Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
Condition:	Pulmonary Hypertension
Interventions:	Drug: UT-15C SR Drug: Placebo

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 recruitment period for this study was June 2009 to July 2011. Sites were located in North America, Europe and Asia.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
The 310 subjects who received a dose of study drug are presented here.

Reporting Groups

	Description
UT-15C SR	Doses were initiated at 0.25 mg BID and increased by 0.25 mg BID every three days (as clinically indicated based on tolerability and symptoms of PAH), to a max dose of 16 mg BID.
Placebo	Identical placebo tablets to UT-15C, doses were titrated in the same manner

Participant Flow: Overall Study

	UT-15C SR	**Placebo**
STARTED	**157**	**153**
COMPLETED	**132**	**138**
NOT COMPLETED	**25**	**15**
Adverse Event	**18**	**5**

Clinical Worsening	**4**	**4**
Death	**2**	**3**
Withdrawal by Subject	**1**	**2**
Lost to Follow-up	**0**	**1**

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
UT-15C SR	Doses were initiated at 0.25 mg BID and increased by 0.25 mg BID every three days (as clinically indicated based on tolerability and symptoms of PAH), to a max dose of 16 mg BID.
Placebo	Identical placebo tablets to UT-15C, doses were titrated in the same manner
Total	Total of all reporting groups

Baseline Measures

	UT-15C SR	Placebo	Total
Number of Participants [units: participants]	**157**	**153**	**310**
Age [units: participants]			
<=18 years	**0**	**0**	**0**
Between 18 and 65 years	**119**	**122**	**241**
>=65 years	**38**	**31**	**69**
Age [units: years] Mean (Full Range)	**51.5 (18 to 76)**	**50.4 (20 to 75)**	**51.0 (18 to 76)**
Gender [units: participants]			

Female	**119**	**122**	**241**
Male	**38**	**31**	**69**
PAH Etiology [units: participants]			
Idiopathic or familial	**104**	**99**	**203**
Collagen vascular disease	**48**	**49**	**97**
HIV infection	**2**	**4**	**6**
Repaired congenital heart disease	**3**	**1**	**4**
World Health Organization (WHO) Functional Class [1] [units: Participants]			
Class II	**43**	**37**	**80**
Class III	**110**	**115**	**225**
Class IV	**3**	**0**	**3**
Unknown	**1**	**1**	**2**
Baseline Six-minute walk distance [units: meters] Mean ± Standard Deviation	**329.4 ± 69.2**	**336.8 ± 63.5**	**333 ± 66.4**
Background PAH therapy [2] [units: participants]			
PDE-5i	**67**	**65**	**132**
ERA	**25**	**28**	**53**
PDE-5i + ERA	**65**	**60**	**125**
Time since PAH diagnosis [units: years] Mean ± Standard Deviation	**2.5 ± 2.6**	**3.3 ± 4.1**	**2.9 ± 3.4**

[1] Class I: No limitation of physical activity. Class II: Slight limitation of physical activity. Class III: Marked limitation of physical activity. Class IV: Inability to carry out any physical activity without symptoms.

[2] Eligible subjects were receiving background PAH therapy of either a phosphodiesterase-5 inhibitor (PDE-5i) and/or endothelin receptor antagonist (ERA)

Outcome Measures

Hide All Outcome Measures

1. Primary: 6-minute Walk Distance (6MWD) [Time Frame: Baseline and 16 weeks]

Measure Type	Primary
Measure Title	6-minute Walk Distance (6MWD)
Measure Description	Placebo-corrected change in 6MWD from Baseline to Week 16, correlates with the current clinical standard for assessing patient functional status in the treatment of PAH and is considered an objective measure of patient functional status by the American Thoracic Society (ATS). The 6MWD was to be assessed between 3 and 6 hours after the morning dose of study drug and background therapy(ies).
Time Frame	Baseline and 16 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
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	**Placebo**
Number of Participants Analyzed [units: participants]	**157**	**153**
6-minute Walk Distance (6MWD) [units: meters] Median (Inter-Quartile Range)		
Week 16 Values	**370 (292 to 419)**	**365 (300 to 405)**
Change from Baseline	**15 (-12 to 55)**	**11 (-14 to 39)**

