Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Condition:	Pulmonary Hypertension
Interventions:	Drug: Inhaled treprostinil Drug: Placebo inhalation solution

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
The first subject was enrolled on 7 June 2005 and the last subject exited the study on 12 Oct 2007.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Identical placebo inhalation solution

Participant Flow: Overall Study

	Inhaled Treprostinil	**Placebo**
STARTED	**115**	**120**
COMPLETED	**102**	**110**
NOT COMPLETED	**13**	**10**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Identical placebo inhalation solution
Total	Total of all reporting groups

Baseline Measures

	Inhaled Treprostinil	Placebo	Total
Number of Participants [units: participants]	**115**	**120**	**235**
Age [units: years] Mean (Full Range)	**55 (20 to 75)**	**52 (18 to 75)**	**54 (18 to 75)**
Gender [units: participants]			
Female	**93**	**98**	**191**
Male	**22**	**22**	**44**
PAH Etiology [units: participants]			
Idiopathic PAH (IPAH)	**64**	**67**	**131**
Connective Tissue Disease (CTD)	**40**	**37**	**77**
Other	**11**	**16**	**27**
Background PAH Therapy [units: participants]			
Bosentan	**77**	**88**	**165**
Sildenafil	**38**	**32**	**70**
Time on Background Therapy [units: weeks] Mean (Standard Deviation)			

Bosentan	**98 (79)**	**90 (75)**	**94 (77)**
Sildenafil	**65 (60)**	**77 (69)**	**70 (64)**
Baseline NYHA Class [units: participants]			
Class III	**112**	**118**	**230**
Class IV	**3**	**2**	**5**
Baseline Six-Minute Walk Distance (6MWD) [units: meters] Mean (Standard Deviation)	**346 (63)**	**351 (69)**	**348 (66)**

Outcome Measures

Hide All Outcome Measures

1. Primary: Peak 6-minute Walk Distance [Time Frame: 12 weeks]

Measure Type	Primary
Measure Title	Peak 6-minute Walk Distance
Measure Description	Change in peak 6-minute walk distance from baseline to Week 12. Peak 6MWD was defined as a 6-minute walk test (6MWT) within 10 to 60 minutes after study drug inhalation
Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat analysis

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

		Placebo

	Inhaled Treprostinil	
Number of Participants Analyzed [units: participants]	**115**	**120**
Peak 6-minute Walk Distance [units: meters] Median (Inter-Quartile Range)		
Week 12	**366.0 (300.0 to 423.0)**	**360.0 (296.0 to 414.9)**
Change from Baseline	**21.6 (-8.0 to 54.0)**	**3.0 (-26.0 to 31.5)**

Statistical Analysis 1 for Peak 6-minute Walk Distance

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.00044
Hodges-Lehmann Estimate [4]	20.0
95% Confidence Interval	8.0 to 32.8

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Sample size was calculated based on the primary endpoint; change in 6MWD at Week 12. Assuming a between-treatment difference of 35m, a standard deviation of 75m, and a type I (alpha) error of 0.05 (i.e., two-sided p-value of less than 0.05), in order to have 90% power to detect this difference, 100 subjects per treatment group were required for this trial (total n=200). This allowed for a dropout rate of 10% as 110 subjects per group was planned.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	Lowest rank was assigned for death, discontinuation due to disease progression, and for patients who initiated additional approved PAH therapy.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

2. Secondary: Clinical Worsening Events [Time Frame: 12 weeks]

Measure Type	Secondary
Measure Title	Clinical Worsening Events
Measure Description	Clinical worsening was defined as the first incidence of clinical worsening from randomization to the first occurrence of death, transplantation, hospitalization for PAH, or initiation of additional approved PAH therapy.
Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat population

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	**Placebo**
Number of Participants Analyzed [units: participants]	**115**	**120**
Clinical Worsening Events [units: clinical worsening events]	**4**	**6**

No statistical analysis provided for Clinical Worsening Events

3. Secondary: Borg Dyspnea Score [Time Frame: 12 weeks]

Measure Type	Secondary
Measure Title	Borg Dyspnea Score
Measure Description	The Borg dyspnea score is a patient reported number between 0 (no perceived shortness of breath) and 10 (maximum perceived shortness of breath), obtained at the completion of each 6MWT.

Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat population. A Week 12 observation was not present for one subject and that data point is not included in the analysis.

