Table 45. Baseline characteristics (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh N=109	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Age, years	Mean ±SE	43.2 ±1.4	45.3 ±1.4	45.5 ±1.3	43.9 ±1.3	44.4 ±0.9	44.6 ±1.0
Gender	F/M %F	95/16 [86%]	96/17 [85%]	90/35 [72%]	101/19 [84%]	185/51 [78%]	197/36 [85%]
Caucasian		86	91	112	107	198	198
Black		5	8	3	5	8	13
Asian		6	4	2	1	8	5
Hispanic		13	8	6	6	19	14
Other		1	2	2	1	3	3
Primary pulmonary hypertension		59	61	77	73	136	134
Collagen Vascular		30	25	19	16	49	41
Cardiac Shunts		22	27	29	31	51	58
NYHA Class (%)	II III IV	16 (14) 85 (77) 10 (9)	10 (9) 93 (82) 10 (9)	12 (10) 107 (86) 6 (5)	15 (13) 97 (81) 8 (7)	28 (12) 192 (81) 16 (7)	25 (11) 190 (82) 18 (8)
Duration at current NYHA, months	Mean ±SE	12.1 ±2.5	17.2 ±2.9	19.0 ±2.4	17.8 ±2.1	15.7 ±1.8	17.5 ±1.8
Weight, Kg	Mean ±SD	73.8 ±19.9	73.3 ±21.1	72.1 ±16.3	67.6 ±18.0	72.9 ±18.1	70.4 ±19.8
Height, cm	Mean ±SD	162.5 ±9.9	161.2 ±10.5	163.4 ±9.5	163.0 ±8.5	163.0 ±9.7	162.1 ±9.6
BSA, m^2	Mean ±SD	1.8 ±0.2	1.8 ±0.3	1.8 ±0.2	1.7 ±0.2	1.8 ±0.2	1.7 ±0.2
Pulse, bpm	Mean ±SD	82.4 ±12.6	83.5 ±12.5	81.8 ±12.7	82.1 ±11.5	82.1 ±12.6	82.8 ±12.0
Systolic blood pressure, mmHg	Mean ±SD	117.3 ±16.9	116.7 ±13.8	116.3 ±16.3	115.5 ±14.1	116.8 ±16.6	116.1 ±14.0
Diastolic blood pressure, mmHg	Mean ±SD	75.9 ±11.1	73.3 ±12.0	74.3 ±10.5	73.4 ±11.5	75.1 ±10.8	73.3 ±11.7
Respiratory rate, min^{-1}	Mean ±SD	19.5 ±3.1	19.2 ±2.8	19.1 ±3.5	18.9 ±3.9	19.3 ±3.4	19.1 ±3.4

The demographics were fairly well balanced across studies and across treatment groups. There were however, more males in the 01:05 vehicle group than in any other group. The vast majority of subjects were NYHA class III subjects (approximately 80%). The vast majority of those enrolled were also females approximately 85%). There proportion of subjects with primary pulmonary hypertension in the 01:05 study was greater than in the 01:04 study. The distribution of these subjects between UT-15 and vehicle were, however similar. There were a greater fraction of those enrolled in study P01:04 who had their pulmonary hypertension as a consequence of collagen vascular disease than in study P01:05.

Those with collagen vascular disease consisted of those with scleroderma (12-treatment, 13-vehicle), limited scleroderma (13-treatment, 7-vehicle); mixed connective tissue disease (8-treatment, 9-vehicle); systemic lupus erythematosis (7-treatment, 18-vehicle); and overlap syndromes (1-treatment; 2-vehicle). There were relatively more subjects in the vehicle group whose etiology of pulmonary hypertension was a consequence of SLE.

Those defined as having pulmonary hypertension as a consequence of primary disease probably consisted of those who had idiopathic pulmonary hypertension as well as whose disease was a consequence of anorexogenic drug use.

Comment. This reviewer does not know if the natural history of pulmonary hypertension as a consequence of anorexognic drug use as primary pulmonary hypertension are the same. For those with primary pulmonary hypertension secondary to anorexogenic use, the ongoing stimulus has been removed. The other causes in general (with the exception of repaired congenital shunts) do not have the inciting stimulus for pulmonary hypertension terminated.

The number of subjects in each cohort is shown in Table 50. There were very few subjects with low exercise capacity in the entire cohort.

A.4.4.2 Disposition of subjects

The flow of subjects through the study is shown in Table 46.

