baseline/Day 1, and any significant medical conditions that have resolved.
4. Pulmonary function testing includes measurement of spirometry and TLC, with FEV1, FVC and FEV1/FVC ratio (predicted and % predicted values of each), unless performed within 6 months (180 days) prior to Baseline/Day 1 and within acceptable values.
5. The EOS or Termination visit pulmonary function testing must be performed post-dose. This PFT does not include measurement of TLC, but does include FEV1, FVC and FEV1/FVC ratio (with predicted and % predicted values of each), and spirometry. For ease of scheduling procedures, EOS or Termination visit PFTs can be performed on a different day, 3 days prior to or up to 7 days post when other visit procedures are performed. Sites must call and remind the subject to

abstain from study medication the day of this procedure (i.e. test performed at trough levels) and also remind the subject to bring study medication and nebulizer to the visit.

6. A cardiac catheterization is required prior to Screening that is consistent with a diagnosis of PAH meeting the criteria in Inclusion Criterion #4. A qualification RHC is also required, to confirm the persistence and severity of PAH, if the diagnostic RHC (see criteria in Inclusion Criterion #4) was performed more than 1 month (30 days) prior to Baseline/Day 1. The qualification RHC will serve to provide Baseline hemodynamic values for further efficacy analysis. If a diagnostic RHC performed within 1 month (30 days) prior to Baseline/Day 1, per the subject standard medical care (not for the purposes of this study) confirms the PAH diagnosis as per the required data points (PVR, PVRI, CI, CO, mPAP, mRAP, PCWP, SVR, SVRI, PVR/SVR ratio, SvO_2, and SaO_2 (if Fick method for CO is used)), and has a PVR above 300 dyn.sec/cm^5, and all further cardiac catheterizations (to determine efficacy) will be performed in the same diagnostic laboratory; and no change in disease specific PAH therapy has occurred since the catheterization used to qualify the subject for the study, then the test does not need to be repeated. Results of the cardiac catheterization at 1 month (30 days) prior or at Screening will also serve as the Baseline evaluation.
7. Subjects who are terminated from the study PRIOR to Week 8 should complete all safety and efficacy procedures, except cardiac catheterization. The EOS or Termination visit cardiac catheterization will be measured pre-dose at greater than 5 hours after last AIR001 nebulization (trough) and post-dose at immediately post completion of AIR001 nebulization (as soon as feasible), but no more than 20 minutes after completion of AIR001 nebulization. Cardiac catheterization should be performed while the subject is on study medication. For ease of scheduling procedures, EOS or Termination visit Cardiac Catheterizations can be performed on a different day, but must be within 3 days prior to or up to 7 days post when other EOS or Termination visit procedures are performed. Subjects should be contacted the day prior to this procedure as a reminder of the appointment and to ensure they bring study drug and nebulizer to the appointment and the subject should be advised by the investigator or authorized designee to adjust the dosing schedule as required for this procedure.
8. . After all screening procedures are complete; supportive, properly de-identified documentation of the subject's eligibility will be submitted to the Chief Medical Officer who will review the subject's documentation and approve the subject for randomization if study specific entry criteria are met.
9. Study drug should be dispensed at the applicable clinic visits; drug supplies are collected and accounted for at each subsequent visit.
10. At each clinic visit, after downloading adherence data from nebulization device, a demonstration of preparation, use and proper cleaning of the device is required.
11. Vital sign measurements are to include sitting BP, HR, RR, pulse oximetry, and temperature. These measurements are required at Screening, and pre-dose at all subsequent clinic visits. Orthostatic BP and HR (supine and standing) are required during the Screening visit and if applicable, during an Unscheduled dose reduction visit. If oxygen saturation at rest decreases by more than 5 percentage points from Baseline (i.e. 98% to 92%, or falls below 90% saturation, it must be confirmed by 3 separate measurements at different sites. The requirement for additional measurements does not apply to decreases in oxygen saturation during the 6MWT.
12. The NT-proBNP blood sample will be collected after a minimum of at least a 1-hour rest period and must be done before the 6MWT.
13. See Protocol Section 6.3 for a list of required lab tests.
14. Venous methemoglobin will be analyzed at the study site's local lab. See instructions in protocol Appendix 3 for elevations in methemoglobin.
15. A negative urine pregnancy test must be obtained at all clinic visits prior to dose of study drug. Any subject who becomes pregnant must be immediately discontinued from the study.
16. Coagulation testing (PT and INR) is required at Baseline/Day 1 for all subjects who are taking an oral vitamin K antagonist.
17. The 6MWD at screening must be ≥50 meters. If the 6MWD is not ≥50 meters, a second 6MWT may be conducted. The distance walked must be ≥50 meters, with the test conducted on a separate day, and must be within 15% of the previous result. During the Treatment Phase, the 6MWT will be performed prior to and immediately <u>after</u> completion of AIR001 nebulization (as soon as feasible, but no more than 40 minutes after completion of AIR001 nebulization) at Baseline/Day 1 and Week 16 (EOS or Termination visit). At all other clinic visits (with the exception of the week 2 and if applicable, the unscheduled dose reduction visit), the 6MWT will be performed immediately <u>after</u> completion of AIR001 nebulization (as soon as feasible, but no more than 40 minutes after