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	**Placebo**
Number of Participants Analyzed [units: participants]	**115**	**119**
Borg Dyspnea Score [units: score] Mean (Standard Deviation)		
Week 12	**3.68 (2.26)**	**3.91 (2.33)**
Change from Baseline	**0.0 (2.07)**	**0.0 (1.72)**

Statistical Analysis 1 for Borg Dyspnea Score

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.623
Hodges-Lehmann (H-L) [4]	0.0
95% Confidence Interval	-0.5 to 0.0

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:

	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

4. Secondary: New York Heart Association (NYHA) Functional Classification [Time Frame: 12 weeks]

Measure Type	Secondary
Measure Title	New York Heart Association (NYHA) Functional Classification
Measure Description	Change in NYHA functional class at Week 12. NYHA classifications: Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope. Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope. Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope. Class IV – Patients with pulmonary hypertension in the inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.
Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat population

Reporting Groups

	Description

Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	Placebo
Number of Participants Analyzed [units: participants]	**115**	**120**
New York Heart Association (NYHA) Functional Classification [units: participants]		
NYHA Class II	**22**	**22**
NYHA Class III	**88**	**93**
NYHA Class IV	**5**	**5**

Statistical Analysis 1 for New York Heart Association (NYHA) Functional Classification

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.807
Hodges-Lehmann (H-L) [4]	0.0
95% Confidence Interval	0.0 to 0.0

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	Imputation strategies were implemented for 16 inhaled treprostinil subjects and 9 placebo subjects without values reported at Week 12
[4]	Other relevant estimation information:
	No text entered.

5. Secondary: Trough 6MWD at Week 12 [Time Frame: 12 Weeks]

Measure Type	Secondary
Measure Title	Trough 6MWD at Week 12
Measure Description	Change in 6MWD from Baseline to trough 6MWD at Week 12. Trough was defined as a 6MWT conducted at least 4 hours following study drug inhalation.
Time Frame	12 Weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat population

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	**Placebo**
Number of Participants Analyzed [units: participants]	**115**	**120**
Trough 6MWD at Week 12 [units: meters] Median (Inter-Quartile Range)		
Week 12 trough	**364.0 (313.0 to 420.0)**	**365.0 (289.0 to 422.0)**
Change from Baseline	**12.4 (-10.0 to 51.3)**	**0.8 (-17.9 to 25.0)**

Statistical Analysis 1 for Trough 6MWD at Week 12

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.007

Hodges-Lehmann (H-L) [4]	13.7
95% Confidence Interval	4.0 to 24.8

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

6. Secondary: Peak 6MWD at Week 6 [Time Frame: 6 weeks]

Measure Type	Secondary
Measure Title	Peak 6MWD at Week 6
Measure Description	Change in peak 6MWD between Baseline and Week 6.
Time Frame	6 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	**Placebo**

Number of Participants Analyzed [units: participants]	**115**	**120**
Peak 6MWD at Week 6 [units: meters] Median (Inter-Quartile Range)		
Week 6 Values	**375 (305 to 421)**	**367 (292 to 419)**
Change from Baseline	**21.6 (-4.0 to 51.8)**	**3.0 (-16.5 to 22.0)**

Statistical Analysis 1 for Peak 6MWD at Week 6

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.0003
Hodges-Lehmann (H-L) [4]	18.5
95% Confidence Interval	8.5 to 28.3

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

7. Secondary: Quality of Life (Minnesota Living With Heart Failure) [Time Frame: 12 weeks]

Measure Type	Secondary
Measure Title	Quality of Life (Minnesota Living With Heart Failure)
Measure Description	Quality of life as measured by the Minnesota Living With Heart Failure (MLWHF) questionnaire was evaluated at baseline and at Week 12. The MLWHF questionnaire consists of 21 questions assessing how the patient's

	heart failure has prevented them from living the way they wanted during the defined time period. Each question was graded by the patient with a numeric value between 0 (No/none) and 5 (very much). These scores were then summed across the 21 questions for a Global Score. Global scores ranged from 0 to 105. These questions were further grouped into Physical (8 of the questions) and Emotional (5 of the questions) dimensions to further characterize the effect of heart failure on the patient's life. Physical scores ranged from 0 to 40, and emotional scores ranged from 0 to 25. For all 3 categories, the lower the score, the better the outcome. Values presented as change from Baseline.
Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat population.

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	**Placebo**
Number of Participants Analyzed [units: participants]	**115**	**120**
Quality of Life (Minnesota Living With Heart Failure) [units: units on a scale] Median (Inter-Quartile Range)		
Global Score	**-3.0 (-14.0 to 2.0)**	**0.0 (-9.0 to 6.0)**
Physical Dimension	**-1.4 (-6.0 to 2.0)**	**0.0 (-4.0 to 3.0)**
Emotional Dimension	**0.0 (-4.0 to 1.0)**	**0.0 (-3.0 to 3.0)**

Statistical Analysis 1 for Quality of Life (Minnesota Living With Heart Failure)

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.027
Hodges-Lehman Estimate [4]	-4.0
95% Confidence Interval	-8.0 to 0

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Global Score
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 2 for Quality of Life (Minnesota Living With Heart Failure)

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.037
Hodges-Lehman Estimate [4]	-2.0
95% Confidence Interval	-3.0 to 0.0

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Physical Dimension
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

Statistical Analysis 3 for Quality of Life (Minnesota Living With Heart Failure)

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.173
Hodges-Lehman Estimate [4]	-1.0
95% Confidence Interval	-2.0 to 0.0

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Emotional Dimension Score
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

8. Secondary: Change in Signs and Symptoms of PAH [Time Frame: 12 weeks]

Measure Type	Secondary
Measure Title	Change in Signs and Symptoms of PAH
Measure Description	Signs and symptoms of PAH (Loud P2 sound, Ascites, Right ventricular S3 sound, Dyspnea, Right ventricular S4 sound, Orthopnea, Right ventricular heave, Dizziness, Murmur of tricuspid insufficiency, Syncope, Murmur of pulmonic insufficiency, Chest pain, Hepatomegaly, Palpitations, Jugular venous distension at 45 degrees, Fatigue, Edema) were assessed at Baseline and Week 12. The status of each sign and symptom (“absent” or “present”) was assessed at each visit. To assess overall change from baseline in signs and symptoms, a “1” was assigned for each sign and symptom that was “present” at the Week 12 but was “absent” at baseline, a “-1” was assigned for each sign and symptom that was “absent” at Week 12 but was “present” at baseline, and a “0” was assigned for no change. An overall change score at each post-baseline assessment was then calculated by summing these values for all signs and symptoms. The overall change score had the potential to range from -17 to 17.

Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat population.

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	**Placebo**
Number of Participants Analyzed [units: participants]	**115**	**120**
Change in Signs and Symptoms of PAH [units: units on a scale] Median (Full Range)	**0 (-6 to 5)**	**0 (-6 to 16)**

No statistical analysis provided for Change in Signs and Symptoms of PAH

9. Secondary: N-terminal Pro-B-Type Natriuretic Peptide (NT Pro-BNP) [Time Frame: 12 weeks]

Measure Type	Secondary
Measure Title	N-terminal Pro-B-Type Natriuretic Peptide (NT Pro-BNP)
Measure Description	Change in NT pro-BNP from Baseline to Week 12. Plasma samples were collected from patients at Baseline and Week 12 in order to measure any change over time in circulating plasma levels of this biomarker.
Time Frame	12 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as

imputation technique, as appropriate.
Per protocol

Reporting Groups

	Description
Inhaled Treprostinil	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.
Placebo	Initial dose: 3 breaths. Titrated to 9 breaths, four times daily.

Measured Values

	Inhaled Treprostinil	Placebo
Number of Participants Analyzed [units: participants]	**73**	**82**
N-terminal Pro-B-Type Natriuretic Peptide (NT Pro-BNP) [units: pg/mL] Median (Inter-Quartile Range)		
Week 12	**377 (124 to 1091)**	**756 (177 to 2213)**
Change from Baseline	**-57 (-396 to 34)**	**40 (-93 to 288)**

Statistical Analysis 1 for N-terminal Pro-B-Type Natriuretic Peptide (NT Pro-BNP)

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.001
Hodges-Lehman Estimate [4]	-167
95% Confidence Interval	-333 to -64

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

[4]	Other relevant estimation information:
	No text entered.

Serious Adverse Events

Show Serious Adverse Events

Other Adverse Events

Show Other Adverse Events

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.