Table 14. Baseline hemodynamic parameters (P01:01)[18]

	Flolan N=14	UT-15 N=14
HR (bpm)	83±4	81±3
Right Atrial Press (mmHg)	10±1	11±1
Cardiac Index	2.5±0.1	2.7±0.3
Pulmonary Artery Press (mm Hg)	56±5	55±5
PVRI (mmHg/L-min-m^2)	19±2	18±3
SVRI (mmHg/L-min-m^2)	37±5	31±3
SvO_2 (%)[19]	66±3	66±3

Table 15 below summarizes the change from baseline for the same parameters. There was a consistent acute effect to increase cardiac index (CI) and decrease pulmonary vascular resistance index (PVRI). No clear dose-related effect on any of the measured parameters was demonstrated.

Table 15. Change from baseline in hemodynamic parameters (P01:01)[20]

	Flolan MTD[21] N=14	UT-15	
		MTD N=14	Maint N=10
HR (bpm)	+10±3%	+8±2%	-1±5%
Right Atrial Press (mmHg)	-10±6%	-19±6%	-39±11%
Cardiac Index	+32±9%	+26±12%	+27±17%
Pulmonary Artery Press (mm Hg)	-1.6±2%	-0.6±3%	-9±3%
PVRI (mmHg/L-min-m^2)	-22±5%	-14±7%	-20±9%
SVRI (mmHg/L-min-m^2)	-26±5%	-8.5±8%	-6±10%
SvO_2 (%)	—	—	+8±5%

Hemodynamic changes during washout. Patients were followed for 120 minutes after discontinuation of UT-15 with hemodynamic measurements. During that period the hemodynamic changes seen during UT-15 did not return to baseline (see table 14.2.3 in study report for details). No patient had rebound pulmonary hypertension during the 120 minutes after UT-15 discontinuation.

Maximum tolerated doses of UT-15. The table below summarizes the MTD of UT-15 for the patients who completed the initial UT-15 infusions, as well as the patients who completed the maintenance phase of the UT-15 infusion. The four subjects who discontinued were receiving different doses of UT-15. However, most of the patients at the higher doses of UT-15 were either discontinued or had to have their dose reduced.

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[18] *Data from NDA vol. 2.16, table 11.4.1A.*

[19] *Mixed venous O_2 saturation.*

[20] *Data from NDA vol. 2.16, table 11.4.1C.*

[21] *Maximally tolerated dose*

Table 16. Dosing of UT-15 (P01:01)[22]

Dose	Initiation of maintenance	Completion of maintenance	Completion without dose reduction
5	1	1	1
10	5	4	4
20	1	0	0
30	3	2	0
40	3	3	1
60	1	0	0
All doses	14	10	6

A.1.4.5 Safety

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs are shown in Table 17.

Table 17. Disposition of subjects (P01:01)[23]

Event	N
Initiated UT-15	14
Completed initial infusion	14
Discontinued with adverse event	4
Serious adverse event	0
Deaths	0

A.1.4.5.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.1.4.5.2 Comments on specific safety parameters

Deaths. There were no deaths reported for subjects in the trial.

Serious adverse events. No SAEs occurred during the administration of study drug.

Adverse events. Table 18 below summarizes the reported AEs.

Table 18. Subjects with adverse events on UT-15 (P01:01).[24]

Event	N (%)
Headache	13 (52%)
Infusion site reaction	4 (16%)
Flushing	8 (32%)
Nausea	4 (16%)
Dizziness	2 (8%)

Discontinuations. There were four discontinuations during the maintenance phase of the UT-15 infusion. Three of these were for nausea, headache and or vomiting. The fourth patient experienced pulmonary hypertension and is detailed below.

Subject 02005 had four SAEs: pulmonary hypertension, atelectasis, bronchitis and pneumonia.

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[22] *Data from NDA vol. 2.16, table 12.1.3.*

[23] *Data from NDA 21-272, vol. 2.16, section 12.1.3.*

[24] *Data from NDA 21-272, table 12.2.2.2B.*

This 12-year old girl with Class III CHF was hospitalized for evaluation. At baseline her pulmonary pressures were 152/68, mean 102 mmHg, exceeding her systemic arterial BP (mean 81 mmHg). Following initiation of UT-15 her cardiac output and systemic pressure rose, and her pulmonary pressures fell. She achieved a dose of UT-15 of 80 ng/kg/min, where she had a dose-limiting side effect of agitation and restlessness. She was then entered into the maintenance phase at 69 ng/kg/min. After 35 minutes her PAP rose abruptly to 218/147 and arterial saturation fell to 75%. Treatment was stopped, and patient received milrinone and O_2 with slow resolution of the elevated PAP. The investigators felt that her cardiac left-to-right shunt, along with her agitation, contributed to the pulmonary hypertensive crisis.

Effects on ECG. Review of the summary data from the ECGs collected during the trial showed no pattern of QT prolongation independent of heart rate. See NDA vol. 2.18, table 16.2.8.4 for details.

A.1.5 Summary

A.1.5.1 Efficacy summary

Study P01:01 measured the acute hemodynamic effects of UT-15 in patients with Primary Pulmonary Hypertension. Samples were also collected for pharmacokinetic assessments. The changes measured in this open-label trial were consistent with an acute effect of UT-15 on pulmonary vascular pressures, leading to an improvement in cardiac index. The pharmacokinetic assessment will be performed by other reviewers.

A.1.5.2 Safety summary

There were no new safety concerns identified in this small study. One potentially useful observation was that no evidence for rebound hypertension was seen in the 120 minutes following UT-15 discontinuation.

A.1.5.3 Reviewer's conclusions

This small study of the acute effects of UT-15 on central hemodynamics found data consistent with an acute effect of UT-15 to cause pulmonary vascular dilatation. No clear dose-relationship for this effect was demonstrated. Doses higher than 10 ng/kg were not tolerated without dose reduction in this short-term trial, most commonly due to headaches, nausea and/or vomiting. No new safety concerns emerged from this small trial.

A.2 Study P01:02: A dose-range-finding study comparing intravenous and subcutaneous 15AU81 (UT-15) in NYHA Class III/IV patients with primary pulmonary hypertension.

A.2.1 Sites and Investigators

P01:02 was conducted at 10 sites in the United States. The investigators are shown in Table 19.

Table 19. Investigators (P01:02)

Site	Investigator	Site	Investigator
01	Sean Gaine, MB	06	David Badesch, MD
02	Robyn Barst, MD	07	Ivan Robbins, MD
03	Stuart Rich, MD	08	Victor Tapson, MD
04	Bruce Brundage, MD	09	Adaani Frost, MD
05	Michael McGoon, MD	10	Robert Bourge, MD

A.2.2 Background

Initial protocol submitted: 6.18.97

Protocol amendments: one

Amendment #1, submitted on 12.22.97, enrolled 7 additional patients to Cohort II following the completion of Cohort III. Cohort III (20 ng/kg/min SQ dose), was deemed the maximum tolerated acute dose by the sponsor. The enrollment of seven additional patients to Cohort II resulted in a total of 13 patients completing the 10 ng/kg/min dose.

Subject enrollment: 10.4.97 to 1.27.98

Case report form cutoff: 4.29.94

A.2.3 Study design

In this multi-center, parallel, sequential, open-label dose-escalation trial, eligible patients underwent cardiac catheterization and then entered a treatment phase, which consisted of four segments: (a) an IV UT-15 75-minute Dosing Segment, (b) an IV UT-15 150 minute Washout Segment, (c) a subcutaneous (SQ) UT-15 150-minute Dosing Segment (see below for doses), and (d) a SQ UT-15 150-minute Washout Segment.

During the sub-cutaneous (SQ) period of the trial, subjects received IV dosing at 10 ng/kg/min followed by one of three SQ doses:

1) 5 ng/kg/min (n=6 subjects)

2) 10 ng/kg/min (n=13 subjects), or

3) 20 ng/kg/min (n=6 subjects).

The primary goals of the trial were to collect safety, hemodynamic and pharmacokinetic data on the use of SQ UT-15 in pulmonary hypertension.

A.2.3.1 Objectives

To characterize the pharmacokinetic profile of subcutaneous (SQ) administration of UT-15 in patients with severe primary pulmonary hypertension (PPH).

A.2.3.2 Number of subjects/ randomization

Twenty-five (25) patients with pulmonary hypertension were enrolled into the study: 6 each at the 5 and 20 ng/kg/min dose and 13 at the 10 ng/kg/min dose.

A.2.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- ≥ 12 years of age;
- Females must be post-menopausal or surgically sterile, or if female of child bearing potential, had a negative pregnancy test;
- had a diagnosis of severe, symptomatic PPH and were classified NYHA Class III or IV at Screening/Baseline;
- had a chest radiograph consistent with the diagnosis of PPH performed within the previous six months;
- had pulmonary function tests consistent with the diagnosis of PPH performed within the previous year;
- had a pulmonary ventilation/perfusion scan or pulmonary angiography performed since the onset of symptoms with results consistent with the diagnosis of PPH;
- had an echocardiogram within previous year consistent with the diagnosis of PPH, specifically: evidence of right ventricular hypertrophy or dilation, evidence of normal left ventricular function, and absence of mitral valve stenosis;
- had a cardiac catheterization at Baseline consistent with the diagnosis of PPH, specifically:

  PAPm ≥ 25 mmHg, and PCWP or a left ventricular end diastolic pressure ≤ 15 mmHg, and PVR > 3 mmHg/L/min, and absence of congenital heart disease (including atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous drainage, but presence of a patent foramen ovale would not exclude a patient);
- had indicated willingness to participate by signing an informed consent form.

Exclusion criteria (may not be present)

- had a new type of chronic therapy (e.g., a different category of oral vasodilator, a diuretic, digoxin) for PPH added within the last month, excepting anticoagulants;
- had any PPH medication, excepting anticoagulants, discontinued within the last week;
- had any disease known to cause secondary pulmonary hypertension (e.g., obstructive lung disease, collagen vascular disease, parasitic disease affecting the pulmonary system, sickle cell anemia, mitral valve stenosis, portal hypertension, or human immunodeficiency virus infection); or
- were currently receiving an investigational drug or have participated in investigational drug study within the past 30 days;

A.2.3.4 Dosage/ administration

UT-15 was administered IV or via sub-cutaneous infusion placed in the abdominal wall. After right-heart catheterization and baseline hemodynamic parameters, subjects received IV dosing at 10 ng/kg/min min followed by a SC dose of

1) 5 ng/kg/min (n=6 subjects)

2) 10 ng/kg/min (n=13 subjects), or

3) 20 ng/kg/min (n=6 subjects).