Statistical Analysis 1 for 6-minute Walk Distance (6MWD)

Groups [1]	All groups

Method [2]	non-parametric ANCOVA
P Value [3]	0.089
Hodges-Lehmann (H-L) [4]	10.0
95% Confidence Interval	(-2.0 to 22.0)

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	Using an allocation ratio of 1:1 between UT-15C SR and placebo, a fixed sample size of approximately 266 subjects would provide at least 90% power at a significance level of 0.05 (two-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline in distance traversed during the 6-Minute Walk, assuming a standard deviation of 75 meters. A total sample size of approximately 300 subjects was determined to account for discontinuations during the enrollment period.
[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.

2. Secondary: Clinical Worsening Assessment [Time Frame: Baseline and 16 Weeks]

Measure Type	Secondary
Measure Title	Clinical Worsening Assessment
Measure Description	Definition of clinical worsening included patients who met at least one of the following criteria during the 16 weeks of study: 1. Death (all causes excluding accident) 2. Transplantation 3. Atrial septostomy 4. Hospitalization as a result of right heart failure 5. Greater than or equal to a 20% decrease in 6MWD from Baseline (or too ill to walk) AND addition of an inhaled prostacyclin analogue, ERA, or PDE-5i 6. Initiation of parenteral prostacyclin therapy (i.e., epoprostenol, iloprost, or treprostinil) for the treatment of PAH
Time Frame	Baseline and 16 Weeks

Safety Issue	Yes

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
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**157**	**153**
Clinical Worsening Assessment [units: number of clinical worsening events]	**11**	**10**

Statistical Analysis 1 for Clinical Worsening Assessment

Groups [1]	All groups
Method [2]	Fisher Exact
P Value [3]	1.00

[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.

3. Secondary: Borg Dyspnea Score [Time Frame: Baseline and 16 Weeks]

Measure Type	Secondary
Measure Title	Borg Dyspnea Score
Measure Description	The Borg dyspnea score is a 10-point scale rating the maximum level of dyspnea experienced during the six-minute walk test (6MWT). The Borg dyspnea score was assessed immediately following the 6MWT. Scores ranged from 0 (for no shortness of breath) to 10 (for the greatest shortness of breath ever experienced).
Time Frame	Baseline and 16 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.
All subjects with a Baseline Borg Score were included in the analysis. One subject in the placebo group did not have a Baseline Borg Score recorded.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	**Placebo**
Number of Participants Analyzed [units: participants]	**157**	**152**
Borg Dyspnea Score [units: score] Median (Inter-Quartile Range)		
Week 16 Value	**3.0 (2.0 to 5.0)**	**4.0 (2.0 to 5.0)**
Change from Baseline	**0 (-1.0 to 1.0)**	**0 (-1.0 to 1.0)**

Statistical Analysis 1 for Borg Dyspnea Score

Groups [1]	All groups

Method [2]	Wilcoxon rank sum test
P Value [3]	0.22
Hodges-Lehmann (H-L) Estimate [4]	0.0
95% Confidence Interval	(-1.0 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:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

4. Secondary: World Health Organization (WHO) Functional Class [Time Frame: Baseline and 16 Weeks]

Measure Type	Secondary
Measure Title	World Health Organization (WHO) Functional Class
Measure Description	Class I: No limitation of physical activity. Class II: Slight limitation of physical activity. Class III: Marked limitation of physical activity. Class IV: Inability to carry out any physical activity without symptoms.
Time Frame	Baseline and 16 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.
Subjects with a WHO functional class assessment at Week 16

Reporting Groups

	Description

UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**131**	**136**
World Health Organization (WHO) Functional Class [units: participants]		
WHO Class I	**1**	**3**
WHO Class II	**58**	**47**
WHO Class III	**70**	**83**
WHO Class IV	**2**	**3**

Statistical Analysis 1 for World Health Organization (WHO) Functional Class

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.43
Hodges-Lehmann (H-L) estimate [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 the 26 UT-15C subjects and 17 placebo subjects without values reported at Week 16.
[4]	Other relevant estimation information:
	No text entered.