Table 46. Disposition of subjects (P01:04-05)

	P01:04		P01:05		Pooled	
	Vehicle	UT-15	Vehicle	UT-15	Vehicle	UT-15
Randomized	224		246		470	
Received treatment	224		245		469	
	111	113	125	120	236	233
Completed 12 weeks	104	96	117	104	221	200
Did not complete	7	17	8	16	15	33
Death	4	4	3	3	7	7
Deteriorated	2	1	4	5	6	6
Transplant	1	0	0	0	1	0
Adverse event	0	12	1	6[79]	1	18
Withdrew consent	0	0	0	2	0	2

A.4.4.3 Oversight Committees

In a supplement dated 3 November 2000, United Therapeutics submitted summaries of the DSMB meetings. The members of the committee were Drs. Brundage, Harrell, Churchill and Fishman. Reports are available for three meetings 20 July 1999; 18 October 1999, and 24 November 1999. After the second meeting the DSMB requested baseline hemodynamic data and 6-minute walk for analysis at the last meeting. The committee requested more information on the nature and treatment of the infusion site pain.

With respect to the Steering Committee, there were apparently two steering committees. One committee for North American sites and the members were Drs. Barst, Rich, Rubin, Crow and Blackburn. A second committee labeled the European Steering committee. The members of this committee were Drs Rubin, Simonneau, Galie, Naeiije, Crow and Blackburn. Drs Rubin, Crow and Blackburn were inviolved with both committees. Meeting dates were as follows: 16 December 1998 (North American), 2 March 1999 (European), 28 April 1999 (North American), and 7 November 1999 (both North American and European)

The only changes to the submitted protocols were made at the 16 December 1998 meeting. This meeting occurred approximately 1 month after the first subject was enrolled into study P01:04 and several days after the first subject enrolled into study P01:05. The changes were in response to a FDA teleconference call. The changes can be summarized as follows. 1) A global QOL in the form of the Minnesota QOL questionnaire was added to the assessments at weeks 1, 6, and 12. 2) The interim

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[79] *Subject 04503 developed sepsis secondary to an elective abortion and died while on study drug. The database captured this patient as a discontinuation due to AE. This error was discovered after the data base lock.*

efficacy assessment was dropped. 3) The last value carried forth approach was used. 4) The Ultrafast CT was incorporated to rule out thromboembolic disease. These changes were incorporated in the protocol by Amendment #3.

A.4.4.4 Conduct

There were 60 subjects whose were stratified inaccurately. Thirty-one of these subjects were vehicle treated subjects and 29 were UT-15 treated subjects. The specifics are shown in Table 47 below:

Table 47. Mistakes in stratification (P01:04-05)

	Vehicle	UT-15
Stratified as primary disease—really secondary pulmonary hypertension	1	1
Stratified as secondary disease—really primary pulmonary hypertension	2	4
Stratified as low exercise—really high exercise	2	6
Stratified as high exercise—really low exercise	8	4
Stratified as high exercise but exercise exceeds upper limits allowed	0	2
Mis-stratified as low exercise capacity and secondary pulmonary hypertension and vasodilator use—in reality high exercise capacity, primary disease and no vasodilator use	1	0
Stratified as low exercise capacity and no vasodilator use—really high exercise capacity and yes vasodilator use	1	1
Stratified as high exercise capacity and vasodilator use—really low exercise capacity and no vasodilator use	1	1
Stratified as primary pulmonary disease with vasodilator use—really secondary pulmonary hypertension with no vasodilator use	3	3
Stratified as vasodilator use—really no vasodilator use	4	4
Stratified as no vasodilator use—really vasodilator use	8	3

There was no overwhelming bias in the errors in of stratification. The mITT considers subjects with appropriate stratification. The pITT analysis considers these subjects as randomized.

Blinding. By protocol, the treatment was blinded to both the physician and subject. An additional barrier to unblinding was included. The physician who performed the exercise distance test was not the physician who was in charge of the subject's care. Other metrics, particularly the dyspnea-fatigue index, however, were performed (and often completed) by the treating physician.

Blinding, however, was not perfect. At the end of the 12-week period the blind of each subject was broken to facilitate treatment into long term therapy. Common drug-related adverse events would rapidly be associated with a given treatment, certainly after the subject's treatment was unblinded.