Concomitant medications. Drugs routinely used for PPH patients, including calcium channel blockers, digoxin, diuretics, anticoagulants and oxygen were provided by the hospital pharmacy and administered as deemed appropriate by each investigator. Prostacyclin analogues were not allowed as therapy.

A.2.3.5 Duration/ adjustment of therapy

Study drug was administered in hospital, and where patients remained throughout the drug administration and for 24 hours thereafter.

A.2.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.19. Invasive hemodynamic measurements were made during the period of the infusions and at the end of the washout period along with pharmacokinetic sampling and routine vital signs. After washout and through the first 24 hours vital signs and ECGs were collected every 8 hours.

A.2.3.7 Statistical considerations

The statistics in the trial were observational in nature given the small numbers with the exception of the pharmacokinetic assessments. These pharmacokinetic analyses are discussed in a separate review by Nhi Nyugen, Ph.D. and Joga Gobburu, Ph.D.

A.2.4 Results

A.2.4.1 Subject demographics & baseline characteristics

The majority of the patients in the trial were white (72%) and female (80%), with a mean age of 40 and a mean duration since diagnosis of PPH of 0.9 years. The majority (19/25) were NYHA Class III and the remainder NYHA Class IV. The reader is referred to the study report for additional demographics.

A.2.4.2 Disposition of subjects

Of the 25 patients enrolled, 10 patients had to terminate either the 75-minute iv infusion or the 150-minute SQ infusion prematurely due to intolerability or technical problems. Hence, only 15 patients completed both the iv and SQ infusions in their entirety.

Subject selection. No information is available about subject selection in protocol P01:02.

Protocol violations & deviations. Patient 04002 received 20 ng/kg/min due to staff error. His course will be discussed in the safety section of this review.

Concomitant therapies. Given the short duration of the trial no concomitant medications were used during the administration of the study drug.

A.2.4.3 Pharmacokinetics analyses

The pharmacokinetic results from the trial are reviewed elsewhere by Drs. Nguyenand Gobburu. The sponsor estimated the half-life of subcutaneous UT-15 at between 55 to 117 minutes, and the half-life for the IV form of UT-15 as 25 to 42 minutes.

A.2.4.4 Hemodynamic changes

Table 20 below summarizes the hemodynamic changes from baseline for the IV and SC administration of UT-15. Baseline is taken as the last value before starting the infusion, either following baseline hemodynamics (for the IV) or at the end of the 150 minute washout period (for the SC). The data from patient 04002 are not included here. Of the 25 patients enrolled, 10 patients had to terminate either the 75-minute iv infusion or

the 150-minute SQ infusion prematurely due to intolerability or technical problems (see Safety below). Hence, only 15 patients completed both the iv and SQ infusions in their entirety (and have data available for inclusion into Table 20 below).

Table 20. Baseline hemodynamic parameters (P01:02)[25]

	IV N=24	UT-15 SC dose (ng/kg/min)		
		5 N=6	10 N=13	20 N=6
HR (bpm)	85±2	88±7	82±2	86±7
Right Atrial Press (mmHg)	10.2±1	10.2±2	10.2±2	13.3±3
Cardiac Index	2.1±0.1	2.0±0.2	2.0±0.2	2.0±0.3
Pulmonary Artery Press (mm Hg)	63±4	65±8	65±6	69±5
PVRI (mmHg/L-min-m^2)	28±4	30±5	30±6	27±4
SVRI (mmHg/L-min-m^2)	45±4	47±3	45±5	47±9
SvO_2 (%)[26]	59±2	59±6	56±4	56±3

Table 21 below summarizes the change from baseline for the same parameters. There was a consistent acute effect to increase cardiac index (CI) and decrease pulmonary vascular resistance index (PVRI). No clear dose-related effect on any of the measured parameters was demonstrated.

Table 21. Change from baseline hemodynamic parameters (P01:02)[27]

	IV N=24	UT-15 SC dose (ng/kg/min)		
		5 N=6	10 N=13	20 N=6
HR (bpm)	-0.6±2.0%	+2.3±3.2%	+0.2±1.9%	+0.9±5.8%
Right Atrial Press (mmHg)	+6.7±13%	+26.7±30%	-19.6±13%	+13.0±37%
Cardiac Index	+12.1±4%	+6.5±7%	+19.4±6%	+7.4±2%
Pulmonary Artery Press (mm Hg)	-5.2±2%	+4.3±3%	-13.4±3%	-7.8±5%
PVRI (mmHg/L-min-m^2)	-17.1±4%	+1.6±13%	-26.6±7%	-15.5%
SVRI (mmHg/L-min-m^2)	-10.4±4%	-4.6±4%	-13.9±4%	-14.4±12%
SvO_2 (%)	+8.0±4%	-1.1±4%	+6.2±2%	+6.0±14%

Rebound hypertension. No evidence of rebound hypertension was seen during the 150 minutes following the discontinuation of UT-15. The vasodilatation persisted to the 150 minute timepoint following discontinuation of UT-15, limiting the usefulness of this data in ruling out a rebound phenomenon. Data for the 10 ng/kg/min dose group is shown below as representative.

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[25] *Data from NDA vol. 2.19, table 11.4.1A.*

[26] *Mixed venous O_2 saturation.*

[27] *Data from NDA vol. 2.19, table 11.4.1C.*

Table 22. Baseline, peak, and end-of-washout hemodynamic parameters (P01:02)[28]

	Baseline	End of	
		Infusion	Washout
Right Atrial Press (mmHg)	10.8	8.3	8.1
Cardiac Index	1.9	2.2	2.3
Pulmonary Artery Press (mm Hg)	67.3	58.8	60.9
PVRI (mmHg/L-min-m^2)	31.4	22.3	22.5

A.2.4.5 Safety

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below. The number of subjects with any SAE and subject discontinuations due to AEs were

Table 23. Disposition of subjects (P01:02)[29]

	UT-15 SQ (ng/kg/min)		
	5 N=6	10 N=13	20 N=6
Initiated UT-15	6	13	6
Completed 150 min infusion	5	12	3
Discontinued with adverse event	1	1	3
Serious adverse event[30]	0	0	0
Deaths[31]	0	0	0

A.2.4.5.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.2.4.5.2 Comments on specific safety parameters

Deaths. Two deaths occurred within three days of discontinuation from the trial.

Subject 02005 completed the trial without problems, and remained in the hospital for a Hickman catheter to be placed for Flolan initiation. After placement of the Hickman, the patient remained in the hospital, and was found cyanotic and pulseless that night. Flolan was not initiated.

Subject 04004 with PPH (NYHA Class III) completed the trial without complications and then received a Hickman to start Flolan. Flolan was initiated without difficulty at a dose of 4 ng/kg/min. The patient was readmitted the next day with worsening CHF and had a bradycardic then asystolic arrest and died.

Serious adverse events. No SAEs occurred during the administration of study drug.

Adverse events. Table 24 below summarizes the reported AEs.

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[28] *Data from NDA vol. 2.19, table 11.4.1.5 and 16.2.6.1. Shown for the SQ 10 ng/kg/min group.*

[29] *Data from NDA 21-272, table 12.1.1A and narratives.*

[30] *One SAE occurred before initiation of infusion of study drug.*

[31] *Two deaths occurred 8 hours and 3 days after dismissal from the study. See section below for details.*

Table 24. Subjects with adverse events (P01:02)[32]

Event	N (%)
Headache	13 (52%)
Infusion site reaction	4 (16%)
Flushing	8 (32%)
Nausea	4 (16%)
Dizziness	2 (8%)

ECGs and vital signs. No effect of UT-15 on ECG parameters, including the QT interval, was seen. See vol. 2.21, table 16.2.8.4 for details. Following administration of UT-15 the heart rate rose by a mean of 3.3 bpm, and the mean blood pressure fell by 6.8/8.7 mmHg (table 16.2.8.3).

A.2.5 Summary

A.2.5.1 Efficacy summary

Study P01:02 measured the acute hemodynamic effects of UT-15 in patients with Primary Pulmonary Hypertension. Samples were also collected for pharmacokinetic assessments. The changes measured in this open-label trial were consistent with an acute effect of UT-15 on pulmonary vascular pressures, leading to an improvement in cardiac index. The pharmacokinetic/ pharmacodynamic assessment will be performed by other reviewers.

A.2.5.2 Safety summary

There were no new safety concerns identified in this small study. One observation was that no evidence for rebound hypertension was seen in the 150 minutes following UT-15 discontinuation. Unfortunately, the fact that vasodilatation persisted for the period of measurement limits the usefulness of this observation.

The two deaths occurring so shortly after completion of the trial are of concern, especially the death that occurred the night after completion, before Flolan was initiated. While no evidence implicating the drug exists, the timing raises concerns about changes that occurred following discontinuation of UT-15 such as hemodynamic changes or shifts in fluids or electrolytes.

A.2.5.3 Reviewer's conclusions

This small study of the acute effects of UT-15 on central hemodynamics found data consistent with an acute effect of UT-15 to cause pulmonary vascular dilatation. No clear dose-relationship for this effect was demonstrated. No new safety concerns were identified, but two deaths occurred soon after drug discontinuation. These deaths will be considered in the context of the integrated safety summary elsewhere.

[32] *Data from NDA 21-272, table 12.2.2.2B.*

A.3 Study P01:03: A multicenter, double-blind, randomized, parallel comparison of the safety and efficacy of chronic subcutaneous UT-15 plus conventional therapy to conventional therapy in patients with severe primary pulmonary hypertension: an 8-week study.

A.3.1 Sites and investigators

P01:03 was conducted at 5 sites in the United States. The investigators are shown in Table 25.

Table 25. Investigators (P01:03).

Site	Investigator
01	Sean Gaine, MB
02	Robyn Barst, MD
03	Stuart Rich, MD
04	Ronald Oudiz, MD & Shelley Shapiro, MD
10	Robert Bourge, MD

A.3.2 Background

Initial protocol submitted: 2.25.98

Protocol amendments: 4.21.98 and 6.16.98

Amendment #1 (4.21.98) reduced the number of pharmacokinetic blood samples collected.