5. Secondary: Symptoms of PAH [Time Frame: Baseline and 16 Weeks]

Measure Type	Secondary
Measure Title	Symptoms of PAH
Measure Description	Symptoms of PAH including fatigue, dyspnea, edema, dizziness, syncope, chest pain and orthopnea were assessed by the physician at Baseline and Week 16. Severity grade values (i.e., 0, 1, 2 or 3) for each symptom were provided each subject. A severity of 0 indicated no symptoms, the maximum severity was 3, indicating severe symptoms. Mean change in symptom severity from Baseline to Week 16 is described.
Time Frame	Baseline and 16 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.
Subjects without Baseline assessments of PAH symptoms were not included in the analysis.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**156**	**150**
Symptoms of PAH [units: units on a scale] Mean ± Standard Deviation		
Change in Fatigue Symptoms	**0.0 ± 0.9**	**0.0 ± 1.0**
Change in Dyspnea Symptoms	**-0.1 ± 0.9**	**-0.2 ± 0.9**
Change in Edema Symptoms	**0.0 ± 1.0**	**0.0 ± 0.9**
Change in Dizziness Symptoms	**0.1 ± 1.0**	**0.0 ± 1.0**
Change in Syncope Symptoms	**0.2 ± 0.8**	**0.2 ± 0.7**
Change in Chest Pain Symptoms	**0.1 ± 1.0**	**0.1 ± 1.0**

Change in Orthopnea Symptoms	**0.2 ± 1.0**	**0.1 ± 0.9**

No statistical analysis provided for Symptoms of PAH

6. Secondary: Dyspnea Fatigue Index [Time Frame: Baseline and 16 Weeks]

Measure Type	Secondary
Measure Title	Dyspnea Fatigue Index
Measure Description	The dyspnea-fatigue index was assessed at Baseline and Week 16. Each of the three components of the dyspnea-fatigue index were rated on a scale 0 to 4, with 0 being the worst condition and 4 being the best condition for each component. The dyspnea-fatigue index is computed by summing the three component scores.
Time Frame	Baseline and 16 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.
Subjects without a Dyspnea Fatigue Index score at Baseline were not included in the analysis.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	**Placebo**
Number of Participants Analyzed [units: participants]	**154**	**149**
Dyspnea Fatigue Index [units: units on a scale] Mean ± Standard Deviation	**5.7 ± 2.6**	**6.0 ± 2.5**

Statistical Analysis 1 for Dyspnea Fatigue Index

Groups [1]	All groups
Method [2]	Wilcoxon rank sum test
P Value [3]	0.30
Hodges-Lehmann (H-L) estimate [4]	0.0
95% Confidence Interval	(0.0 to 1.0)

[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.

7. Secondary: N-terminal proBNP (NT-proBNP) [Time Frame: Baseline and 16 Weeks]

Measure Type	Secondary
Measure Title	N-terminal proBNP (NT-proBNP)
Measure Description	Serum N-terminal pro-BNP concentration was assessed at Baseline and Week 16.
Time Frame	Baseline and 16 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.
Subjects who were missing Week 16 samples were not included in the analysis.

Reporting Groups

	Description

UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**120**	**135**
N-terminal proBNP (NT-proBNP) [units: pg/mL] Mean ± Standard Deviation		
Week 16 Value	**1310 ± 1663**	**1627 ± 2401**
Change from Baseline	**135 ± 913**	**136 ± 1242**

No statistical analysis provided for N-terminal proBNP (NT-proBNP)

8. Secondary: Quality of Life (QoL) Assessment: Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [Time Frame: Baseline and 16 Weeks]

