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-m²)	19±2	18±3
SVRI (mmHg/L-min-m²)	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-m²)	-22±5%	-14±7%	-20±9%
SVRI (mmHg/L-min-m²)	-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)

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