Amendment #2 (6.16.98) lowered the starting dose (i.e., from 5 ng/kg/min to 2.5 ng/kg/min or below) and the in-hospital dose increment from 5 ng/kg/min to 2.5 or 5 ng/kg/min. This change resulted in a reduction in the maximum achievable doses at the end of Week 1 through Week 8 of the Treatment Phase

These changes resulted in a lower number of UT-15 concentration values per patient for pharmacokinetic analysis, resulting in a less precise pharmacokinetic analysis.

Subject enrollment: 4.23.98 to 10.7.98

Case report form cutoff: 4.29.94

The safety and efficacy results of the study were presented at the 1999 European Congress of Cardiology and published in abstract form[33].

A.3.3 Study design

Eligible patients were randomized (2:1) to receive conventional therapy plus a continuous subcutaneous infusion of UT-15 or conventional therapy plus a continuous subcutaneous infusion of placebo for an 8-week infusion period. During the Treatment Phase, in addition to efficacy measurement (exercise capacity) and assessment of clinical signs and symptoms of the disease at scheduled visits (Weeks 1, 4 and 8), blood samples were collected for pharmacokinetic analysis. Hemodynamic and symptom assessments were not available to the individual who conducted the primary efficacy analysis (6-minute walk). Similarly, the walk results were only known by an independent exercise administrator.

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[33] *McLaughlin V, Barst R, Rich S,* et al. *Efficacy and safety of UT-15, a prostacyclin analogue, for primary pulmonary hypertension.* Eur Heart J *1999; **20** (Abstr Suppl):486.*

A.3.3.1 Objectives

1) The primary objective of this study was to assess the safety of continuous subcutaneous infusion of UT-15 in an out-patient environment to patients with primary pulmonary hypertension (PPH).

2) The secondary objective of this study was to characterize the pharmacokinetic disposition of chronic, subcutaneous administration of UT-15 in this patient population.

3) Exercise, hemodynamics and symptoms of disease were monitored, including invasive hemodynamic measurements were made at baseline and week 8.

The primary efficacy end-point was exercise capacity (6-minute walk) at weeks 1, 4 and 8. Additional efficacy measurements included changes in the signs and symptoms of pulmonary hypertension and heart failure, including the Borg Dyspnea Scale and the Dyspnea-Fatigue Rating.

Pharmacokinetic evaluation focused on the plasma UT-15 concentration versus time profiles in individual patients.

A.3.3.2 Number of subjects/ randomization

Twenty-six (26) patients with PPH were enrolled into the study: 17 received UT-15, 9 received placebo.

A.3.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- ≥8 years of age;
- If female, be physiologically incapable of child bearing or practicing an acceptable method of birth control;
- have a diagnosis of severe, symptomatic PPH and remain NYHA Class III or IV despite the use of chronic oral vasodilators for at least one month;
- have a chest radiograph consistent with the diagnosis of PPH performed within the previous six months;
- have pulmonary function tests consistent with the diagnosis of PPH performed within the previous year;
- have a ventilation perfusion scan or pulmonary angiography consistent with the diagnosis of PPH;
- have an echocardiogram within previous year consistent with the diagnosis of PPH, specifically: evidence of right ventricular hypertrophy or dilation, evidence of normal left ventricular function, and absence of mitral valve stenosis;
- have hemodynamics consistent with PPH, specifically:
  - PAPm ≥ 25 mmHg, and
  - PCWP or a left ventricular end diastolic pressure ≤ 15 mmHg, and
  - PVR > 3 mmHg/L/min, and
- Absence of congenital heart disease (atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous drainage);
- be mentally and physically capable of learning to administer study drug using an infusion pump and a subcutaneous access;

- signed informed consent.

Exclusion criteria (may not be present)

- be pregnant (women of childbearing potential must have a negative pregnancy test);
- have a new type of chronic therapy (other than anti-coagulation) for PPH added within the last month;
- have any oral PPH medication excepting anticoagulants discontinued within the last week;
- received any chronic prostaglandin or prostaglandin analogue therapy (IV or inhaled) within the past 30 days;
- have any disease known to cause secondary pulmonary hypertension (e.g., obstructive lung disease, collagen vascular disease, parasitic disease affecting the pulmonary system, sickle cell anemia, mitral valve stenosis, portal hypertension, HIV);
- have a musculoskeletal disorder (e.g., arthritis, artificial leg, etc.) or any other disease which could limit ambulation, or be connected to a machine which was not portable;
- have a baseline exercise capacity of less than 50 meters or greater than 450 meters walked in six minutes;
- be receiving an investigational drug or have participated in investigational drug study within the past 30 days;
- have the presence of any physiological condition which contraindicates the administration of UT-15.

A.3.3.4 Dosage/ administration

UT-15 or placebo was administered via sub-cutaneous infusion. Of the 17 patients randomized to receive UT-15, only one patient received a starting dose of 5 ng/kg/min. Fifteen 15 patients received a starting dose of 2.5 ng/kg/min and one patient received a starting dose of 1 ng/kg/min.

Study drug was administered subcutaneously using a positive pressure [redacted] infusion pump. The subcutaneous catheter was placed in the abdominal wall of patients, and the infusion site was moved, if needed, at the discretion of the investigator. There was to be no washout period between changes in UT-15 infusion rates (doses).

The original starting dose was to by 5 ng/kg/min, but the protocol was amended to a starting dose of 2.5 ng/kg/min.

Concomitant medications. Short-terms (<5 days) of therapy with other agents to treat CHF were permitted with the exception of prostacyclin (Flolan) and its analogues. All other agents were permitted in both treatment groups.

Duration/ adjustment of therapy

Study drug was started in hospital, and where patients remained for the first week to assure stabilization. Study drug was up-titrated weekly to maximum tolerated dose. If a dose was not tolerated, it could be decreased to the maximum tolerated dose for each patient.

A.3.3.5 Safety and efficacy endpoints measured

Table 26. Timetable for clinical observations and lab measurements (P01:03)[34]

	Screen	Baseline		Treatment			
		Week 0		Week 1	Week 4	Week 8	
		Day 1	Day 2	Day 9	Day 29	Day 58	Day 59
Informed consent	X						
Inclusion/exclusion criteria	X		X				
Clinical chemistry/hematology[35]		X				X	
Medical history/physical exam	X						
PPH signs and symptoms[36]/dyspnea-fatigue[37]		X		X	X	X	

[34] *Data from table 9.5.1 from P01:03 Clinical Study Report.*

[35] *See Clinical report for P01:03, section 9.5.2.1 for list of labs measured.*

[36] *Evaluation of PPH signs and symptoms was conducted for each study patient at Baseline and Weeks 1, 4, and 8. To ensure consistency, these parameters were evaluated by the same physician for a given patient throughout the study. The following relevant PPH signs and symptoms were assessed as present or absent; severity, extent or grade was evaluated as shown:*

Loud P2 sound	Dyspnea at rest
Right ventricular S3 sound	Dyspnea on exertion
Right ventricular S4 sound	Paroxysmal nocturnal dyspnea
Right ventricular heave	Dizziness (extent)
Murmur of tricuspid insufficiency (grade)	Syncope (extent)
Murmur of pulmonic insufficiency (grade)	Chest pain (extent)
Hepatomegaly (extent)	Palpitations (extent)
Jugular venous distention at 45 degrees (extent)	Fatigue
Edema (extent)	Orthopnea (severity)

For each patient at Weeks 1, 4, and 8, each parameter was assigned a change score as follows:

Baseline	Treatment Phase	Change Score
Absent	Present	-1
Present	Present	0
Absent	Absent	0
Present	Absent	+1

A composite change score for each assessment period (Week 1, Week 4, or Week 8) was calculated for each patient by adding change scores of the individual signs and symptoms.

[37] *The Dyspnea-Fatigue Rating was assessed at Baseline and Weeks 1, 4, and 8 by study staff that were responsible for patient care. This clinical index of dyspnea and fatigue consists of three components, each rated on a scale of 0 to 4 (worst to best), for* magnitude of the task *that evokes dyspnea or fatigue, the* magnitude of the pace *(or effort) with which the task is performed, and the associated* functional impairment *in general activities. The ratings for each component are added to form an aggregate score, which can range from 0 (for the worst condition) to 12 (for the best).*

The ratings for the three components of the Dyspnea-Fatigue Rating are:

1. Magnitude of task (at normal pace):

- 4 **Extraordinary**. *Becomes short of breath or fatigued (hereafter called "symptomatic") only with extraordinary activity such as carrying very heavy loads on level ground, lighter loads uphill or running. No symptoms with ordinary tasks.*
- 3 **Major**. *Becomes symptomatic only with such major activities as walking up a steep hill, climbing more than three flights of stairs or carrying a moderate load on the level.*
- 2 **Moderate**. *Becomes symptomatic with moderate or average tasks such as walking up a gradual hill, climbing less than three flights of stairs or carrying a light load on level ground.*
- 1 **Light**. *Becomes symptomatic with light activities, such as walking on the level, washing or standing.*

	Screen	Baseline		Treatment			
		Week 0		Week 1	Week 4	Week 8	
		Day 1	Day 2	Day 9	Day 29	Day 58	Day 59
Exercise capacity[38]/Borg dyspnea[39]		X	X[40]	X	X	X	
Invasive hemodynamic measurements			X				X
Randomization (2:1)			X[f]				
12-lead ECG	X					X	
Pharmacokinetic blood samples[41]			X	X	X	X	
Infusion of study drug/chronic infusion				X	X	X	X
Concomitant medication report	X	X	X	X	X	X	X
Adverse event report	X	X	X	X	X	X	X

The six-minute walk was assessed along a level, limited-access corridor with a minimum length of 33 meters. The test area was marked with gradations to permit distance calculation of partial laps. At a given center, the walk test was to be conducted by the same test administrator, who was otherwise uninvolved in the study or care of the study patients and was blinded to the treatment assignment.