Measure Type	Secondary
Measure Title	Quality of Life (QoL) Assessment: Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)
Measure Description	Change in CAMPHOR Scores from Baseline to Week 16. The CAMPHOR is a health related quality of life instrument validated for pulmonary hypertension that assesses impairment (symptoms), disability (activities) and quality of life. The questionnaire is divided into three sections; Symptoms (Scores 0-25; high scores indicate more symptoms), Activity (Score 0-30; low score indicates good functioning)and Quality of Life (0-25; high scores indicate poor QoL). The sum of these scores equates to the Total score (0-80). In the CAMPHOR scores, lower scores indicate improvements.
Time Frame	Baseline and 16 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.
Subjects in countries where the CAMPHOR has not been validated in the local language were not included in these analyses. Additionally, only subjects with completed questionnaires at Baseline and Week 16 were analyzed.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**102**	**85**
Quality of Life (QoL) Assessment: Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [units: units on a scale] Median (Inter-Quartile Range)		
Symptom Score	**10.0 (6.0 to 16.0)**	**9.0 (4.0 to 14.0)**
Activity Score	**10.0 (7.0 to 14.0)**	**10.0 (6.0 to 13.0)**
Quality of Life Score	**9.0 (4.0 to 15.0)**	**5.0 (1.5 to 13.0)**
Total Score	**28.0 (19.0 to 43.0)**	**24.5 (12.0 to 40.5)**

No statistical analysis provided for Quality of Life (QoL) Assessment: Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)

9. Post-Hoc: 6-minute Walk Distance by PAH Etiology: Idiopathic PAH (IPAH) / Heritable PAH(HPAH) [Time Frame: Baseline and 16 Weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Distance by PAH Etiology: Idiopathic PAH (IPAH) / Heritable PAH(HPAH)

Measure Description	Covariate analysis of change in 6MWD by PAH etiology, specifically idiopathic or heritable PAH
Time Frame	Baseline and 16 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.
Subjects with IPAH/HPAH

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**104**	**99**
6-minute Walk Distance by PAH Etiology: Idiopathic PAH (IPAH) / Heritable PAH(HPAH) [units: meters] Median (Inter-Quartile Range)	**21.5 (-0.5 to 64.5)**	**13 (-14 to 39)**

Statistical Analysis 1 for 6-minute Walk Distance by PAH Etiology: Idiopathic PAH (IPAH) / Heritable PAH(HPAH)

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.058
Hodges-Lehman Estimate [4]	14.0
95% Confidence Interval	(0.0 to 28.0)

[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.

10. Post-Hoc: 6-minute Walk Distance by Background PAH Therapy: PDE-5i Only [Time Frame: 16 weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Distance by Background PAH Therapy: PDE-5i Only
Measure Description	No text entered.
Time Frame	16 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.
Subjects receiving only a PDE-5i at Baseline

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**67**	**65**
6-minute Walk Distance by Background PAH Therapy: PDE-5i Only [units: meters] Median (Inter-Quartile Range)	**30 (4 to 55)**	**14 (-7 to 39)**

Statistical Analysis 1 for 6-minute Walk Distance by Background PAH Therapy: PDE-5i Only

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.054
Hodges-Lehmann Estimate [4]	15.0
95% Confidence Interval	(-1.0 to 29.0)

[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.

11. Post-Hoc: 6-minute Walk Test by Background PAH Therapy: ERA Only [Time Frame: Baseline and 16 weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Test by Background PAH Therapy: ERA Only
Measure Description	No text entered.
Time Frame	Baseline and 16 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.
Subjects who were only receiving an ERA at Baseline

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**25**	**28**
6-minute Walk Test by Background PAH Therapy: ERA Only [units: meters] Median (Inter-Quartile Range)	**-5 (-43.0 to 42.0)**	**-2.5 (-49.0 to 30.0)**

No statistical analysis provided for 6-minute Walk Test by Background PAH Therapy: ERA Only

12. Post-Hoc: 6-minute Walk Test by Background PAH Therapy: ERA + PDE-5i [Time Frame: 16 weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Test by Background PAH Therapy: ERA + PDE-5i
Measure Description	No text entered.
Time Frame	16 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.
Subjects receiving both an ERA and a PDE-5i at Baseline.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo

Number of Participants Analyzed [units: participants]	**65**	**60**
6-minute Walk Test by Background PAH Therapy: ERA + PDE-5i [units: meters] Median (Inter-Quartile Range)	**14.0 (-17 to 59)**	**15.5 (-14.5 to 39)**

Statistical Analysis 1 for 6-minute Walk Test by Background PAH Therapy: ERA + PDE-5i

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.674
Hodges-Lehman Estimate [4]	4.0
95% Confidence Interval	(-16.0 to 24.0)

[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.