A second and related compromise to the blind of this study is that subjects who were treated with active drug were more likely to have infusion site pain/infusion site reaction. Furthermore, the intensity and severity of such pain, much more frequently required concomitant medications including narcotics and anti-inflammatory drugs among UT-15 subjects than those treated with vehicle. The onset of such pain was early during the course of treatment. It is, therefore, unclear to what extent measurements performed by the treating physician was compromised by the potential unblinding.

Major assessments of those enrolled may have been by an investigator who had a good idea as to the randomized therapy. Most notably, assessments of signs and symptoms of CHF, quality of life measurements, as well as certain important classifications such as the reason for discontinuations were perhaps biased by the knowledge of treatment.

Protocol violations. The sponsor cites the following criteria as major deviations. There were relatively few subjects who deviated from protocol.

Table 48. Protocol deviations (P01:04-05)[80]

	P01:04		P01:05		Pooled	
	Veh	UT-15	Veh	UT-15	Veh	UT-15
Subjects who received the incorrect treatment for any part of the treatment period	1	0	2	0	3	0
Crossed over to alternative study drug during the treatment period	1	0	2	0	3[81]	0
Were in violation of inclusion criteria for diagnosis of pulmonary hypertension the appropriate hemodynamic parameters	2	1	0	2	2	3
Were in violation of exclusion of criteria for portal hypertension, history of left sided disease, other diseases (i.e. sickle cell anemia, schistosomiasis), musculoskeletal disorder that could alter ambulation, or exercise distance between 40-450 m.	0	0	1	0	1	0
Received any prostaglandin (or analogs) therapy for 7 days of the week 12-exercise test	0	0	0	0	0	0
Received chronic concomitant use of iv or inhaled medications to treat PAH	4	4	0	3	4	7
Other protocol violatons considered on an individual basis prior to unblinding (received rescue therapy[82], interstitial lung disease[83].	1	1	1	0	2	1

A.4.4.5 Definitions of subject cohorts used in analyses[84]

The "Pure Intent-to Treat" (or pITT") Is defined as all subjects randomized in either study. Subjects are counted to the group to which they were randomized, regardless of the treatment they were actually given, or whether any study drug was given at all. All original stratification information used in the randomization procedure is used, regardless of whether it was later found to be incorrect.

The "Modified Intent-to Treat" or ("mITT") population is the same as the "pITT" population except that subjects who did not receive either study drug medication were excluded from the analysis. In addition, the efficacy data for any subject who was inadvertently given the alternative treatment during the trial (i.e. crossed over) due to errors in resupply of study medication was censored at the time of cross-over (by not having data after cross-over included in the analysis). Incorrect stratification data was corrected for this cohort.

The "Per-Protocol" population was defined as all subjects in either study who actually receiving study drug for at least 8 weeks and who had baseline and week 12 exercise test assessments or discontinued due to death, transplantation or clinical deterioration. This population excluded subject with major protocol violations, and those who were not receiving study drug during their Week 12-exercise test due to premature discontinuation. Subjects were counted as being in the group corresponding to the treatment they actually received at the start of the dosing period. Subjects who crossed-

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[80] *Sponsor's analysis.*

[81] *These are the same subjects who received the wrong treatment.*

[82] *Two subjects on vehicle.*

[83] *One subject on UT-15.*

[84] *Volume 33A, page 6365.*

over to the alternative treatment during the trial were excluded from this cohort. Subjects with the following protocol violations were excluded from this cohort:

- Subjects who violate inclusion criteria #3 and #6.That is, subjects who do not satisfy the criteria for the diagnosis of pulmonary hypertension and exclude left sided cardiac dysfunction.
- Subjects who violate exclusion criteria #9, #10, #11 and #12. That is those with portal hypertension, a history of left sided disease, a history of other diseases (i.e. sickle cell anemia, schistosomiasis), Musculoskeletal disorder that could alter ambulation or who had an exercise distance outside the range of 40-450 meters at baseline.
- Subjects who are treated with prostaglandin or their analogues for pulmonary hypertension.
- Subjects who are treated with chronic or inhaled medications to treat pulmonary hypertension.
- Other protocol violations

The "Safety Population" is defined as all subjects in either study who actually receiving study drug, and all subjects will be counted as being in the group corresponding to the treatment that they actually received. If a subject received UT-15 at any point during the study, they will be counted in that treatment group.

Comment. Subjects who are inadvertently treated with UT-15 should also be included in the denominator of the vehicle group. These subjects were only included in the UT-15 group. The denominator of the vehicle group and consequently, the rate of adverse events was mildly inflated in the vehicle group.

The specifics of the cohorts are shown in Table 49.

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