A.3.3.6 Statistical considerations

Power. Trial P01:03 had limited enrollment, and was conducted to provide safety data and to characterize the pharmacokinetics of UT-15. In addition, the sponsor used it to provide estimates of between-treatment changes (and associated variances) of exercise

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0 None. *Symptomatic at rest, while sitting or lying down.*

2. Magnitude of pace:

4 Extraordinary. *Essentially all conceivable physical tasks are performed at normal pace.*

3 Major. *Major tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Less strenuous tasks can be done at normal pace.*

2 Moderate. *Moderate tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Light tasks can be done at normal pace.*

1 Light. *Light tasks are done at a reduced pace.*

0 None. *Symptomatic at rest.*

3. Functional impairment:

4 None. *Can carry out usual activities and occupation (if employed before onset of PPH) without symptoms.*

3 Slight. *Distinct impairment in at least one activity but no activities completely abandoned. A change in activity may have occurred at work or in other activities, but the change is slight or is not clearly caused by shortness of breath or fatigue.*

2 Moderate. *Patient has changed jobs or has abandoned at least one usual activity.*

1 Severe. *Patient is unable to work or has given up most or all usual activities.*

0 Very severe. *Unable to work and has given up most or all usual activities.*

[38] *Assessed using the 6-minute walk test.*

[39] *The Borg Dyspnea Scale is a continuous scale from 0 (no dyspnea) to 10 (maximum dyspnea) indicating the maximal shortness of breath experienced by a patient during performance of the Six-Minute Walk Test (Baseline and Weeks 1, 4, and 8). A standardized script was used in the assessment. The data from the exercise test and Borg Dyspnea Scale were then recorded directly onto the appropriate CRF and were not available to the other study staff.*

[40] *Used as baseline for later comparisons.*

[41] *Blood samples for pharmacokinetic collected pre dose increase, and 30, 60, 120, 240, and 300 minutes following initial dose and next three dose increases, and one sample each at Weeks 1, 4, and 8.*

capacity to aid in the design of pivotal clinical studies. As such, no formal power calculations were performed by the sponsor.

Multiplicity. There was no adjustment for multiplicity.

Interim analyses. There was no interim analysis.

Statistical analysis. The primary efficacy endpoint was analyzed using an ITT group consisting of all randomized patients. All other efficacy analyses were conducted on available (nonmissing) data for the ITT group. Safety analyses were conducted on all randomized patients.

The distance walked analyzed by nonparametric and parametric methods. The nonparametric analysis was the primary analysis and used extended Cochran-Mantel-Haenszel (CMH) test. The secondary, parametric analysis used ANCOVA with terms for treatment group and center with baseline distance walked as covariates. Both parametric and nonparametric analyses utilized imputed values or ranks in the event that a patient had no Week-8 exercise test result or the Week 8 exercise test result was invalid. The rules for imputing values or ranks are shown in Table 27.

Table 27. Rules for imputing distance in 6-minute walk (P01:03)[42]

Event	Primary procedure for nonparametric analysis	Imputed values for parametric analysis
Death within 8 weeks; excluding transplantation and accidents	Lowest standardized rank of zero	0 m
Clinical decompensation within 8 weeks; excluding transplantation and accidents	Lowest standardized rank of zero	0 m
Transplantation	Lowest standardized rank of zero	0 m
Accident unrelated to disease or study	Last standardized rank carried forward	LOCF[43]
Adverse event (Survivor, Week 8)	Last standardized rank carried forward	LOCF
Lost to follow-up (Survivor, Week 8)	Last standardized rank carried forward	LOCF
Consent withdrawn (Survivor, Week 8)	Last standardized rank carried forward	LOCF

Other efficacy measures were defined and analyzed as follows. Statistical tests comparing these outcomes between treatment groups were added to the statistical methods after the final analysis plan was completed and after the database was unblinded.

Week 1 and Week 4 exercise capacity. The distances walked during exercise tests at 1 and 4 weeks were summarized and analyzed as secondary efficacy parameters. The methods used at Week 8 were applied to Weeks 1 and 4.

Borg Dyspnea score. The Borg Dyspnea Score, recorded at the time of exercise testing, was summarized descriptively, by treatment group, at Baseline, Week 1, Week 4, and Week 8. Treatment group differences in the change from Baseline were assessed using the Wilcoxon rank sum test.

Dyspnea-Fatigue Rating total score. The Dyspnea-Fatigue Rating Total Score was defined as the sum of scores for the three components: magnitude of task, magnitude of pace, and functional impairment. Treatment group differences in the change from baseline were assessed using the Wilcoxon rank sum test.

PPH Signs and Symptoms. The total PPH Signs and Symptoms Score was defined as the number of symptoms present out of those queried at a visit. In order to assess

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[42] Data from NDA 210272, study report for P01:03, table 9.7.

[43] Last observation carried forward.

overall change from baseline to follow-up in the signs and symptoms of PPH, a "-1" was assigned for each sign and symptom present at the follow-up assessment and absent at baseline, a "+1" was assigned for each sign and symptom absent at the follow-up assessment but present at baseline, and a "0" was assigned otherwise. The overall change score from baseline to follow-up was calculated by summing these values over all signs and symptoms. All 16 signs and symptoms had to be assessed at both baseline and follow-up in order for the change score to be calculated. Treatment group differences in the change from baseline were assessed using the Wilcoxon rank sum test.

Hemodynamic measurements. Each hemodynamic parameter was summarized descriptively, along with change from Baseline and Week 8. Treatment group differences in the change from baseline were assessed using the Wilcoxon rank sum test. The hemodynamic parameters summarized included the parameters recorded directly on the CRF as well as the derived parameters CI, PVR, PVRI , SVR, SVRI , TPR, SV, and SI.

Subgroup analyses. With the small number of patients included in this study, no subgroup analyses were planned.

Pharmacokinetics. The plasma UT-15 concentration profile would be examined for achievement of steady state. The relationship between UT-15 concentration immediately prior to dose escalation (pseudo-steady-state concentrations) and UT-15 dose was to be examined. Apparent plasma clearance was to be determined for each infusion rate from each steady state concentration. Pharmacokinetic linearity was to be investigated based on individual plots of steady state concentration versus UT-15 doses. Attempts were to be made to correlate selected hemodynamic parameters (PVRI, CI, PAPm, RAPm, SAPm SI, HR and S_vO_2) and changes in these parameters with steady-state plasma UT-15 concentrations

A.3.4 Results

A.3.4.1 Subject demographics & baseline characteristics

The demographic and clinical background data for the 93 subjects enrolled in P01:03 are summarized in Table 28 below. Overall, the demographics were relatively balanced. The placebo population had been diagnosed with primary pulmonary hypertension (PPH) for a relatively short period of time (0.9 years) compared with the group that received UT-15 (3.1 years). The majority of patients were receiving digoxin and warfarin at baseline and around 40% were on lasix (see table 14.1.9.1 for details).

Table 28. Demographics (P01:03)[44]

	Placebo N=9	UT-15 N=17
Age mean±sd Range	37±15 13-55	37.5±19 12-73
Gender Male (%)	7 (78)	14 (82)
Race Caucasian n (%) Black Hispanic, other	7 (78) 0 2 (22)	17 (100) 0 0
NYHA Class III n (%) Class IV	9 (100) 0	16 (94) 1 (6)
Blood pressure mean±sd	117±17 / 81±8	111±14 / 75±10

[44] *Data from NDA 21-272, volume 2.24, table 14.1.5.*

Table 29. Complications of PPH at baseline (P01:03)[45]

	Placebo N=9	UT-15 N=17		Placebo N=9	UT-15 N=17
Cough	2 (22%)	5 (29%)	Hypoxia	0 (0%)	2 (12%)
Cyanosis	2 (22%)	2 (12%)	'Low cardiac output'	2 (22%)	4 (24%)
Dizziness	5 (56%)	12 (77%)	Orthopnea	3 (33%)	3 (18%)
Dyspnea on exertion	9 (100%)	17 (100%)	Peripheral edema	4 (44%)	4 (23%)
Edema	4 (44%)	5 (29%)	Right heart failure	1 (11%)	2 (12%)
Fatigue	6 (67%)	13 (76%)			

A.3.4.2 Disposition of subjects

Subject selection. No information is available about subject selection in protocol P01:03.

Protocol violations & deviations. There were two types of relevant protocol violations. Six patients were able to walk further than allowed per protocol on the six-minute walk (4 UT-15, 2 placebo). Additionally, because the some of the first five patients treated (UT-15, 02001, 02004, 03001, Placebo, 02002, 02003) tolerated UT-15 less well than anticipated, the DSMB requested an unblinding of these individuals. This unblinding was discussed with the FDA.

The remainder of the reported protocol violations were minor (see Clinical study report, section 10.2 for details).

Concomitant therapies. A majority of the subjects in both groups were taking anticoagulants, vasodilators, diuretics and digoxin during the trial, with no relevant differences in their use between treatment groups (see NDA vol. 2.24, table 14.2.7.3 for details). About 35% of both groups received oxygen during the study.

A.3.4.3 Six-minute walk

While all of the patients attempted the six-minute walk at baseline, 2 patients in the UT-15 group and 1 in the placebo group did not complete it. Table 30 summarizes the distances walked, counting only those patients with available data. There was a favorable numerical trend in distance walked for the UT-15 group evident by week 4. In analyses not shown, none of the differences approached nominal statistical significance of p=0.05.

Table 30. Distances (m; mean±sd) on 6-minute walk, actual and LOCF (P01:03)

	Actual distance[46]				Distance by LOCF[47]			
	Distance		Change		Distance		Change	
	Placebo N=9	UT-15 N=13-17	Placebo N=9	UT-15 N=13-17	Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17
Baseline	384±82	373±103	—	—	384±82	373±103	—	—
Week 1	396±82	420±97	+12±46	+25±101	396±82	393±107	+12±46	+19±88
Week 4	395±120	414±91	+10±70	+41±90	395±120	401±93	+10.3±70	+27±95
Week 8	379±111	422±96	-6±83	+39±72	379±111	410±95	-5.8±83	+37±68

Similar results were seen when the last-observation carried forward analysis was performed, although the differences did not achieve nominal significance of <0.05.

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[45] *Data from NDA 21-272, volume 2.24, table 14.1.6.*

[46] *Data from NDA vol. 2.24, table 14.2.2.1*

[47] *Data from NDA vol. 2.24, table 14.2.2.1*

A.3.4.4 Hemodynamic changes

Invasive monitoring of several hemodynamic parameters and measurement of vital signs were performed at baseline, 1, 4, and 8 weeks. The results from selected relevant hemodynamic measures are shown below. Trends in favor of UT-15 on cardiac index (increased) and pulmonary vascular resistance (decreased) were reported for the UT-15 group.