13. Post-Hoc: 6-minute Walk Distance by Time to PAH Diagnosis: 0 - 0.9 Years [Time Frame: Baseline and 16 weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Distance by Time to PAH Diagnosis: 0 - 0.9 Years
Measure Description	No text entered.
Time Frame	Baseline and 16 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.
Subjects who have been diagnosed with PAH between 0 to 0.9 years prior to Baseline.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	**Placebo**
Number of Participants Analyzed [units: participants]	**40**	**38**
6-minute Walk Distance by Time to PAH Diagnosis: 0 - 0.9 Years [units: meters] Median (Inter-Quartile Range)	**21.5 (-12.5 to 50.5)**	**-6.0 (-63.0 to 26.0)**

Statistical Analysis 1 for 6-minute Walk Distance by Time to PAH Diagnosis: 0 - 0.9 Years

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.059
Hodges-Lehmann Estimate [4]	28.0
95% Confidence Interval	(1.0 to 59.0)

[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.

14. Post-Hoc: 6-minute Walk Distance by Time Since PAH Diagnosis: 0.9 - 1.74 Years [Time Frame: 16 Weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Distance by Time Since PAH Diagnosis: 0.9 - 1.74 Years
Measure Description	No text entered.
Time Frame	16 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.
Subjects who had been diagnosed with PAH between 0.9 and 1.74 years prior to Baseline.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**40**	**37**
6-minute Walk Distance by Time Since PAH Diagnosis: 0.9 - 1.74 Years [units: meters] Median (Inter-Quartile Range)	**20.1 (1.0 to 61.0)**	**13.0 (-2.0 to 45.0)**

Statistical Analysis 1 for 6-minute Walk Distance by Time Since PAH Diagnosis: 0.9 - 1.74 Years

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.22

Hodges-Lehmann Estimate [4]	10.0
95% Confidence Interval	(-10.0 to 31.0)

[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.

15. Post-Hoc: 6-minute Walk Distance by Years Since PAH Diagnosis: 1.8 - 3.5 Years [Time Frame: Baseline and 16 weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Distance by Years Since PAH Diagnosis: 1.8 - 3.5 Years
Measure Description	No text entered.
Time Frame	Baseline and 16 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.
Subjects who were diagnosed with PAH between 1.8 and 3.5 years prior to Baseline.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	Placebo
Number of Participants Analyzed [units: participants]	**40**	**37**
6-minute Walk Distance by Years Since PAH Diagnosis: 1.8 - 3.5 Years [units: meter] Median (Inter-Quartile Range)	**15.5 (-16.0 to 51.5)**	**4.0 (-14.0 to 42.0)**

Statistical Analysis 1 for 6-minute Walk Distance by Years Since PAH Diagnosis: 1.8 - 3.5 Years

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.99
Hodges-Lehmann Estimate [4]	3.0
95% Confidence Interval	(-23.0 to 28.0)

[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.

16. Post-Hoc: 6-minute Walk Distance by Time Since PAH Diagnosis: 3.6 - 26.4 Years [Time Frame: Baseline and 16 weeks]

Measure Type	Post-Hoc
Measure Title	6-minute Walk Distance by Time Since PAH Diagnosis: 3.6 - 26.4 Years
Measure Description	No text entered.
Time Frame	Baseline and 16 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.
Subjects who had been diagnosed with PAH for 3.6 to 26.4 years prior to Baseline.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1mg (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1mg (3.6).

Measured Values

	UT-15C SR	**Placebo**
Number of Participants Analyzed [units: participants]	**37**	**41**
6-minute Walk Distance by Time Since PAH Diagnosis: 3.6 - 26.4 Years [units: meters] Median (Inter-Quartile Range)	**14.0 (-23.0 to 59.0)**	**16.0 (-5.0 to 36.0)**

Statistical Analysis 1 for 6-minute Walk Distance by Time Since PAH Diagnosis: 3.6 - 26.4 Years

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.84
Hodges-Lehmann Estimate [4]	-2.0
95% Confidence Interval	(-25.0 to 22.0)

[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.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Adverse events were recorded throughout the 16 week study.
Additional Description	No text entered.