completion of AIR001 nebulization). Depending on the result of these walks, the 6MWT may need to be repeated on a separate day within 2 days of the first 6MWT with this 6MWT performed immediately post AIR001 nebulization (but no more than 40 minutes after the completion of AIR001 nebulization), for potential CWE evaluation. A Borg dyspnea index test is required following the completion of all 6MWT.

18. At each clinic visit, after baseline/Day 1, the subject must be assessed for potential CWEs (see criteria in Protocol Section 6.1.5). Should the criteria be met, an NT-proBNP laboratory assessment is required at the time of the event confirmation.
19. Subjects completing AIR001-CS05 must be discontinued in the IWRS before they will be allowed to continue onto AIR001-CS06.
20. In addition to all of the main study procedures, sub-study subjects will have the noted sub-study procedures completed at baseline and Week 16 (EOS or Termination) visits. See Protocol Section 7.4 for more details.
21. The consent containing sub-study information will be signed by all sub-study subjects at the screening visit.
22. At select centers participating in the PK and Endothelin-1 sub-study, at baseline and Week 16 visits, PK samples will be collected according to the time points outlined in protocol Section 7.1 and Section 7.2.
23. At the selected sub-study sites correlation of PK and ET-1 evaluations with cardiac catheterization data will be performed in those subjects who consent to participate. Cardiac Catheterization will be conducted at peak and trough time points to collect data points outlined in protocol Section 7.3.
24. For subjects who complete the study as planned (i.e. through Week 16), this visit will be referred to as the EOS visit. Subjects who are terminated from the study PRIOR to Week 8 should complete all safety and efficacy procedures, except cardiac catheterization. For subjects who prematurely discontinue (i.e. prior to Week 16), this visit will be referred to as the Termination Visit. In addition, all subjects who terminate from the study prematurely will be contacted at the time of their originally anticipated Week 16 (EOS) visit to assess vital status yearly thereafter on the anniversary of their first AIR001 dose until the termination of AIR001-CS06.
25. At the Investigator's discretion, an in-person clinical evaluation may be conducted to ensure continued subject safety.
26. If clinically indicated.
27. All subjects who terminate from the study prematurely will be contacted at the time of their originally anticipated Week 16 (EOS) visit and yearly thereafter on the anniversary of their first AIR001 dose to assess vital status, until AIR001-CS06 concludes. Subjects who complete AIR001-CS05, but choose not to continue into AIR001-CS06 will also be followed yearly on the anniversary of their first AIR001 dose for vital status until AIR001-CS06 concludes. The vital status follow-up contact of subjects who withdraw consent will depend on local regulations or specific agreement with the subject.

Table 12 Schedule of Events for Study AIR001-CS06

	TREATMENT PHASE				**FOLLOW UP PHASE**	
	Clinic Visit				**Phone/Remote Visit**	
	Baseline[1]	**Unscheduled Dose Reduction**	**Every 24 Weeks**	**End of Study (EOS)/ Termination**	**Safety Follow-up Visit (Term. Subjects)**	**Survival Follow-up Visit**
	Day 1	**Anytime between Day 1 and EOS**	**(±2 Days)**	**(±2 Days)**	**28 Days following last visit[12]**	**Every 12 months**
Informed consent[2]	X					
Inclusion/exclusion screen	X					
Medical history [3]	X					
Concomitant medication collection	X	X	X	X	X	
AE collection	X	X	X	X	X	
IWRS allocation	X					
Administration of study drug	X	X	X	X		
Dispense/return study drug [4]	X	X	X	X		
Download adherence/ compliance data from nebulizer device[5]		X	X	X		
Physical examination	X	X	X	X	X[13]	
Weight	X	X	X	X	X[13]	
Vital sign measurements [6]	X	X	X	X	X[13]	
WHO/NYHA functional class	X	X	X	X		
QOL (SF-36)	X		X	X		
Venous Methemoglobin	X		X	X		
NT-proBNP blood sample [7]	X		X	X		
Serum/Urine pregnancy test [8]	X	X	X	X		
6-Minute Walk Test [9]	X		X	X		
Borg Dyspnea Index [9]	X		X	X		
CWE Determination [10]		X	X	X		
Discontinuation in IWR				X		
Survival Assessment [11]						X

1. All applicable EOS procedures from the lead-in protocol (AIR001-CS05) may be used as the AIR001-CS06 baseline assessments if they are performed within 2 weeks of the first dose of study drug, otherwise they must be repeated. All baseline/Day 1 procedures must be performed prior to the first dose of study medication, with the exception of the 6MWT.
2. Informed consent must be performed before any AIR001-CS06 study procedures are performed. If the AIR001-CS05 EOS procedures will be used to fulfill the AIR001-CS06 Baseline/Day 1 visit, subjects must be consented to AIR001-CS06 prior to any AIR001-CS05 EOS procedures being performed.
3. Updated medical history should include any medical condition still ongoing as of the baseline from AIR001-CS05.
4. Study drug should be dispensed at the applicable clinic visits; drug supplies are collected and accounted for at each subsequent visit.
5. At each clinic visit, after downloading adherence data from nebulization device, a demonstration of preparation, use and proper cleaning of the device is required (see Protocol Appendix 7).
6. Pre-dose vital sign measurements are to include sitting blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. At each unscheduled clinic visit, orthostatic blood pressure and heart rate (supine and standing) are also required. If oxygen saturation at rest decreases by more than 5 percentage points from Baseline (i.e. 98% to 92%, or falls below 90% saturation, it must be confirmed by 3 separate measurements at different sites. See Protocol Section 6.2.2 for further details. The requirement for additional measurements does not apply to decreases in oxygen saturation during the 6MWT.
7. NT-proBNP blood sample will be collected after a minimum of at least a 1-hour rest period and must be done before the 6MWT.
8. A negative urine pregnancy test must be obtained at all clinic visits prior to dose of study drug for women of childbearing potential. Any subject who becomes pregnant must be immediately discontinued from the study.
9. The 6MWT will be performed immediately after completion of AIR001 nebulization (as soon as feasible, but no more than 40-minutes after completion of AIR001 nebulization) at baseline/Day 1, and if applicable every 24 weeks after the week 24 visit. The 6MWT will be performed prior to and immediately after completion of AIR001 nebulization (as soon as feasible, but no more than 40 minutes after completion of AIR001 nebulization) at the Week 24 visit and EOS or Termination visit. Depending on the result of these walks, the 6MWT may need to be repeated on a separate day within 2 days of the first 6MWT with this 6MWT performed immediately post AIR001 nebulization (but no more than 40-minutes after the completion of AIR001 nebulization), for potential CWE evaluation. A Borg dyspnea index test is required following the completion of all 6MWT.
10. At each clinic visit, after baseline/Day 1, the subject must be assessed for potential CWEs (see criteria in Protocol Section 6.1.3). If a CWE is confirmed by a second 6MWT, then an NT-proBNP laboratory assessment is required on the day of the second 6MWT with the NT-proBNP obtained after 1-hour of rest.
11. All subjects who terminate from the study prematurely will be contacted at the time of their originally anticipated month 6 visit and yearly thereafter yearly thereafter on the anniversary of their first AIR001 dose to assess vital status, until AIR001-CS06 concludes. All subjects completing the study will be followed yearly on the anniversary of their first AIR001 dose until the study is closed to assess survival status. The vital status follow-up contact of subjects who withdraw consent will depend on local regulations or specific agreement with the subject.
12. At the Investigator's discretion, an in-person clinical evaluation may be conducted to ensure continued subject safety.
13. If clinically indicated.