Table 31. Hemodynamic assessments (P01:03)

		Value		Mean change		Median change	
		Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17
Heart rate[48], bpm	Baseline Week 8	85±21 82±21	77±10 84±17	—	—	-3±6	+7±16
Cardiac index[49]	Baseline Week 8	2.43±0.6 2.40±1.0	2.32±0.9 2.73±1.0	-0.03±0.6	+0.42±0.6	-0.20	+0.36
Mean right atrial pressure[50], mmHg	Baseline Week 8	10.0±4 8.2±3.7	9.4±6 8.1±5.6	-1.8±3.6	-0.5±3.7	-1.0	-1.0
Mean pulmonary artery pressure[51], mmHg	Baseline Week 8	64±18 62±18	59±16 59±13	-2±3.6	0±12	—	—
Pulmonary vascular resistance[52], mmHg/L/min	Baseline Week 8	15.7±8 15.9±8	14.3±7 11.4±4	+0.2±3	-3.1±4[53]	+0	-2.6
Systemic vascular resistance[54], mmHg/L/min	Baseline Week 8	22.4±7 22.3±7	21.2±8 18.6±6	0±5	-3.2±5	+1.0	-2.7

In results not shown, no trends towards differences between the treatment groups were seen for the respiratory rate or mixed venous saturation.

A.3.4.5 Signs and symptoms of heart failure

The sponsor measured changes in the signs and symptoms of heart failure using three separate instruments. These scales are explained in Appendix One, where the reader is referred for details.

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[48] *Data from NDA vol. 2.24, table 14.2.3.1.*

[49] *Data from NDA vol. 2.24, table 14.2.3.2.*

[50] *Data from NDA vol. 2.24, table 14.2.3.6.*

[51] *Data from NDA vol. 2.24, table 14.2.3.9.*

[52] *Data from NDA vol. 2.24, table 14.2.3.10.*

[53] *P-value =0.027 per sponsor's comparison of group distributions from Wilcoxon rank sum.*

[54] *Data from NDA vol. 2.24, table 14.2.3.18.*

Table 32. Signs and symptoms of heart failure (P01:03)

		Value		Mean change		Median change	
		Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17	Placebo N=9	UT-15 N=17
Borg dyspnea score[55]	Baseline	2.4±2	3.2±1.3				
	Week 8	3.4±2.5	3.1±1.8	+1.0±2.5	0±1.6	+1.0	0
Fatigue-dyspnea rating[56]	Baseline	6.3±1.9	6.3±1.5				
	Week 8	5.8±1.6	7.1±1.5	-0.25±1.4	+0.57±1.3	0	0
PPH signs and symptoms[57]	Baseline	8.2±3	7.9±2				
	Week 8	8.2±2	6.7±1.9	0±1.7	-1.1±1.5	0	-1

A.3.4.6 Safety

The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown in Table 17.

Table 33. Disposition of subjects (P01:03)[58]

Event	Placebo N=9	UT-15 N=17
Any adverse event	8 (89%)	17 (100%)
Serious adverse event	1 (11%)	4 (24%)
Discontinued with adverse event	0	2 (12%)
Deaths	0	0

A.3.4.6.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.3.4.6.2 Comments on specific safety parameters

Deaths. There were no deaths during the trial.

Serious adverse events. Table 34 below summarizes the SAEs reported in the trial.

Table 34. Serious adverse events (P01:03)[59]

	Subject	Event	Dose	Day of onset
Placebo	02013	Vasovagal reaction	2.5	2
UT-15	02001	Systemic hypotension[60]	5.0	2
	02005	Exacerbation of pulmonary hypertension	2.5	53
	02009	Bradycardia and hypotension, vasovagal[61]	0	2
		Syncope	5.0	28
		Pleural effusion	5.0	41
	03006	Ruptured ovarian cyst	15.0	26

[55] *Data from NDA vol. 2.24, table 14.2.4.*

[56] *Data from NDA vol. 2.24, table 14.2.5.*

[57] *Data from NDA vol. 2.24, table 14.2.4.*

[58] *Data from NDA 21-272, vol. 2.24, table 12.2.1.*

[59] *Data from NDA vol. 2.24, table 12.3.1.2.*

[60] *Occurred during a decrease in UT-15 infusion.*

[61] *Occurred during baseline catheterization, before study drug was commenced.*

Adverse events. Table 35 below summarizes the reported adverse events in the trial, emphasizing the prominent occurrence of infusion site pain in the patients who received UT-15.

Table 35. Subjects with adverse events (P01:03).[62]

	Placebo N=9	UT-15 N=17		Placebo N=9	UT-15 N=17
Infusion site reaction	2 (22%)	16 (94%)	Infusion site bleed/bruise	2 (22%)	5 (29%)
Infusion site pain	2 (22%)	15 (88%)	Abdominal pain	1 (11%)	4 (24%)
Headache	4 (44%)	14 (82%)	Anorexia	0 (0%)	4 (24%)
Diarrhea	1 (11%)	10 (59%)	Hypotension	0 (0%)	4 (24%)
Nausea	1 (11%)	10 (59%)	Vomiting	0 (0%)	4 (24%)
Vasodilatation	1 (11%)	8 (47%)	Insomnia	3 (33%)	1 (6%)
Jaw pain	1 (11%)	7 (41%)	Syncope	3 (33%)	1 (6%)
Pain	0 (0%)	7 (41%)			

Discontinuations. There were two discontinuations in the UT-15 group. Patient 02001 was discontinued on day 3 for chest pressure and hypotension. Patient 03007 discontinued on day 40 due to site pain.

Effects on vital signs. During initiation of UT-15 and at every dose adjustment the sponsor collected blood pressure data for 8 hours (NDA vol. 2.24, table 14.3.7). At every increase in dose there was a small decrease in systolic and diastolic BP within the first 8 hours of approximately 4 to 8 mmHg in both the UT-15 and placebo groups. There were no consistent changes in the pulse rate.

Effects on ECG. Changes in QT interval were assessed at baseline, 8 weeks and at last follow-up. After 8 weeks on UT-15, the QT interval decreased by a mean of 9.6 msecs, compared with an increase of 10 msecs for the patients who received placebo. At last follow-up, the mean QT decreased 0.3 msecs in UT-15 and 4 msecs in placebo (NDA vol. 2.24, table 14.3.6). No significant differences in mean changes in the QRS axis or PR interval were measured.

A.3.5 Summary

A.3.5.1 Efficacy summary

Study PO1:03 enrolled small numbers of patients with pulmonary hypertension in a randomized, double-blind fashion to receive either UT-15 or placebo. Overall, while not powered to detect significant clinical effect, the trial did find several trends in support of a clinical and a hemodynamic effect of UT-15 in patients with pulmonary hypertension.

Hemodynamic effects

- A decrease in pulmonary vascular resistance and an increase in cardiac index of 15-20% between baseline and week 8 was observed in patients who underwent invasive monitoring.
- An increase in the mean heart rate was observed of approximately 10 beats per minute between baseline and week 8 (placebo-subtracted).

Clinical effects

- There was a favorable numerical trend in mean distance walked in six minutes for the UT-15 group evident by week 4, amounting to 45 meters (placebo-subtracted).

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[62] *Data from NDA vol. 2.24, table 12.2.2.*

No difference in distance walked was evident at the end of week one. This trend was evident in the population with available data as well as the LOCF analysis.

- The sponsor used three scales assessing changes in the signs and symptoms of heart failure. For each of these (Borg Dyspnea Scale, Dyspnea-Fatigue Index, and Signs and Symptoms of PPH) the trends were in favor of the UT-15 group. The numerical changes did not achieve nominal statistical significance in any of the three areas.

A.3.5.2 Safety summary

See the Integrated Review of Safety. The current trial enrolled 26 patients, limiting the available safety exposure. Of note:

- Pain at the site of infusion was nearly universal in the group receiving UT-15, but required drug discontinuation in only one of the 16 patients in the UT-15 group.
- A number of other adverse events were substantially more common in the UT-15 group than in the placebo group: headache, nausea, diarrhea, and jaw pain.
- Over the course of 8 hours, no consistent effects on heart rate, blood pressure or on any ECG parameter (including QT) were seen in the trial for UT-15, when compared with placebo.

A.3.5.3 Reviewer's conclusions

Study P01:03 examined the effect of UT-15 in a population with moderately-advanced heart failure related to primary pulmonary hypertension (PPH). It was a double-blind study, and the sponsor made reasonable efforts to blind the assessors to the treatment. Almost all of the patients taking UT-15 experienced site pain, limiting the possibility for true blinding, an apparently unavoidable consequence of the drug's use. For the primary endpoint (6-minute walk distance), the use of UT-15 was associated with an increase in the mean distance walked of around 45 meters. In addition, this study provided data that support, but do not demonstrate, an effect of UT-15 on the hemodynamics and symptoms of heart failure related to pulmonary hypertension.

This trial enrolled few patients and was necessarily limited in its power to detect significant effects of UT-15, but was a blinded comparison with placebo. It also enrolled only patients with Primary Pulmonary Hypertension (PPH), in distinction to the other blinded clinical trials that enrolled patients with pulmonary hypertension due to both primary and secondary causes. Data from the trial support, but do not demonstrate, an effect on clinically-relevant measures of heart failure due to pulmonary hypertension (6-minute walk distance, signs and symptoms of CHF) as well as changes in hemodynamics consistent with a salutary effect of UT-15. The primary finding from the safety was the nearly universal occurrence of site pain following the use of UT-15.

A.4 Studies P01:04, P01:05: An international multicenter, double-blind, randomized, parallel placebo-controlled comparison of the safety and efficacy of chronic subcutaneous UT-15 plus conventional therapy to conventional therapy in patients with pulmonary hypertension: a 12-week study.

A.4.1 Sites and investigators

The two studies were run concurrently. There was overlap in study investigators/sites for the two protocols. Many investigators that enrolled subjects in study P01:04 also enrolled subjects in Study P01:05. Those who enrolled subjects into study P01:04 were all North American Sites (includes Canada and Mexico). There were additional 16 sites all outside of North America for which subjects were enrolled into study P01:05. The individual investigators and sites as well as the number enrolled in P01:04 and P01:05 are shown in Table 36.