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1 (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1 (3.6).

Serious Adverse Events

	UT-15C SR	Placebo
Total, serious adverse events		
# participants affected / at risk	**23/157 (14.65%)**	**23/153 (15.03%)**
Cardiac disorders		
Right ventricular failure [*1]		
# participants affected / at risk	**5/157 (3.18%)**	**2/153 (1.31%)**
# events	**5**	**2**
Atrial fibrillation [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**
Cardiac failure [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**
Cardio-respiratory arrest [*1]		
# participants affected / at risk	**0/157 (0.00%)**	**1/153 (0.65%)**
# events	**0**	**1**
Palpitations [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**

Gastrointestinal disorders		
Diverticulum [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**
Lower gastrointestinal hemorrhage [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**
General disorders		
Pyrexia [*1]		
# participants affected / at risk	**2/157 (1.27%)**	**1/153 (0.65%)**
# events	**2**	**2**
Sudden death [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**1/153 (0.65%)**
# events	**1**	**1**
Peripheral edema [*1]		
# participants affected / at risk	**0/157 (0.00%)**	**1/153 (0.65%)**
# events	**0**	**1**
Hepatobiliary disorders		
Hepatic ischemia [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**
Infections and infestations		
Lower respiratory tract infection [*1]		
# participants affected / at risk	**3/157 (1.91%)**	**0/153 (0.00%)**
# events	**3**	**0**
Gastroenteritis [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**
Infection [*1]		
# participants affected / at risk	**0/157 (0.00%)**	**1/153 (0.65%)**
# events	**0**	**2**
Sepsis [*1]		
# participants affected / at risk	**1/157 (0.64%)**	**0/153 (0.00%)**
# events	**1**	**0**
Tracheobronchitis [*1]		
# participants affected / at risk	**0/157 (0.00%)**	**1/153 (0.65%)**

# events	0	1
Upper respiratory tract infection [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Injury, poisoning and procedural complications		
Fall [*1]		
# participants affected / at risk	2/157 (1.27%)	0/153 (0.00%)
# events	2	0
Rib fracture [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Metabolism and nutrition disorders		
Fluid overload [*1]		
# participants affected / at risk	2/157 (1.27%)	1/153 (0.65%)
# events	2	1
Fluid retention [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Hypervolemia [*1]		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Hypoglycemia [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Hypokalemia [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Musculoskeletal and connective tissue disorders		
Back pain [*1]		
# participants affected / at risk	2/157 (1.27%)	0/153 (0.00%)
# events	2	0
Bone pain [*1]		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Rheumatoid arthritis [*1]		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)

# events	0	1
Nervous system disorders		
Cerebrovascular accident [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Depressed level of consciousness [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Dizziness [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Dysarthria [*1]		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Hypoesthesia [*1]		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Presyncope [*1]		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Psychiatric disorders		
Affect lability [*1]		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Reproductive system and breast disorders		
Ovarian mass [*1]		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Respiratory, thoracic and mediastinal disorders		
Dyspnea [*1]		
# participants affected / at risk	4/157 (2.55%)	2/153 (1.31%)
# events	4	2
Pulmonary hypertension [*1]		
# participants affected / at risk	2/157 (1.27%)	4/153 (2.61%)
# events	2	4
Hemoptysis [*1]		

# participants affected / at risk	1/157 (0.64%)	1/153 (0.65%)
# events	1	1
Chronic obstructive pulmonary disease * 1		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	3
Cough * 1		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Orthopnea * 1		
# participants affected / at risk	0/157 (0.00%)	1/153 (0.65%)
# events	0	1
Pulmonary embolism * 1		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Respiratory failure * 1		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Skin and subcutaneous tissue disorders		
Stasis dermatitis * 1		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Urticaria * 1		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Surgical and medical procedures		
Joint arthroplasty * 1		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0
Vascular disorders		
Deep vein thrombosis * 1		
# participants affected / at risk	1/157 (0.64%)	0/153 (0.00%)
# events	1	0

* Events were collected by non-systematic assessment

1 Term from vocabulary, MedDRA (14.0)

Other Adverse Events

Hide Other Adverse Events

Time Frame	Adverse events were recorded throughout the 16 week study.
Additional Description	No text entered.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
UT-15C SR	At Week 16, the mean(SD) dose of UT-15C was 3.1 (1.9).
Placebo	At Week 16, the mean(SD) dose of placebo was 6.1 (3.6).