Case Narratives

Cast narratives are provided for the following subjects:

Subject Number	SAE	AE leading to withdrawal
105002	X	X
105003	X	
108001	X	X
113001	X	
115001		X
118002	X	X
131002		X
132001	X	
141001	X	

Subject Number: **105002**
Case Number: **2014-US-0000004**
SAE Preferred Term: **Right Ventricular Failure**
Withdrawal AE Preferred Term: **Right Ventricular Failure**

Subject 105002 was 59-year-old woman with a medical history of pulmonary arterial hypertension associated with systemic sclerosis diagnosed in February 2012. The subject was randomized into study AIR001-CS05 with a baseline visit date of 9 April 2013. The subject was hospitalized on 24 June 2013 with symptoms of diarrhea, headache, and weakness. Additional information was obtained from the subject's treating physician on 27 June 2013 indicating that the diagnosis was viral gastroenteritis; however, the subject had ongoing hypotension, and after excessive fluid resuscitation, an elevated right atrial pressure of 15. Therefore, the subject remained hospitalized for treatment with dopamine and diuretics.

Follow up information was obtained from the site on 04 September 2013. The initial SAE term of gastroenteritis was downgraded to an AE. Right ventricular failure was upgraded as the principle diagnosis. The subject was withdrawn from the study on 03 July 2013 and the event was considered resolved on 06 July 2013. The subject was discharged with intravenous treprostinil with the sequelae of worsening PAH.

The subject was randomized to AIR001 46 mg QID, which was held during the event, and the subject subsequently discontinued from study. The subject took her last dose of study drug on 24 June 2013.

Relevant concomitant medications at the time of the event included ambrisentan 5 mg daily, sildenafil 40 mg three times daily, and pantoprazole 20 mg three times daily.

The subject died on 25 August 2013 of progressive PAH, which was more than 28 days after the last dose of study drug.

Analysis of Similar Events:

No prior similar events to report. This was an expected complication of dehydration and gastroenteritis associated with progressive worsening of PAH.

Subject Number: **105003**
Case Number: **2013-US-000005, 2013-US-000006, 2014-US-000001**
SAE Preferred Term: **Hyponatremia, Atrioventricular Block Second Degree**
Atrioventricular Block Complete
Cardiac Failure Acute

Subject 105003 was a 73-year-old female with a medical history significant for pulmonary arterial hypertension associated with systemic sclerosis. The subject was randomized into AIR001-CS05 with a baseline visit 30 April 2013 and subsequently entered AIR001-CS06 on 21 August 2013.

Hyponatremia, Atrioventricular Block Second Degree

The subject was hospitalised on 21 August 2013 after presentation for a week 16 cardiac catheterization where she was noted to have Mobitz Type I 2nd degree AV block and hyponatremia (Sodium 121-122 confirmed on separate labs) with symptoms of weakness. She was on Bystolic (nebivolol) with heart rates in the 40 to 50 beats per minute range. Her nebivolol was held and upon ambulation heart rate continued in the same range but the subject was asymptomatic. Additional information was obtained from the subject, in that she had been placed on Bactrim (sulfamethoxazole/ trimethoprim) for cellulitis of the left toe. She was also on thiazide diuretic which could contribute to hyponatremia. The Bactrim was held and she was started on doxycycline, with AM lab on 22 August 2013 improved 129 (sodium).

On 22 August 2013 the Mobitz Type I 2nd degree AV block was resolved and the hyponatremia was considered to be resolved with sequelae. The subject was discharged from hospital.

The subject was randomised to AIR001 46 mg QID, which was continued.

Relevant concomitant medications at the time of the event included nebivolol, Bactrim, hydrochlorothiazide and doxycycline.

The investigator considered the Mobitz Type I 2nd degree AV block unlikely to be related and the hyponatraemia to be unrelated to AIR001.

Follow-up information received on 23 October 2013 provided the outcome and causality of the hyponatraemia (detailed above).

Follow-up information received on 25 April 2014 provided the outcome the hyponatraemia (detailed above).

Analysis of Similar Events: No prior similar events to report.

Atrioventricular Block Complete

The subject underwent an ECG in her local cardiologist's office and was noted to be in complete (3rd degree) heart block and was hospitalized the same day on 29 August 2013. She had complaints of progressive fatigue, weakness and dyspnea on exertion. Her usual dyspnea was worsened, such that light physical activity induced it. ECG revealed complete heart block with bradycardia to 40 to 50 beats per minute.

The subject was randomized to AIR001 46 mg QID, which was held after the morning dose prior to admission, and during in-subject confinement.

Relevant concomitant medications at the time of the event included hydrochlorothiazide losartan, montelukast, omeprazole, prednisone, potassium, ranitidine, amlodipine, doxepin, ferrous sulfate, celecoxib, diphenhydramine, hydroxychloroquine, albuterol, and ergocalciferol.

The event was considered ongoing until placement of a permanent dual chamber pacemaker on 30 August 2013. Treatment with AIR001 resumed on 03 September 2013.

Also noted on discharge summary reported on 03 September 2013, was continued asymptomatic hyponatremia (previously reported; evaluations ongoing). Additionally, the subject was noted to have asymptomatic hypoglycemia on admission laboratory. Evaluation was inconclusive. The laboratory value was not reported as an AE and it was considered resolved at the time of discharge.

Analysis of Similar Events: No prior similar events to report. This event appeared to be a continuation or progression of the same subject's previous event of Mobitz type I, incomplete heart block. Event resolved post implantation of permanent dual chamber pacemaker.

Cardiac Failure Acute

The subject was hospitalized on 16 January 2014 after presentation to the emergency department with progressive shortness of breath since November. She was treated for URI/sinus infection with doxycycline and a Zpak prior to presentation to the emergency department. She saw her home cardiologist on 14 January 2014 who suggested referral to the PAH center. Her complaint in the ED was progressive dyspnea with minimal exertion.

Physical exam findings were consistent with jugular venous distention, bibasilar lung rales, wheezing throughout and non-productive cough.

While hospitalized and after diuresis with furosemide, the creatinine increased from 1.4 to 1.7, thus catheterization was performed on 17 January 2014. The results were RA 2 mmHg, RV 43/4 mmHg, PAP 43/19 with mean 25 mmHg, PCWP 5 and TPG 20. CO was 4.4 lpm and CI 2.7 l/kg/min, so the decision was to limit further diuresis.

The subject was randomized to AIR001 46 mg QID, which was interrupted the day of emergency evaluation but was continued during hospitalization. The study coordinator reported noncompliance by the subject at home.

Relevant concomitant medications at the time of the event hydrochlorothiazide, amlodipine, potassium chloride, hydroxychloroquine, doxepin, montelukast, albuterol/foradil, omeprazole, ranitidine, celecoxib, vitamins B6 and D, and tramadol.

The event was considered resolved on 18 January 2014.

This subject had a previous SAE of Complete Heart Block (2013-US-000006).

Subject Number: **108001**
Case Number: **2013-US-000003**
SAE Preferred Term: **Abnormal Behaviour**
Withdrawal AE Preferred Term: **Abnormal Behaviour**

A 39-year-old female subject experienced hospitalization for severe depression while participating in Study AIR001-CS05.

Subject 108001 was a 39-year-old woman with a history of PAH as well as depression, anxiety, heroin and methamphetamine abuse, headaches and migraine cephalgia. Additionally the subject suffered from Hepatitis B and C, irritable bowel syndrome, syncope, tricuspid regurgitation, gastroesophageal reflux, interstitial cystitis and increased urine frequency, neck pain and astigmatism.

The subject was randomized to AIR001 by nebulization QID. Study drug was started on 30 April 2013; dose up-titration from 46 mg QID to 80 mg QID was not performed due to side effects.

The subject self-reported suicidal ideation, onset 23 May 2013, and was hospitalized under the care of her usual psychiatrist overnight. She reported being worried and depressed about her headaches and her ability to detox from tylenol. She stated she had placed a rope around her neck, then removed it and called behavioural health department. Variable doses of AIR001 were given during the event, and restart of study medications is not reported.

The diagnosis was Behavioural Disorder, considered worsening of underlying depression. The event resolved on 24 May 2013.

No changes to concomitant medications were reported.

The subject reported desire to discontinue from study AIR001-CS05 on 28 May 2013. Study treatment was discontinued due to the SAE of abnormal behaviour.

The investigator's clinical assessment was that the event was resolved with sequelae of continuation of prior depressive disorder and considered the event as unrelated to study drug.

Company medical evaluation and comment

The medical monitor for AIR001-CS05 agrees with the Investigator's clinical assessment of the event.

Analysis of Similar Events: No similar events are reported.

Subject Number: **113001**
Case Number: **2013-US-000008, 2013-US-000004**
SAE Preferred Term: **Respiratory Acidosis**

Subject was a 64-year-old woman with a history of pulmonary arterial hypertension, depression, fibromyalgia, attention deficit disorder, hypercholesterolemia and hypertriglyceridemia randomized into study AIR001-CS05 with baseline visit date 02 October 2013.

On 20 October 2013, the sponsor was notified electronically that the subject was hospitalized with respiratory acidosis and a preliminary diagnosis of renal impairment with urinary tract infection.

On 20 December 2013, the sponsor received the following information from the Investigator. The subject was on vacation in Barcelona. She reported drinking wine then ingesting Ambien, and was taken by a travel companion to the emergency department of the hospital possibly on 18 or 19 October 2013. She was initiated on BiPAP and admitted to the hospital. Reportedly the subject left against medical advice on 21 October 2013. The subject reported to the sponsor's nurse liaison that she was not treated for renal impairment or urinary tract infection. Additional information was requested but no response was received by the investigator.

Concomitant medications included: Ambien, Aspirin 81mg, Buspar, Celexa, Ditropan XL, furosemide, gabapentin, gemfibrozil, methadone, mirtazapine, trazodone, niacin, multivitamin, and fish oil.

The subject was randomized to AIR001 46 mg QID, which was continued at the time of the incident report.

The event was considered resolved 21 October 2013.

Final discharge diagnosis and further information was requested but not received from the hospital.

Analysis of Similar Events: No prior similar events to report.

Subject Number: **115001**
Case Number: **N/A**
Withdrawal AE Preferred Term: **Fatigue, Cough**

Subject 115001 was a 61-year-old Hispanic woman with a history of IPAH/HPAH, migraine headaches, osteoarthritis, depression, insomnia, nasal congestion, hyperlipidemia, gastroesophageal reflux, dermatitis, rotator cuff syndrome, and sciatica. The subject was a past smoker. The subject was randomized into study AIR001-CS05 with a baseline visit date 08 March 2013. Baseline concomitant medications included warfarin, a multivitamin, furosemide, fluoxetine, celecoxib, zolpidem, fluticason, fenofibrate, ranitidine, trazodone, simvastatin, duloxetine, oxycodone, acetaminophen/hydrocodone, gabapentin, acetaminophen/butalbital/caffeine, and fluocinonide ointment.

On 08 March 2013, the subject developed a mild cough and mild throat pain following the initiation of study treatment. The cough and throat pain were considered probably related to study drug by the investigator. The throat pain resolved on 22 March 2013. On 06 April 2013, the subject's cough worsened in severity to moderate and she also developed moderate fatigue. These events were non-serious and considered probably related to study treatment by the investigator. The subject received no additional medications for these events. Administration of 46 mg QID AIR001 was initially continued, but was then permanently withdrawn due to the fatigue and cough on 23 April 2013. The events were reported as resolved on 26 April 2013.

Subject Number: **118002**
Case Number: **2013-US-000007**
SAE Preferred Term: **Pulmonary Hypertension**
Withdrawal AE Preferred Term: **Pulmonary Hypertension**

Subject 118002 was a 44-year-old Hispanic woman with a history of pulmonary arterial hypertension associated with congenital heart disease (VSD repair age 10). The subject was randomized into study AIR001-CS05 with baseline visit date 13 September 2013. The subject complained of moderate abdominal pain with severe burping onset 11 December 2013. She presented to an Emergency Department and was hospitalized. At the time of the initial SAE report, the investigator considered the pain unrelated and due to possible gastroesophageal reflux disease.

On 30 January 2014, follow-up information was received including a description of the hospitalization by the principal investigator and all hospitalization records. The principal investigator reported upper abdominal pain onset 11 December 2013 with severe "burping". In the ED, she was noted to have oxygen saturation in the low 80%'s and red injected sclera in the left eye. Hospital evaluations included gastroenterology, whose diagnosis was possible uterine fibroids, but recommended EGD and colonoscopy after discharge. Ophthalmology consult excluded non-arteritic ischemic optic neuropathy from sildenafil and expressed the scleral injection was possibly migraine cephalgia equivalent versus cellulitis and recommended erythromycin ophthalmic solution with resolution. Other evaluations included CT Angiogram, negative for pulmonary embolus, abdominal CT with no acute intra-abdominal pathology, and echocardiography consistent with severe PAH and decreased RV systolic function. The pain was resolved and the subject was discharged from the hospital 16 December 2013.

The subject was randomized to AIR001 80 mg QID, which was discontinued due to the SAE of pulmonary hypertension on 16 December 2013.

Relevant concomitant medications at the time of the event included sildenafil citrate 20mg Q 8 H, pantoprazole 20mg Q day, and garlic oil 1000 mg daily.

Analysis of Similar Events: Continued PAH with a resolved episode of worsening was expected in this disease state.

Subject Number: **131002**
Case Number: **N/A**
Withdrawal AE Preferred Term: **Cough**

Subject 131002 was a 40-year-old female with PAH (diagnosed on 19 June 2013) secondary to an atrial septal defect. The subject had a medical history of septal defect repair in 2009 and an allergy to penicillin. She was randomized into Study AIR001-CS05 on 02 July 2013. Concomitant medications included bosentan.

On 17 July 2013, 17 days after the start of study drug, the subject developed a non-serious mild cough, which was considered related to study drug by the investigator. In August 2013, the subject's cough worsened to a severe dry cough. She was treated with benzocaine. The severe cough improved on 06 September 2013 (to mild), but was ongoing. On 30 September 2013, the subject discontinued treatment with AIR001 80 mg QD due to the AE of cough, which was reported as resolved on 06 October 2013.

Subject Number: **132001**
Case Number: **2013-HU-000001**
SAE Preferred Term: **Calculus Urinary**

A 64-year-old male subject was randomized in Study AIR001-CS05 on 03 May 2013 and experienced hospitalization for what was termed initially as nephrolithiasis. Medical history included a history of IPAH as well as hyperuricemia since 2008, hypercholesterolemia, and hypertension. Additional surgical history included cholecystectomy and inginal herniorraphy.

Concomitant medications included sildenafil, allopurinol, amlodipine, atorvastatin, acenocoumerol, and furosemide. Subject 132001 was randomized to AIR001 by nebulization 80 mg QD, which was continued.

The subject reported to the principal investigator that he was hospitalized on 18 August 2013 for acute abdominal pain and was diagnosed with nephrolithiasis. The event resolved on 23 August 2013. The outcome of the event was resolved with sequelae, presumably of continued urinary stone propensity given the ongoing hyperuricemia.

No changes to concomitant medications were reported.

The investigator's clinical assessment was that the event was unlikely related to study drug.

Subject Number: **141001**
Case Number: **2013-DE-000001**
SAE Preferred Term: **Pulmonary Arterial Hypertension**

Subject 141001 was a 41-year-old woman with a medical history significant for Idiopathic PAH diagnosed March 2013 on sildenafil, who was randomized to AIR001 on 07 August 2013. She was treated on target dose with AIR001 80 mg QID on 22 August 2013. Other pertinent medical history includes partial respiratory insufficiency, asplenia, hypothyroidism, and cholelithiasis.

The subject was noted to complain of increased weight, progressive dyspnea, and belief that the study drug was not beneficial. The investigator's plan was for hospitalization for invasive evaluation of the underlying disease by right heart catheterization. The subject was hospitalized on 15 October 2013 and the SAE was considered ongoing at the time of the initial report.

Subsequently on 30 October 2013 follow-up information was received. The subject was hospitalized and noted to have a worsening of PAH considered to be triggered by, or made more apparent by, a bronchopulmonary infection. The subject was treated with antibiotics (oral cefuroxime and then iv cefpodoxime), diuretics (torsemide, furosemide, spironolactone) and the addition of ambrisentan on 17 October 2013. The SAE was reported as resolved on 24 October 2013, with cause of the SAE considered to be worsening of PAH, with lack of efficacy of prior medications. Follow-up BNP revealed decrease from 547 to 273 pg/ml.

Relevant Concomitant medications at the time of the event included Sildenafil, levothyroxine, warfarin, xipamide until 17 July 2013, then hydrochlorothiazide/triamterene from 18 July 2013, oxygen, and kalinor (potassium supplement). Addition of torsemide/furosemide/spironolactone, and ambrisentan occurred during the hospitalization. Following discharge, the subject continued on sildenafil, ambrisentan, AIR001, and returned to prior hydrochlorothiazide/triamterene.

No prior similar events to report; however, this was an expected complication of possibly worsening PAH.