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Table 36. Sites and investigators (P01:04-05)

Site	Investigator	Location	N	
			:04	:05
01	Sean Gaine MD	University of Maryland,Baltimore, MD	1	0
02	Robyn Barst, MD	Columbia Presbyterian ,New York, NY	22	1
03	Stuart Rich, MD	Rush Presbyterian-St. Lukes Med Center, Chicago, IL	18	3
04	Ronald Oudiz, MD	Harbor-UCLA Medical Center, Torrance, CA	19	5
05	Michael McGoon, MD	Mayo Clinic, Rochester, MN	12	2
06	David Badesch	Univ of Colorado Health Science Center, Denver, CO	3	0
07	Ivan Robbins	Vanderbilt University Medical Center, Nashville, TN	10	3
08	Victor Taspon	Duke University Medical Center, Durham, NC	10	1
09	Adaani Frost. MD	Baylor Coll of Medicine and Methodist Hosp, Houston, TX	19	3
10	Robert Bourge, MD	University of Alabama, Birmingham, AL	27	8
11	Ramona, Doyle, MD	Stanford University Medical Center, Stanford, CA	3	1
12	Theresa DeMarco, MD	University of California Moffitt Hosp, San Francisco, CA	7	3
13	Joel Wirth, MD	Maine Medical Center, Portland, ME	2	0
14	Richard Channick, MD	Univ of Calif at San Diego Medical Center, San Diego, CA	13	1
15	Gregory Elliott, MD	Latter Day Saints Hospital, Salt Lake City, UT	8	1
16	Srinivas Murali, MD	University of Pittsburgh Medical Center, Pittsburgh, PA	10	2
17	David Langelben, MD	Jewish General Hospital, Montreal Quebec, Canada	7	2
18	David Ostrow, MD	Vancouver Gen Hosp, Vancouver, BC, Canada	1	1
19	Robert Schilz. MD	The Cleveland Clinic, Cleveland, OH	8	4
20	Julio Sandoval	Instituto Nacional de Cardiologia, Mexico City, Mexico	10	5
21	Nicholas Hill, MD	Rhode Island Hospital, Providence, RI	4	2
22	Ben deBoisblanc, MD	Louisiana State Univ Medical Center, New Orleans, LA	7	5
23	Dunbar Ivy, MD	Children's Hospital, Denver, CO	3	0
24	Shelley Shapiro	University of Southern California, Los Angeles, CA	0	6
50	Anne Keogh, MD	St Vincent's Hospital, Sidney NSW, Australia	0	24
51	Meinhard Knuessl,MD	Allgemeines Krankenhaus, Wein, Austria	0	7
52	Marion Delcroix, MD	University Hospital, Brussels, Belgium	0	9
53	Robert Naeije, MD	Free University of Brussels, Brussels, Belgium	0	22
54	Gerald Simmonneau, MD	Hospital Antioine Beclere, Clamart, France	0	28
55	Marius Hoeper, MD	Medical School of Hanover, Hanover. Germany	0	5
56	Neville Berkman, MD	Hadassah Ein Kerem Medical Center, Jerusalem, Israel	0	2
57	Isaschar Ben-Dov, MD	The Chaim Sheba Medical Center, Tel-Hashomer, Israel	0	8
58	Mordechai Kramer, MD	Rabin Medical Center, Petach Tikvah, Israel	0	10
59	Nazzareno Gaile, MD	University of Bologna, Bologna, Italy	0	15
60	Adam Tobicki, MD	National Tuberculosis Research Center, Warsaw, Poland	0	15
61	Miguel Gomez-Sanchez, MD	Hospital 12 de Octubre, Madrid, Spain	0	12
62	Carol Black, MD	Royal Free Hospital, London, UK	0	0
64	Tim Higgenbottam, MD	Sheffield University, Sheffield, UK	0	5
65	Andrew Peacock, MD	West Glasgow Hospitals, Glasgow, UK	0	15
66	Paul Corris, MD	Freeman Hospital, Newcastle Upon Tyne, UK	0	10

A.4.2 Background

Table 37. Dates (P01:04-05)

	P01:04	P01:05		P01:04	P01:05
Initial protocol	5/7/98	5/798	Last subject complete	12/2/99	2/3/00
Amendment 1	9/5/98	9/5/98	Original Analysis Plan	11/9/99	
Amendment 2	11/9/98	11/9/98	Analysis Plan Submitted	3/6/00	
Amendment 3	12/22/98	12/22/98	Analysis Plan Amended	3/23/00	
First subjects randomized	11/12/98	12/15/98	Unblinded	3/24/00	

The sponsor proposed to perform protocols P01:04 and P01:05 concurrently. The description in this review reflects the incorporation of all protocol amendments. As seen from the pivotal dates of the study, all amendments were dated prior to the completion of the initial subject's 12-week assessment. . The specifics of each amendment, therefore, will not be summarized in this review.

A.4.3 Study design

The timing of the procedures is shown in Table 38.

Table 38. Procedures (P01:04-05)

Week	Screen	Baseline		Treatment			
				1[63]	6[64]	12[65]	
Day		1[66]	2	9	44	87	88
Informed consent, medical history, physical exam	X						
Inclusion/exclusion criteria	X		X[67]				
Global Quality of Life, PHT Signs and Symptoms		X		X	X	X	
12-Lead ECG/chemistry/hematology		X				X	
Exercise capacity		X[68]	X[69]	X	X	X	
Swan-Ganz catheterization/hemodynamics			X				X
Randomization			X[70]				
Monitor: ECG/vital signs/TCO_2			X				
Pharmacokinetic samples[71]			X	X	X	X	
Infusion of study drug/evaluation of infusion site		X	X	X	X	X	X
Concomitant medication/AE reports	X	X	X	X	X	X	X

A.4.3.1 Number of subjects/ randomization

Four hundred seventy [470] with pulmonary hypertension with diverse etiologies were randomized.

A.4.3.2 Inclusion/ exclusion criteria

Inclusion criteria. Subjects were eligible to enroll if they were mentally and physically competent to administer study drug by the subcutaneous route. They could be of either gender between the ages of 8-75 years. These subjects were to have a diagnosis of pre-capillary pulmonary hypertension that could be a consequence of any of the following:

- Primary disease (primary pulmonary hypertension).
- Pulmonary hypertension secondary to connective tissue disease e.g. systemic sclerosis (scleroderma), limited scleroderma, mixed connective tissue disease, systemic lupus erythematosus, or overlap syndrome

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[63] *±2 days*

[64] *±5 days*

[65] *±7 days*

[66] *May be conducted up to one week prior to enrollment.*

[67] *Includes hemodynamic criteria.*

[68] *Within 6 weeks of enrollment.*

[69] *Before catheterization.*

[70] *Within 48 hours of hemodynamic eligibility.*

[71] *Blood samples to be drawn between 9am- noon.*

- Pulmonary hypertension with congenital systemic left-right shunts (repaired or unrepaired).

Catheterization results at baseline had to demonstrate an increase in pulmonary pressures with normal left-sided function as defined by the following measurements:

- PAPm $\geq$ 25 mm Hg (at rest)
- PCWP (or left ventricular end diastolic pressure) $\leq$ 15 mm Hg
- PVR > 3 mm Hg

An echocardiogram performed within 3 months of enrollment had to demonstrate evidence of right sided dysfunction (dilatation or hypertrophy), with no evidence of left sided dysfunction and a the absence of mitral valve stenosis.

Other causes of CHF were to be excluded prior to enrollment. A chest X-ray was to exclude primary pulmonary alveolar disease, or severe interstitial disease. Thromboembolic disease was to be excluded by a ventilation/perfusion scan. If the scan was read as indeterminate or suggested a high probability of embolic disease then thromboembolic disease was excluded by either a pulmonary angiogram or spiral/helical/ultrafast computed tomography.

Subjects were to be optimally treated for pulmonary hypertension with stable medication for at least one month prior to baseline measurements. For those treated with corticosteroids stable doses of $\leq$ 20 mg/day of prednisone (or equivalent) for at least one month were required prior to enrollment. For those who such treatment was not contraindicated, anticoagulation with either warfarin (to an INR of between 1.5 and 2.5) or heparin to produce an aPTT between 1.3-1.5 times control was recommended. Higher levels of anticoagulation would be acceptable if clinically warranted. Despite the optimization of treatment, these subjects had symptom limited CHF (NYHA > II).

Comment. The population enrolled into this study differed from the population that was enrolled in the studies that led to the approval of Flolan. Only subjects with primary pulmonary hypertension were enrolled in the studies pivotal for Flolan approval. In the studies for UT-15 subjects whose pulmonary hypertension was secondary to either collagen vascular disease or left to right cardiac flow shunts also were recruited for enrollment.

In addition, the population with primary pulmonary hypertension in this study may contain the same or a different proportion of subjects whose pulmonary hypertension is a consequence of anorexogenic drug treatment. In contrast to other forms of pulmonary hypertension, those previously taking anorexogenic drugs have the stimulus of disease removed, i.e. the anorexogenic drug has been stopped. Those with their primary pulmonary hypertension as well as whose pulmonary hypertension is secondary to collagen vascular disease have ongoing disease processes.]

Exclusion criteria. Subjects were excluded if they were pregnant or nursing (women); if they had any new therapy or experimental therapy added or withdrawn within the last month; or if they were treated within the last month with approved or experimental prostaglandin analogues by any route of administration. Anticoagulants could be discontinued up to one month prior to enrollment.

Subjects were excluded if they had evidence of parenchymal lung disease based on the results of pulmonary function test that demonstrated:

- Total lung capacity $\leq$70% of predicted.
- If [redacted] was between [redacted] then a high resolution CT which demonstrated diffuse interstitial fibrosis or alveolitis.

- FEV1/FVC ≤50%
- A Diffusion Lung Capacity (D_{LCO}) <50%

Subjects were also excluded if they had pulmonary hypertension associated with: HIV infection, portal hypertension, uncontrolled sleep apnea, sickle cell disease, schistosomiasis, recent (within 3 months) use of prescription appetite suppressants, or left sided heart disease (aortic or mitral valve disease); constrictive pericardial disease, congestive or restrictive cardiomyopathy, uncontrolled blood pressure (SBP >160 or DBP >100 mm Hg) or evidence of left sided disease (a PCWP >15 mm Hg; left sided EF <40%; left ventricular shortening fraction <22% by echocardiography), or cardiac ischemia.

Subjects who were incapable of exercise because of a musculoskeletal disorder or who required a machine that precluded free ambulation were excluded from the study.