Other Adverse Events

	UT-15C SR	Placebo
Total, other (not including serious) adverse events		
# participants affected / at risk	**157/157 (100.00%)**	**136/153 (88.89%)**
Cardiac disorders		
Palpitations [*1]		
# participants affected / at risk	**6/157 (3.82%)**	**12/153 (7.84%)**
# events	**6**	**12**
Gastrointestinal disorders		
Diarrhea [*1]		
# participants affected / at risk	**87/157 (55.41%)**	**38/153 (24.84%)**
# events	**105**	**42**
Nausea [*1]		
# participants affected / at risk	**73/157 (46.50%)**	**34/153 (22.22%)**
# events	**77**	**35**
Vomiting [*1]		
# participants affected / at risk	**33/157 (21.02%)**	**16/153 (10.46%)**
# events	**38**	**20**
Abdominal pain [*1]		
# participants affected / at risk	**12/157 (7.64%)**	**11/153 (7.19%)**
# events	**13**	**11**
Abdominal pain upper [*1]		

# participants affected / at risk	12/157 (7.64%)	7/153 (4.58%)
# events	13	7
Dyspepsia [*1]		
# participants affected / at risk	11/157 (7.01%)	8/153 (5.23%)
# events	12	8
General disorders		
Fatigue [*1]		
# participants affected / at risk	23/157 (14.65%)	16/153 (10.46%)
# events	25	17
Peripheral edema [*1]		
# participants affected / at risk	17/157 (10.83%)	10/153 (6.54%)
# events	18	10
Chest Pain [*1]		
# participants affected / at risk	9/157 (5.73%)	10/153 (6.54%)
# events	9	11
Infections and infestations		
Upper respiratory tract infection [*1]		
# participants affected / at risk	17/157 (10.83%)	13/153 (8.50%)
# events	18	13
Metabolism and nutrition disorders		
Decreased appetite [*1]		
# participants affected / at risk	12/157 (7.64%)	4/153 (2.61%)
# events	14	4
Musculoskeletal and connective tissue disorders		
Pain in jaw [*1]		
# participants affected / at risk	39/157 (24.84%)	10/153 (6.54%)
# events	39	10
Pain in extremity [*1]		
# participants affected / at risk	27/157 (17.20%)	11/153 (7.19%)
# events	29	12
Myalgia [*1]		
# participants affected / at risk	18/157 (11.46%)	10/153 (6.54%)
# events	18	11
Arthralgia [*1]		
# participants affected / at risk	12/157 (7.64%)	9/153 (5.88%)
# events	13	9
Back pain [*1]		

# participants affected / at risk	12/157 (7.64%)	6/153 (3.92%)
# events	13	6
Muscle spasms * 1		
# participants affected / at risk	12/157 (7.64%)	5/153 (3.27%)
# events	12	5
Nervous system disorders		
Headache * 1		
# participants affected / at risk	112/157 (71.34%)	61/153 (39.87%)
# events	145	69
Dizziness * 1		
# participants affected / at risk	30/157 (19.11%)	15/153 (9.80%)
# events	36	15
Respiratory, thoracic and mediastinal disorders		
Dyspnea * 1		
# participants affected / at risk	25/157 (15.92%)	10/153 (6.54%)
# events	27	15
Nasal congestion * 1		
# participants affected / at risk	10/157 (6.37%)	0/153 (0.00%)
# events	10	0
Nasopharyngitis * 1		
# participants affected / at risk	17/157 (10.83%)	25/153 (16.34%)
# events	19	28
Vascular disorders		
Flushing * 1		
# participants affected / at risk	55/157 (35.03%)	16/153 (10.46%)
# events	64	18

* Events were collected by non-systematic assessment

1 Term from vocabulary, MedDRA (14.0)

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.