Subjects were excluded if the baseline 6-minute exercise distance was outside the boundaries of 50-450 meters.

A.4.3.3 Formulation

A formulation at a concentration of 1.0 mg/ml of UT-15 was utilized for active drug infusion rates of ≤22.5 ng/kg/min.

A formulation at a concentration of 2.5 mg/ml of UT-15 was utilized for active drug at a doses of >22.5 ng/kg/min

A corresponding reference vehicle[72] was used:

Table 39. Formulations (P01:04-05)

	Vehicle	1.0 mg/ml	2.5 mg/ml
UT-15	0.0	1.0	2.5
Sodium citrate, dihydrate			
Metacresol			
Sodium chloride			
Citric acid			
Sodium Hydroxide			
Lot (P01:04)			
Lot (P01:05)			

Comment. There appears to be an asymmetry in the vehicle formulation. There are two concentrations for active drug and only one for vehicle. Apparently each subject was allocated two bottles with different concentrations of drug/vehicle so that the appropriate dose could be formulated for infusion. For the UT-15 group these two concentrations differed, for the vehicle subjects the concentration was the same. Thus, symmetry was maintained and the study adequately blinded.

A.4.3.4 Dosage/ administration

Criteria for infusion pump. The following are the prespecified criteria for the infusion pump:

- Portable: small size and lightweight.

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[72] *This review will refer to the placebo as a vehicle.*

- Infusion rate increments: sufficient to adjust the dose by [redacted] approximately [redacted] mL/hr.
- Alarms: occlusion, end of infusion, low battery, clogged or obstructed infusion set, motor malfunction or programming error.
- Accuracy of delivery: ±6% or better, with equivalent delivery units.
- Type of action; positive pressure.
- Reservoir composition; [redacted]

Specific pumps listed by the sponsor include: [redacted]

Administration. The formulation was to be administered subcutaneously. The site of infusion was almost invariably abdominal. The catheter was to be changed at least every third day and a new catheter inserted in a different site. Initially, while in hospital, the catheter was changed daily.

A.4.3.5 Randomization and blinding

Randomization. Subjects were randomized in a 1: 1 ratio to vehicle or UT-15. The randomization process was handled at a central location. Randomization was stratified based on three parameters.

- The etiology of disease (primary pulmonary hypertension versus other causes of pulmonary hypertension).
- Six-minute exercise distance (low =50-150 meters, versus high 151-450 m).
- Subjects with pre-capillary hypertension due non-primary causes were also stratified by the use of vasodilator use at baseline.

Within each stratum the stratification was for block sizes of 2.

The initial randomization was intended to include stratification based on study i.e. P01:04 or P01:05 . The initial randomization, however, was inadvertently performed across both studies. On 16 June 99, 238 subjects were already randomized without stratification based on the particular study, the randomization process was amended to include study number as a strata.

Blinding. Amber ampoules were used so blinding of cream colored in the ampoule would not indicate the specific treatment.

The study was double blinded (triple blinded? i.e. sponsor). In addition, during the 12-week exercise portion of the study, for each study site, an independent exercise administrator other than the physician who cared for the subject, administered the exercise test. This administrator was not otherwise involved in the subject's care. The results of the exercise test were not to be made available to other study personnel until both studies were completed at all centers and the database secured.

The blinding, however was not perfect.

- It is clear that the subject was not blinded to their exercise results and consequently, the information may have gotten to the investigator (there is really no way to get around this).
- Subjects were unblinded at the end of the 12-week exercise test to facilitate crossover to open-label treatment. It is unclear to what extent the subjects data was locked in prior to the unblinding of each individual.
- Subjects could also be unblinded if there was a safety issue and that unblinding was pivotal to the subject's care.

- The very nature of the infusion may unblind the treatment.

A.4.3.6 Oversight

Based on amendment #2, a steering committee that was to consist of up to six clinicians who were investigators in the clinical trial as well as one sponsor's representative and one statistician. The steering committee was to guide the study. This committee was to meet at least once when 50% of those enrolled completed the study, to perform an interim analysis for efficacy on the pooled data. The analysis was to be unblinded as to treatment. Amendment #3, however, modified the protocol so that no interim efficacy analysis was performed.

There was a data safety monitoring board (DSMB) that consisted of one statistician as well as up to two clinicians not involved the study. Three interim safety looks were performed, after 20%, after 40% and after 60% of the subjects completed the 12-week period. The committee received and reviewed masked tabulations of serious adverse events and deaths from pooled treatment groups. P-values were supplied and screened for lower rates in the vehicle group. If the p-value favors the vehicle group ($p<0.25$) and if requested, the DSMB would be supplied masked tabulations by treatment group. Unmasked data could be supplied to the DSMB. Under certain circumstances, the DSMB could request efficacy data. Should the DSMB request the efficacy data, a p-value of <0.0001 would be required to terminate the study. (It seems that some one had the ability to construct this data and therefore, had the ability to unblind the study).

A.4.3.7 Duration/ adjustment of therapy

Study drug was initiated after exercise and hemodynamic measurements on Day 2 of the protocol (see table 1.7 for a list and timing of procedures). The initial dose of UT-15 or corresponding vehicle was 1.25 ng/kg/min. This dose was the maximum allowed at the end of week one. If the infusion was not tolerated, the dose could be decreased to a tolerated infusion rate. The initial dosing was to take place in the clinic. Dosing adjustments should, but did not necessarily have to be performed in the clinic.

At the end of week 1 the dose could be increased at rates no greater than 1.25 ng/kg/min till week 4. At week 4, the dose could be increased by rates of 2.5 ng/kg/min. The maximum doses at each week are shown in Table 40.

Table 40. Maximum doses (ng/kg/min) allowed during various weeks of the study (P01:04-05)

Week	1	2	3	4	5	6	7	8	9	10	11	12
Days	2-9	10-16	17-23	24-30	31-37	38-44	45-51	52-58	59-65	66-72	73-79	80-88
Dose	1.25	2.5	3.75	5.0	7.5	10	12.5	15	17.5	20	22.5	22.5

Dose increases were warranted if:

- The subject's symptoms of pulmonary hypertension did not improve, or
- The subject's clinical condition deteriorated and the subject became increasingly symptomatic.

Dose reduction could be entertained based on the judgement of the investigator if there was evidence of:

- Excessive pharmacological action as judged by vital signs.
- Onset of adverse events such as headache, nausea, emesis, restlessness and anxiety.
- Onset of significant pain, or worsening of pain at the infusion site.

Large dose reductions or abrupt cessation of treatment was to be avoided.

Although catheterization was allowed for subject care, dosing modification was to be based on symptoms of pulmonary hypertension and not the outcome of catheterization.

A.4.3.8 Efficacy endpoints

Primary end point. The primary end point is the effect of UT-15 on exercise distance at week 12 of treatment. Each the individual studies as well as the pooled studies were specified for analysis. The planned analysis was an intent to treat, non-parametric covariance analysis (specifically, the sponsor will use a Cochran-Mantel-Haenszel mean score statistic). Covariates in this model were to include center, baseline exercise distance, vasodilator use at baseline, etiology of pulmonary hypertension (i.e. primary versus all other causes) and steroid therapies that were added during the 12-week observation period. For all inferential analyses, the level of significance will set to 0.05 with two sided-alternative hypothesis.

Subjects were removed from study without follow-up for the following reasons:

- Transplantation.
- Rescue with chronic >5 days intravenous Flolan.
- Rescue with chronic >5 days intravenous inotropic therapy.
- AE judged sufficiently serious to warrant discontinuation from the study.

When subjects did not complete the full 12-weeks of treatment for the following reason, death, clinical deterioration of sufficient intensity to be prematurely discontinued from the study, transplantation, accident unrelated to disease adverse event, lost to follow up or withdrawal of consent, values were imputed. The rules for imputation are shown in Table 41. Subjects who discontinued from the study were to be followed for 12-weeks. A 6-minute walk and symptom assessment was to be performed at 12-weeks. The data, however, from the last test while on study drug was to be used in any analysis. For the secondary end points (see below) subjects who prematurely discontinue were to be censored.

Table 41. Rules for imputation among those who had no 12-week measurements (P01:04-05)

Event	Primary procedure for non-parametric analyses	Imputation for parametric analyses	Secondary end-points
Death within 12 weeks Clinical decompensation[73] Transplantation	Lowest standardized rank	0-Meters	Censored
Accident (limits ambulation)	Last rank carried forward	LOCF[74]	Censored
Adverse event (survived)	Last rank carried forward	LOCF	Censored
Lost to follow-up (survived)	Last rank carried forward	LOCF	Censored
Consent withdrawn (survived)	Last rank carried forward	LOCF	Censored
Discontinued prior to week-1 measurement	Not stated	Not stated	Censored

Subjects were not to have medications added during the study unless it was a medical necessity. Since these medications could effect exercise distance, the following analyses were to be included.

- Subjects who began treatment with new pulmonary hypertension medications during the study were to be considered treatment failures. An alternative method was to rank subjects based on vasodilator use changes.

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[73] *Received rescue therapy.*

[74] *Last observation carried forward.*

- Steroid or vasodilator treatment changes were not to be taken into account.
- Steroid therapy or therapies to treat pulmonary hypertension that were added during the 12-week observation period would be treated as a covariate.
- Steroid therapy or therapies to treat pulmonary hypertension were added during the 12-week period as a covariate.

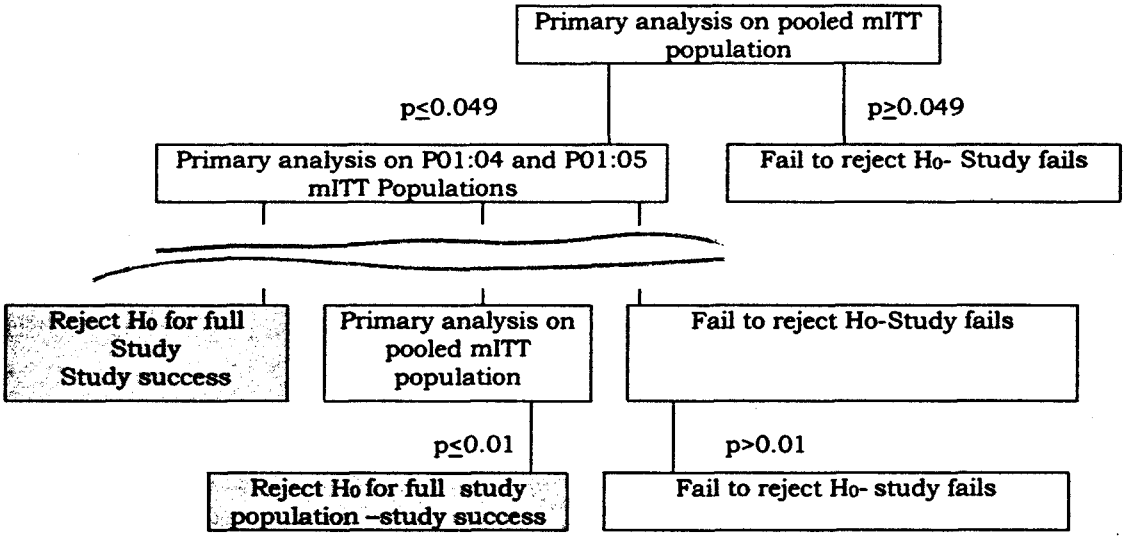
A parametric analysis of covariance was to be performed as a secondary analysis.

A secondary analysis of the primary endpoint is an ANCOVA, with the 6-minute distance walked at Week 12 to be imputed as a function of distance walked at baseline. Other covariates were to include center, etiology of pulmonary hypertension, vasodilator use and steroid therapy (or therapies) to treat pulmonary hypertension that were added during the 12-week observation period.

Additional analyses were to be performed where the last observation carried forward for each subject whether they deteriorated or were discontinued due to adverse events.

Rules by which the study was to be considered a success. The sponsor proposed to define the study as a success based on a hierarchical analysis. In essence the study would be considered a success either if both studies were successful ($p < 0.049$) or either study demonstrated a p value of <0.049 and the overall pooled study showed a p-value of <0.01. The flow sheet for the sponsor's analysis is shown in Figure 10[75].

Figure 10. Flow for demonstrating success (P01:04-05)



Secondary end points. Secondary reinforcing measures of efficacy are as follows:

- Signs and symptoms (see Table 42) as measured by (1) changes in frequency/severity and (2) time to a subject's discontinuation from study due to clinical deterioration, transplant secondary to deterioration (or lack of improvement) or death.

[75] *Derived from figure 8.1 p 6365-3200*

Table 42. Specific signs and symptoms (P01:04-05)[76]

Signs	Symptoms
Weight	Ascites
Blood pressure and pulse rate	Chest pain*
Loud P 2 sound*	Dizziness*
Right ventricular S3 sound* (third heart sound)	Dyspnea at rest*
Right ventricular S4 sound* (fourth heart sount)	Dyspnea on exertion*
Right ventricular heave*	Paroxysmal Nocturnal dyspnea*
Murmur of tricuspid insufficiency* (diastolic murmur)	Fatigue*
Murmur of pulmonic insufficiency * (systolic mumur)	Nausea/vomiting
Hepatomegaly*	Orthopnea*
Jugular venous distention at 45 degrees*	Palpitations*
Edema*	Syncope*
	Thirst

The above signs were rated as a change from baseline. If the sign or symptoms worsens (went from absent to present) a "–1" is assigned, for no change a "0" is assigned and for an improvement (i.e. present to absent) a "+ 1" is assigned. The overall score was assigned based on total # of changes in signs and symptoms, provided at least eight of the 16 signs and symptoms are assessed at both baseline and follow –up. The difference between treatment groups for the individual components is assessed using either a chi-square test (for dichotomous data) or Wilcoxon Rank Sum Test Statistic (for ordinal or continuous variable).

- The "Dyspnea Fatigue Index" evaluated signs and symptoms of pulmonary vascular disease. This index contains three criteria, each with potential values of 0-4 (Table 43). The change of the aggregate index between week 12 and baseline was the key analysis for this parameter. The difference between treatment groups is to be analyzed with a Wilcoxon Rank Sum Statistic. The index as completed by the treating physician (not exercise administrator) in conjunction with the subject's report of symptoms.

Table 43. Dyspnea Fatigue Index criteria (P01:04-05)

	Score	Criteria
Magnitude of task	4	Extraordinary- Symptomatic only with extraordinary activity (e.g. running, carrying heavy loads on level ground)
	3	Major- Becomes symptomatic only with major activities(e.g. climbing more than 3 flights of stairs, carrying a moderate or heavy load on level ground)
	2	Moderate- Becomes symptomatic with moderate or average tasks (e.g. walking up a gradual hill, climbing up less than three flights of stairs, carrying a light load on level ground
	1	Light- Becomes symptomatic with light activities (e.g. walking on level ground)
	0	None- Symptomatic at rest or lying down
Magnitude of pace	4	Extraordinary- All tasks carried out at a normal pace
	3	Major- Major tasks (see above) are performed at a reduced rate
	2	Moderate- Moderate tasks performed at a reduced rate
	1	Light- Light tasks are performed at a reduced rate
	0	None- Symptomatic at rest
Functional impairment	4	None- Can carry out usual activities and occupation
	3	Slight-Distinct impairment in at least one activity . No activities re completely abandoned
	2	Moderate-Changed jobs or abandoned at least one activity
	1	Severe-Unable to work or has given up most of usual activities
	0	Very Severe- unable to work and has given up most or all usual activities

[76] *These were listed in Appendix C of the study report. The CRF, however only collected 16 symptoms noted by an *. Dyspnea at rest, dyspnea on exertion, and paroxysmal nocturnal dyspnea were all assessed as 'dyspnea'.*

- Cardiopulmonary hemodynamic measurements consisted of: heart rate, SAPs, SAPd, SAPm, PAPs, PAPd, PAPm, RAPm, PCWPm, and CO.

Subjects will be catheterized for invasive hemodynamics (Swan Ganz). The time of placement of the catheter relative to measurements is not stated and not standardized. Serial measurements of hemodynamics for cardiac output and PAPm required that the three consecutive measurements must differ by less than or equal to 20% with individual measurements taken at least 10 minutes apart. The last value that defined the stable measurement was to be the value recorded on the CRF. For most subjects cardiac output was to be defined either by the thermal dilution or the Fick method. For those subjects with congenital shunts, however the Fick method was to be used. The differences between treatment groups will be analyzed by ANCOVA (i.e. parametric linear model)

- Mixed venous saturation, FiO_2 and systemic oxygen saturation (by pulse oximetry).
- Global Quality of Life Measurements at baseline and weeks 1, 6 and 12

The specifics of the "Living With Heart Failure" questionnaire[77] are shown below: The questionnaire was validated in 83 subjects with left ventricular dysfunction[78]. The metric has not been validated in subjects with pulmonary hypertension.

Did your heart failure prevent you from living as you wanted during the last month by

1. *Causing swelling in your ankles, legs etc.?*
2. *Making you sit or lie down to rest during the day?*
3 *Making your walking about or climbing stairs difficult?*
4 *Making your working around the house or yard difficult?*
5 *Making your going places away from home difficult?*
6 *Making your sleeping well at night difficult?*
7 *Making your sleeping to or doing things with your friends or family difficult?*
8 *Making your working to earn a living difficult?*
9 *Making your recreational pastimes, sports or hobbies difficult?*
10 *Making you sexual activities more difficult?*
11 *Making you eat less of the foods you like?*
12 *Making you short of breath?*
13 *Making you tired, fatigued, or low on energy?*

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[77] *Copyright University of Minnesota 1986.*

[78] *Rector, TS; Kubo, SH and Cohn, JN; " Content, Reliability and Validity of a New Measure, The Minnesota Living with Heart Failure Questionnaire; Heart Failure, 1987; 198-209.*

14 Making you stay in a hospital?
15 Costing you money for medical care?

16 Giving you side effects from medications?

17 Making you feel you are a burden to your family or friends?

18 Making you feel a loss of self-control in your life?

19 Making you worry?

20 Making it difficult for you to concentrate or remember things?

21 Making you feel depressed?

The QOL questionnaire, per publication, consists of four dimensions:

- A global score (all questions),
- A physical dimension score (questions # 2-7, 12 and 13),
- Emotional dimension (questions 17-21), and
- Economic dimension.

- ***Borg Scale***. The exercise administrator, in conjunction with the exercise test, queried the subject as to the degree of shortness of breath (the Borg Scale) associated with the 6-minute walk. The subject was to be given the following set of instructions:

" I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg Scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you should chose from 0.5 to 2; if you were somewhat short of breath you should select 3 and if the breathing was very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represent the greatest shortness of breath that you have ever experienced in your life, and if you feel more short of breath than you have ever been in your life choose a number greater than 10 that represents how short of breath you feel. If one of the numbers does not exactly represent how short of breath you are, then you can choose a fraction between."

There was no prespecified method to incorporate the Borg Scale in assessing clinical improvement.

A.4.3.9 Pharmacokinetics

A population approach (NONMEM) was to be utilized in the pooled study data. The following covariates were employed: age; gender; ethnic background, use of concomitant calcium channel blockers, anticoagulants and diuretics, renal function (creatinine clearance).

No attempt was made to ascertain whether and to what extent metabolites are formed. There is some uncertainty if any metabolites are accumulated and whether they are active biologically (either as agonists or antagonists).

A.4.3.10 Statistical considerations

Sample size calculations. Based on the assumption of a 55 meter difference between UT-15 and Vehicle and a standard deviation of 110 meters, assuming an alpha of 0.05; a total of 105 subjects/group would have a 95% power to be successful.

Stratification. Subjects were to be randomized centrally and stratified based on type of pulmonary hypertension (primary versus secondary), exercise performance at baseline (low $\leq$150 meters or high >150 meters) and for those with secondary pulmonary hypertension, vasodilator use at baseline (yes versus no). There were therefore a total of 6 potential stratification groups. These are listed in Table 44. After the first 238 subjects were enrolled, stratification also included study.

Table 44. Stratification (P01:04-05)

Etiology	Baseline exercise	Vasodilator use
Primary	High	
Primary	Low	
Secondary	High	Yes
Secondary	High	No
Secondary	Low	Yes
Secondary	Low	No

Interim looks. There were no interim looks for efficacy. The proposed interim look during the second protocol amendment was subsequently dropped.

A.4.4 Results

A.4.4.1 Subject demographics & baseline characteristics

Specific baseline characteristics are shown below: