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	16 (14)	10 (9)	12 (10)	15 (13)	28 (12)	25 (11)
	III	85 (77)	93 (82)	107 (86)	97 (81)	192 (81)	190 (82)
	IV	10 (9)	10 (9)	6 (5)	8 (7)	16 (7)	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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Table 49. Cohorts analyzed (P01:04-05)

	mITT	pITT	Per-Protocol	Safety
Randomized manually to correct treatment	Included	Included	Included	Included
Randomized manually, received incorrect treatment weeks 7-12	Included: Efficacy censored at week 6	Included	Excluded	Included
Incorrect stratification information	Included: Stratification information corrected	Included: Stratification information not corrected	Included: Stratification information corrected	Included: Stratification information corrected
Only one assignment available at site	Included	Included	Included	Included
Received drugs for < 8 weeks	Included	Included	Excluded	Included
Subjects who did not have the diagnosis of pulmonary hypertension or did not have the requisite hemodynamics	Included	Included	Excluded	Included
Subjects who had Portal hypertension, left sided failure, other diseases that cause pulmonary hypertension, musculoskeletal disorders or 6-minute walk outside 50-450 m	Included	Included	Excluded	Included
Subjects with premature discontinuations aside of death, deterioration or transplant	Included	Included	Excluded	Included

The distribution of subjects by stratification cohort is shown in Table 50.

Table 50. Subjects by stratification cohort (P01:04-05)

Stratum[85]			pITT			mITT		
PH	**Exer**	**Vaso**	**Veh**	**UT-15**	**Total**	**Veh**	**UT-15**	**Total**
1°	High	—	133	129	262	132	130	262
	High	—	7	5	12	4	4	8
2°	High	Yes	37	39	76	44	40	84
		No	54	53	107	51	56	107
	Low	Yes	2	2	4	3	0	3
		No	4	5	9	2	3	5

There were few subjects with low exercise performance. Slighly more than half the subjects were stratified as primary pulmonary hypertension with high exercise performance.

Concomitant symptoms at baseline are shown in Table 51. The most common symptoms at baseline were dyspnea on exertion, exercise intolerance and fatigue. The remaining symptoms are listed in approximate decreasing frequency.

[85] *Primary or secondary pulmonary hypertension; high or low exercise capacity; receiving or not receiving vasodilators.*

Table 51. Symptoms at baseline (P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Dyspnea on exertion	109 (98)	110 (97)	125 (100)	120 (100)	234 (99)	230 (99)
Exercise intolerance	97 (87)	109 (97)	110 (88)	115 (96)	217 (92)	224 (96)
Fatigue	97 (87)	106 (94)	107 (86)	105 (88)	204 (86)	211 (91)
Palpitation	50 (45)	60 (53)	50(40)	61 (51)	100 (42)	121 (52)
Dizziness	54 (49)	58 (51)	53 (42)	61 (51)	107 (45)	119 (51)
Peripheral edema	53 (48)	52 (46)	58 (46)	44 (37)	111 (47)	96 (42)
Edema	53 (48)	52 (46)	58 (46)	44 (37)	111 (47)	96 (41)
Chest Pain	43 (39)	46 (41)	48 (38)	49 (41)	91 (39)	95 (41)
Weakness	34 (31)	41 (36)	37 (30)	48 (40)	71 (30)	89 (38)
Orthopnea	35 (32)	44 (39)	38 (30)	32 (27)	73 (31)	76 (33)
Cyanosis	27 (24)	30 (27)	56 (45)	45 (38)	83 (35)	75 (32)
Hypoxia	26 (23)	25 (22)	56 (45)	48 (40)	82 (35)	73 (31)
Cough	35 (32)	38 (34)	34 (27)	30 (25)	69 (29)	68 (29)
Cool extremities	38 (34)	38 (34)	44 (35)	29 (24)	82 (35)	67 (29)
Lightheadedness	28 (25)	34 (30)	31 (25)	33 (28)	59 (25)	67 (29)
Right heart failure	32 (29)	31 (27)	39 (31)	26 (22)	71 (30)	57 (25)
Headache	17 (15)	26 (23)	16 (13)	22 (18)	33 (14)	48 (21)
Low cardiac output	15 (14)	19 (17)	23 (18)	23 (19)	38 (16)	42 (18)
Musculoskeletal pain	17 (15)	25 (22)	20 (16)	15 (13)	37 (16)	40 (17)
Tachycardia	14 (13)	22 (20)	19 (15)	16 (13)	33 (14)	38 (16)
Arrhythmia	11 (10)	17 (15)	18 (14)	16 (13)	29 (12)	33 (14)
Angina	7 (6)	13 (12)	15 (12)	19 (16)	22 (9)	32 (14)
Depression	20 (18)	19 (14)	18 (14)	15 (13)	38 (16)	31 (13)
Paroxysmal nocturnal dyspnea	7 (6)	14 (12)	10 (8)	15 (13)	17 (7)	29 (12)
Dyspnea at rest	8 (7)	17 (15)	19 (15.	9 (8)	27 (11)	26 (11)
Nausea	9 (8)	16 (14)	13 (10)	9 (8)	22 (9)	25 (11)

Baseline medications. Baseline classes of medications are shown in Table 52. The vast majority of subjects were on some class of medications at baseline. The proportion of subjects in both groups on each class of medication was similar. Approximately 2/3 of those enrolled was anti-coagulated at baseline. Loop diuretics were used in approximately 45% of those enrolled. Steroids were actually infrequently used (< 10% of those enrolled] despite the 90 subjects whose etiology of pulmonary hypertension was due to collagen vascular disease.

Table 52. Baseline medications (P01:04-05)

	Veh N=236	UT-15 N=233		Veh N=236	UT-15 N=233
Any	226 (96)	219 (94)	ACE-inhibitors/Angiotensin blockers	29	23
Loop diuretics	103	105			
Oxygen	85	83	Steroids	18	16
Calcium channel blockers	100	98	Anticoagulants/anti-platelets	166	153
Digitalis compounds	56	57	Diuretics (incl spironolactone)	62	73

A.4.4.6 Dosing

The dose level of UT-15 (or vehicle) was predicated on increasing the dose of drug to a point where signs and symptoms of pulmonary hypertension are improved, balanced against any dose-related adverse event profile of the drugs. The dose of drug (or vehicle)

was increased if the signs and symptoms of pulmonary hypertension were not improved or if the subject's clinical condition deteriorated.

The dose of drug (vehicle) was not to be increased or was to be decreased if there were any of the following:

- Changes in hemodynamics, vital signs, or clinical signs or symptoms (e.g. lightheadedness).
- Onset of an adverse experience associated with study drug (headache, nausea, emesis. restlessness and anxiety, or
- Pain at the infusion site (either new onset or worsening of pain).

The mean infusion rates for both vehicle and UT-15 are shown in Figure 11. At the end of the period the infusion rate of UT-15 (mean ±SD) was 9.3 ± 5.4 μg/kg/min and that for vehicle was 19.1 ± 4.8 μg/kg/min. The lower doses of U-15 reflects the limitation imposed by the onset of adverse events or excessive pharmacological effect or UT-15 and should not be construed as demonstrating a benefit of UT-15 in ameliorating the signs and symptoms of pulmonary hypertension.

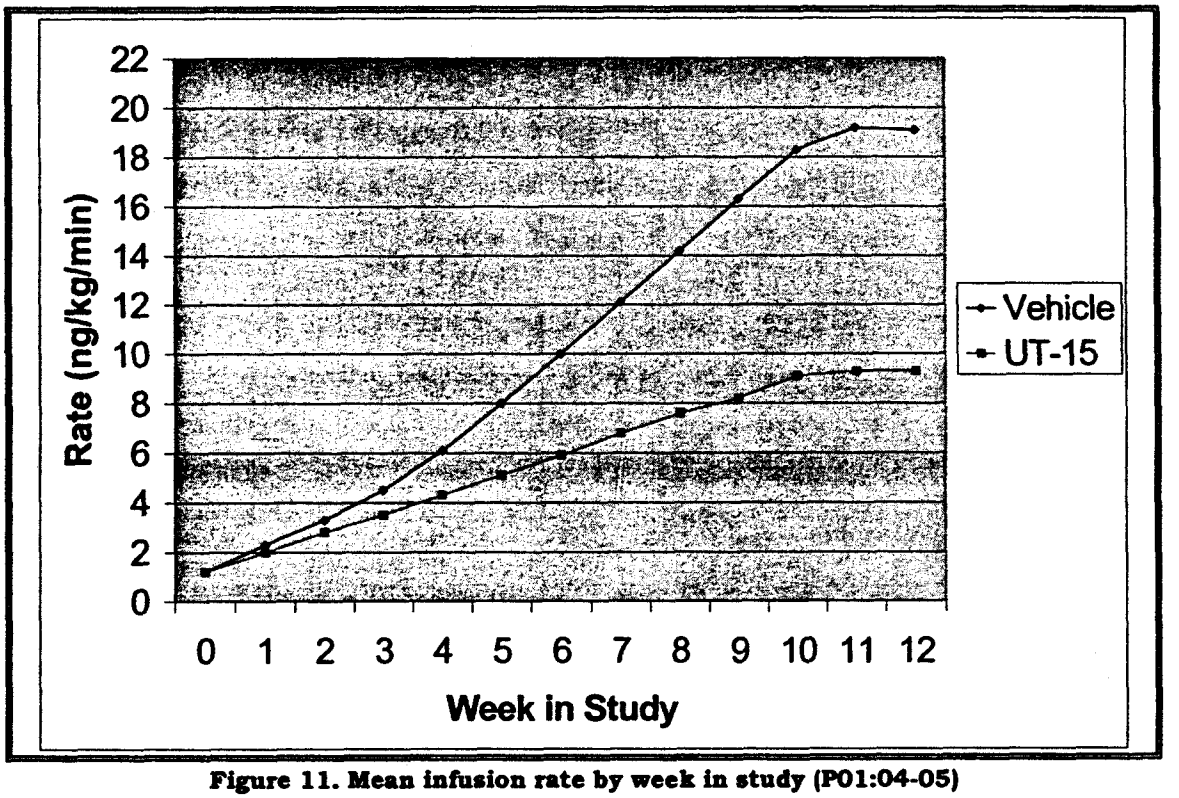

Figure 11. Mean infusion rate by week in study (P01:04-05)

More vehicle subjects were titrated upward than UT-15 subjects (Figure 12). The greater number of such subjects could either reflect the greater need for increased dosing (i.e. a measure of increased benefit for UT-15) or conversely the marginal tolerance of the UT-15 dose so that further dose increases were not well tolerated. More UT-15 subjects required dose reductions than vehicle subjects. Sponsor's Listing 16.2.5.3 only lists the reason for dose changes. The usual reasons for downward change was due to pain at the infusion sites. No reason was listed for not increasing the dose.

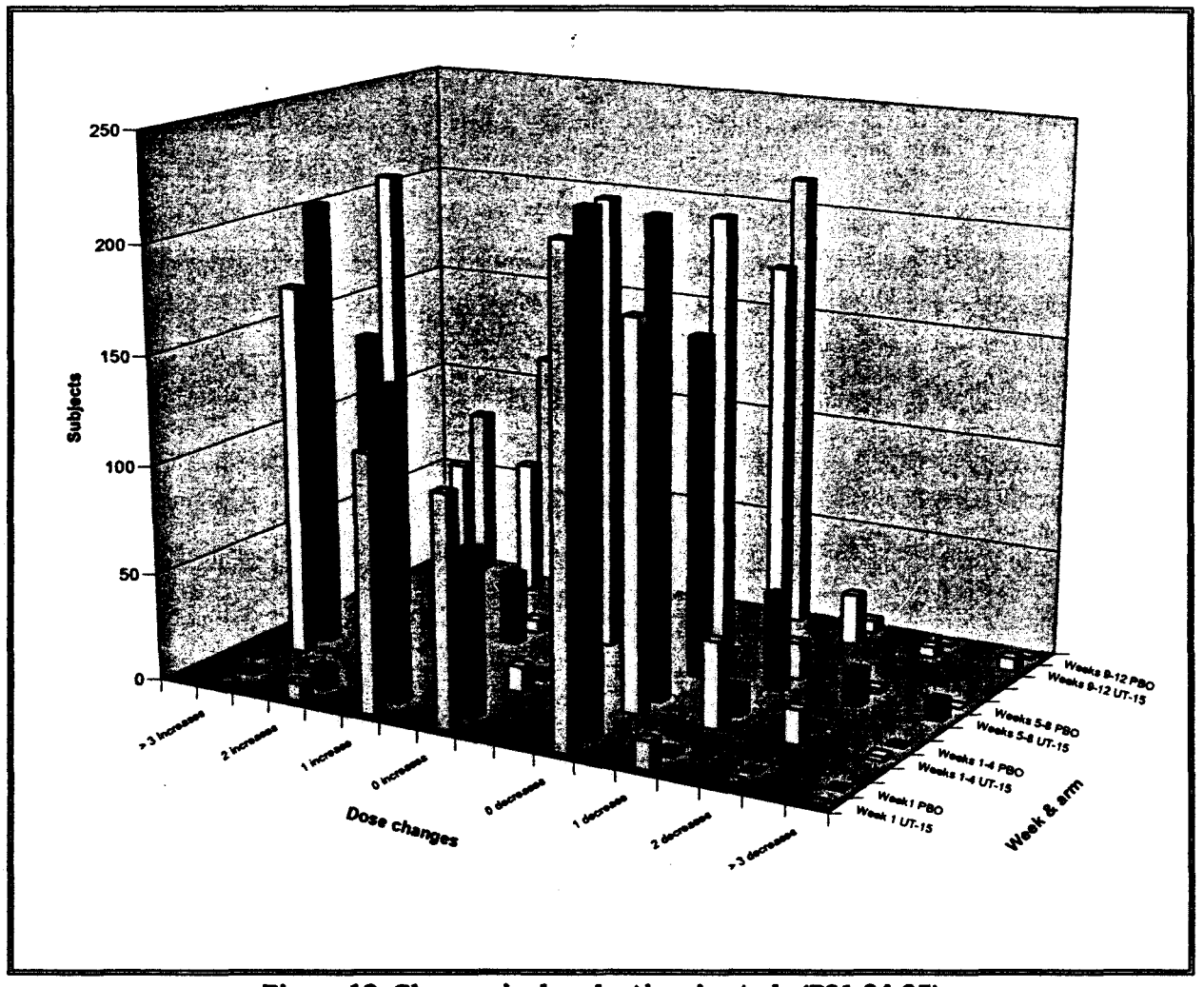

Figure 12. Changes in dose by time in study (P01:04-05)

Adverse events limiting dose. Infusion with UT-15 was less well tolerated than vehicle. Based on the data in Listing 16.2.5.3, ninety-five UT-15 subjects had dose reductions at least once for either infusion site pain or infusion site reaction. An additional twenty-nine had the dose reduced due to excessive pharmacologic function. For those treated with vehicle there was one subject who had the dose decreased due to adverse events related to infusion site pain or reaction and three for excessive pharmacologic effect.

The sponsor also supplies concomitant medications that were required to mitigate pain (redness, bruising, burning or pain). Of the subjects treated with UT-15, 207/ 233 (89%) with data available required some medications for infusion site reaction (pain or erythema). Only 35 /237 vehicle subjects (15%) required medication for infusion site reactions. The medications, which were used to treat these symptoms, ranged from narcotics, anti-inflammatory oral agents to topical steroids, astringents and irritants. More UT-15 required opiate antagonists than vehicle subjects (68 versus 3). There were more subjects treated with UT-15 who required some form of anti-inflammatory medication than those treated with vehicle (131 versus 8).

There were more subjects who discontinued from active treatment than from vehicle. Of the 233 subjects who were randomized to active UT-15, 33 discontinued prior to the

week-12 end point (see Figure 1.2). Eighteen of these subjects discontinued due to adverse events. Seventeen of these subjects had some degree of pain as the attributed reason for discontinuation. Among the 237 subjects who received vehicle, there were 15 subjects who did not complete the 12-week study period. None of these subjects discontinued for site pain.

In summary, UT-15 infusion causes complications at the infusion site at a much greater frequency and greater intensity than vehicle infusion and consequently, these subjects required more frequent and more intense treatment for this pain. This asymmetry of infusion pain across treatments has some consequences. It is quite likely that the investigator had a good idea which subject was receiving active drug and which was receiving vehicle.

Since a blinded, designated, investigator supervised the pivotal six-minute walk, this reviewer does not believe this measurement was compromised. The more frequent pain in the UT-15 infusion group, however, may have compromised the analysis of this metric in a subtler way. Since subjects who discontinued for worsening heart failure are assigned the worst outcomes, whereas those who discontinued for adverse event are given their last observation carried forward, the attribution of a cause of discontinuation is intimately alters the imputed value that was used in the pivotal analysis.

The implications of the much more frequent infusion pain can be considered by the following example. Consider two subjects, one treated with UT-15 and one treated with vehicle that had exactly the same disease course. Both subjects had early and persistent deterioration. The subject treated with UT-15 has some infusion site pain, perhaps even severe in nature. Neither subject was feeling particularly better with respect to their underlying pulmonary hypertension. In fact, these subjects may have been feeling worse. Only the UT-15 subject had the concomitant infusion-site pain and discontinued early. Both subjects eventually went on to die, receive transplant or deteriorate by the criteria of the study. However, only the vehicle subject was treated as the worst outcome. The UT-15 subject who died, deteriorated or was transplanted early was censored and the last observation carried forward. The last observation may have been distant to the time of discontinuation and might not have captured the entirety or even a substantial portion of the status of the subject at the time of the event. Although the study planned to perform exercise measurements on all subjects at 12-weeks, even among those who discontinued, in general, this measurement was not performed. Subjects did not have their status at the end of the study i.e. for 84 days with a window of 71-100 days, with regards to deterioration, death or transplantation ascertained.

If one accepts the possibility that those who ostensibly discontinued for infusion site pain also potentially had a component of worsening disease, then the six minute walk that uses a last observation carried forward analysis produces a more optimistic outcome particularly for the treatment group. The consequence of this asymmetry in adverse events is explored in conjunction with the reviewer's analysis (see section xxxx).

A.4.4.7 Efficacy

A.4.4.7.1 Walking distance

Baseline measurements. The baseline walk-distance (per sponsor) for study 01:04 and 01:05 are shown in Table 53. The distances are relatively consistent across studies. It should be appreciated that a reasonable walking distance for a healthy individual, assuming a 20-minute mile would be approximately 480 meters. Subjects with high baseline measurements, therefore, had modest upside potential. The analysis treated baseline-walking distance as a monotonic covariate and consequently did not correct for differences in exercise performance at the extremes of baseline measurements.

Table 53. Baseline walking distance (P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=233
Mean±SE	336±8	327±8	319±8	326±8	327±6	326±5
Median	349	341	338	349	342	345
25-75 percentile	272-377	264-390	272-377	270-396	272-397	264-395
P-value	0.32		0.50		0.85	

Effect of UT-15 on six-minute walk. The sponsor performed a multitude of analyses of the six-minute walk data. There is a general consistency across all analyses. Neither of the two studies by themselves was statistically significant by most of these analyses. The p-value for the pooled studies as performed by the sponsor was, in general, less than $p<0.01$, but never so overwhelming as to be <0.00125. As such, even by the sponsor's own rules or by the criteria usually proposed by this Division this study could not be considered as sufficient for drug approval.

There were, moreover, ambiguities in the statistical plan as proposed by the sponsor, Dr. Lawrence, the FDA statistician reanalyzed the data by treating the data consistent with the protocol but different to that as performed by the sponsor.

This reviewer performed an alternate set of analyses. The starting point of these analyses revolved around the asymmetry of the study design. The default algorithm for assigning a walk distance for subjects who discontinue without a 12-week walk is shown in Table 1.19. Those subjects who discontinued due to adverse events had their last observation imputed. Those who discontinued either due to death, transplantation or deterioration were treated as a worse outcome. For the non-parametric analysis those who discontinued due to death, deterioration or transplantation were assigned a worst rank, in the non-parametric analysis they were assigned a walking distance of zero feet.

There are several consequences to the imbalance in discontinuations. First, those who discontinue due to adverse events could never receive a worst outcome whereas those who were in the vehicle group could potentially receive the worst outcome due to death, transplantation or deterioration. Second, it is unclear to what extent the attribution of a discontinuation would be preferentially assigned to infusion related problems as opposed to deterioration of status. Third, the imputed value could be so distant to the time of discontinuation that it inaccurately reflects the status at the time of discontinuation. The imputed value would be clearly inaccurate. Lastly, the asymmetric use of medications that may alter hemodynamics could also bias any interpretation of the results.

Since there were many more subjects in the UT-15 group who were discontinued due to ADRs, these subjects could never receive the worst outcome. The analyses performed by this reviewer attempt, in a step-wise manner, to test the consequence of the asymmetry in discontinuations.

The first analysis performed by this reviewer consists of imputing a worse value to those who died, were transplanted during the window of the study (till day 100). These outcomes are not subjective and corrections could easily be performed. The second analysis treated those deaths, transplantation as worst outcomes but also added those who were started on flolan within a month of discontinuing UT-15 and within the 100-day window of the study as worst outcomes. This analysis was based on the assumption was that those who were relatively rapidly started on flolan had some deterioration in status that transformed the optional need for flolan at baseline to the treatment of choice. A third analysis also treated as worst outcomes all those who were

started on flolan during the 100-day window of the study whether they were started within a month or after a month of stopping. Lastly, there was an occasional subject whose status was clearly worse than the LOCF value would imply. In general, the LOCF was at a time point distant to when the subject discontinued. It seemed counter-intuitive to impute a very favorable value where the course was clearly downhill. These subjects were censored without the positive walking distance imputed.

By either Dr. Lawrence's or this reviewer's analyses, the p-value for the pooled studies exceeds p>0.01.

Table 54. Imputation rules for subjects without a week 12 walk (P01:04-05)

	Alternative 1		Alternative 2	
	Non-parametric	**Parametric**	**Non-parametric**	**Parametric**
Death within 12-weeks; excluding accidents or death unrelated to disease or study	Lowest standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Clinical decompensation within 12 weeks; excluding accidents or death unrelated to disease or study	Lowest standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Transplantation	Last standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Accidents or death unrelated to disease or study	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
AE (survivor, week 12)	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
Lost to Follow-up (survivor, Week 12	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
Consent withdrawn (survivor, week 12)	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*

Sponsor's analysis #1

Database: Pooled studies P01:04 and P01:05.

Type of Analysis: Non-parametric analysis of covariance (covariates included: baseline distance walked, center, etiology of pulmonary hypertension (primary versus secondary) and vasodilator use at baseline. Later added a covariate was use of steroids to treat primary pulmonary hypertension).

Population: mITT.

Subjects excluded: One subject with no post baseline measurement (UT-15, pt# 10507), one subject who withdrew before receiving any dose (vehicle; pt # 07501) and three UT-15 subjects were excluded (#05010; #08008 and #66006) because of the absence of other subjects in their stratification cells for baseline walk. The primary analysis, however was modified to remove baseline walk as a stratification variable, to allow inclusion of these three subjects. Baseline walk was used as a continuous covariate, allowing these three subjects to be included.

Imputation methods: Lowest rank assigned to deaths, transplants or clinical deterioration (defined as rescue with either chronic i.e. longer than five days with intravenous medication, chronic inhaled medications other than oxygen or chronic use of prostaglandin analogues). For other missing values the last standard rank in the exercise hierarchy was carried forth.

The results of this analysis are shown in ble 55.

Table 55. Change in 6-min walk (sponsor's analysis #1[86]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=232
Median	1	3	-3	16	0	10
25th,75th percentile	-53, 31	-27, 37	-38, 35	-22, 50	-45, 33	-28, 48
P-value	0.06		0.06		0.006	

The median overall magnitude of effect for the pooled studies was quite small (10 meters or approximately 3% of baseline walk distance) for the pooled studies. None of the individual studies was statistically significant by the standard criteria.

Sponsor's analysis #2

Database: Pooled studies P01:04 and P01:05.

Type of analysis: Non-parametric analysis of covariance [covariates included: baseline distance walked, center, etiology (primary versus secondary) and vasodilator use at baseline]. Later added as a covariate was use of steroids to treat primary pulmonary hypertension)

Population: pITT (see Table for definition of this cohort). The population differs from the mITT in several respects. The key differences are that those subjects who were inadvertently crossed over were included in their randomized group and not the cross-over group. In addition, those who were incorrectly stratified were left analyzed in the incorrect stratification.

Imputation methods: Lowest rank assigned to deaths, transplants or clinical deterioration. For other missing values the last standard rank in the exercise hierarchy was carried forth.

The results are shown in Table 56.

Table 56. Change in 6-min walk (sponsor's analysis #2[87]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=126	UT-15 N=120	Veh N=237	UT-15 N=233
Median	1	3	-2	16	0	10
25th,75th percentile	-53, 31	-27, 37	-37, 35	-20, 50	-43, 32	-24, 47
P-value	0.06		0.06		0.009	

Sponsor's analysis #3

Database: Pooled data studies P01:04 and P01:05.

Population: mITT.

Type of analysis: Parametric analysis. (ANCOA) with the covariates [baseline walk distance, center, etiology of pulmonary hypertension (PPH versus other), vasodilator use at baseline (yes versus no)].

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[86] mITT population, lowest rank imputed for deaths, dropouts and discontinuations and LOCF for those who discontinue due to adverse events, non-parametric analysis of covariance.

[87] pITT analysis Lowest rank imputed for deaths, dropouts and discontinuations and OCF for those who discontinue due to adverse events, non-parametric analysis of covariance. P-values are nominal.

Imputation method: Subjects who died, received transplant or clinically deteriorated a value of zero meters was imputed for the final analysis. Subjects who discontinued for adverse events were given the last value carried forth.

Table 57. Change in 6-min walk (sponsor's analysis #3[88]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=232
Baseline mean	336±8	327±8	319±8	327±8	327±6	327±5
Change	-29±10	-2±9	-15±8	-2±10	-22±6	-2±7
P-value	0.04		0.4		0.04	

Note: This analysis shows only one study with statistical significance and this study drives the pooled analysis. The overall pooled analysis does not approach the pre-specified 0.01.

Sponsor's analysis #4

Database: Pooled data P01:04 and P01:05

Population: mITT cohort

Type of analysis: Non-parametric analysis

Imputation method: For this analysis, six minute walk distances were censored at the time of study discontinuation for any reason and the last standardized rank before discontinuation was carried forth even for those who discontinued due to death deterioration or for missing data.

Table 58. Change in 6-min walk (sponsor's analysis #4[89]; P01:04-05)

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=119	Veh N=236	UT-15 N=232
Median	4	7	3	16	3	11
25th,75th percentile	-39, 37	-23, 37	-33, 36	-17, 50	-35, 34	-21, 48
P-value	0.08		0.07		0.01	

The FDA statistical reviewer's analyses

The analyses performed by the sponsor treated some subjects whose treatment in the primary analysis was somewhat ambiguous. The discussion below is culled from the statistician's review.

[88] *mITT population, Lowest rank imputed for deaths, dropouts and discontinuations and OCF for those who discontinue due to adverse events, parametric analysis of covariance. P-Value is nominal*

[89] *Non-parametric analysis of covariance, All patients who discontinue due to any reason will have the LOCF imputed.*

Table 59. FDA statistician's handling of missing data.

Study/ Subject Treatment	Issue	Statistician's comment
04/7004 UT-15	This subject had a valid baseline week 1 and week 12 data. Week 6 data missing because subject too sick to exercise	The statistician cites the wording in the analysis plan ... "If an exercise test is missing because subject was too critically ill" the lowest standardized rank will be used for the nonparametric analysis and a distance of " 0 meters" will be used for the parametric analysis. Data missing for other reason will have the last standardized ranks carried forward for the nonparametric analyses and last observation carried forward for the parametric analyses". The statistician analyzed such subjects as a worst outcome.
05/61008 Vehicle	This subject had a valid baseline week 1 and week 12 data. Week 6 data was missing because the subject was too sick to exercise.	
04/10507 UT-15	This subject had a baseline walking distance but no subsequent measurements since the subject dropped out on day 9 for an adverse event. The sponsor censors this subject.	The FDA statistician proposed two additional ways of handling the data. • Fit a regression to baseline versus he remaining covariates and carry forward the standardize rank for this subject • Carry forward the worst rank Subjects who do not have complete follow up are imputed by carrying forward the last value after adjusting for several covariates. Using this approach will tend to carry forward a smaller rank (worse outcome). For this subject the standardized rank carried forward was 0.138
05/52006 Vehicle	This subject had baseline and one post-baseline measurement. This subject was discontinued for an ADR. The subject died within 100 days of randomization.	A worst outcome was imputed for this subject
05/60005 Vehicle	This subject dropped informed consent after 46 days, however, a 12-week walking distance was performed.	The sponsor used the rank of the 12 week assessment. The statistician used the 6 week rank
04/2004 05/52003 05/52004	These subjects all received Vehicle for 6 weeks but were inadvertently switched to UT-15 after 6 weeks. The sponsor Carried Forward the standardized risk from week 6	The FDA statistician's analysis uses the 12-week measurement
05/18501 Vehicle	This subject had three measurements of on-treatment a 35, 55 and 71 days, The first two of these measurements would satisfy the criteria for the 6-week visit. The last did not fall within the window for the 12-week visit. The sponsor treated the day 71 visit as the week 12 visit.	The FDA statistician found the rank on Day 55 and carried the rank for this measurement forward.

Lastly the FDA statistician proposes to handle the few subjects stratified to low baseline walk distance (< 150 M) different than the sponsor. The sponsor, because of the few subjects with low baseline measurements analyzed the data without baseline measurements as a covariate. The FDA statistician used baseline distance as a covariate and finds the significance of the means core statistic from the permutation distribution.

Table 60. Nominal p-values from FDA statistician's analyses (P01:04-05)

	P01:04	P01:05	Total
P-value	0.10	0.08	0.015

FDA Medical Officer additional analyses

There was clearly an asymmetry in discontinuations in the study. Those who were treated with active drug were far more likely to discontinue due to infusion site pain. In fact, infusion site pain was nearly pervasive among those who were infused with active drug but infrequent among those infused with vehicle. Subjects who discontinued for adverse events were censored at the time they were discontinued. The consequence of this algorithm was that these subjects could never be saddled with the worst possible outcome for death, deterioration or transplant. This algorithm biases the analysis, favoring UT-15. The number of subjects that discontinue because of pain may have had some component of worsening of status provoking their discontinuation. Lastly, those who had values imputed may have been within the window of the next measurement but did not have this measurement. The imputed value may not reflect the status at the time of discontinuation.

Table 61 contains summaries of those who discontinued prematurely. The information was collected from the sponsor's narratives for those who discontinued (pp5680-522) as well as data contained within a supplement (dated 11 January 2001.

Dr, Lawrence, the FDA statistician, performed the three analyses that were requested by this reviewer. The first analysis included only those subjects who were discontinued as ADR but died or required transplantation (non-subjective outcomes) and treated those as worse outcomes. The second analysis also treated as worse outcomes, subjects who were discontinued because of adverse reactions but were started on Flolan within one month of discontinuation and within the 100-day upper limit of the window of the 12-week visit. The third analysis further incorporates all subjects who were started on Flolan within the 100-day window of the study whether they were started within 1-minth of discontinuation or not. In addition, there were one or two subjects whose values as a LOCF seem so inconsistent with their status as described by the sponsor and a later walk-test could or should have been performed. These subjects were excluded without the LOCF. There were additional subjects whose histories could be interpreted to represent worsening status, however, these subjects did not fall into any of the described categories. These subjects were treated as per sponsor's analyses.

The sponsor submitted narratives for those who discontinued (P 5680 –5722). The sponsor also submitted supplement (dated 11 January 2001) that was used to complete Table 61. The sponsor's analysis of these events differ from that of the reviewer (this reviewer has taken a very conservative approach).

The sponsor's did not consider any of those who discontinued as adverse events as having decompensated. There analysis is appended.

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Table 61. Reviewer's handling of discontinuations for ADR or WC (P01:04-05)

Study Subject Class[90] Arm	Description	Classification by reviewer
01:04/ 2001 ADR UT-15	This was a 42-year old female with NYHA Class III heart failure associated with pulmonary hypertension as a consequence of congenital heart disease who was titrated to a maximum infusion rate of 5.0 ng/kg/min. The subject was discontinued from treatment after 43 days due to intolerable infusion site pain, nausea and vomiting. Dyspnea on exertion worsened 2 days after discontinuation. Approximately 6 weeks later (within the 100-day window) the subject was initiated on Flolan following a pulmonary hypertensive crisis. Day 1 8/9 43 Six minute walk in meters 479 446 132 Dyspnea fatigue index score 6 6 6	Worse outcome by analysis # 3. The subjects exercise performance deteriorated before the subject discontinued and the subject eventually crashed and required flolan. This subject clearly had deterioration during the time course of the study.
01:04/ 2006 ADR UT-15	This was a 42-year old female with NYHA Class III heart failure associated with pulmonary hypertension as a consequence of SLE. The maximum dose of UT-15 was 2.5 ng/kg/min. The dose was reduced a s a consequence to infusion site pain and discontinued on day 71. Within two weeks the subject was started on flolan. Day 1 8/9 43 Six minute walk in meters 388 470 495 Dyspnea fatigue index score 6 6 6	Worse outcome by analysis # 2 The subject received Flolan within two weeks of discontinuation,. The closest exercise test and dyspnea fatigue index was approximately 1 month prior to discontinuation and may not reflect the status of the subject.
01:04/ 2016 ADR UT-15	This was a 49-year old female subject with a 14-year history of pulmonary hypertension and NYHA Class III associated with congenital heart disease. The maximum dose of UT-1 was 3.75 ng/kg/min. The subject discontinued on day 47. The subject experienced worsening pulmonary hypertension after discontinuation of infusion. The subject was alive 30 days post dose. The subject was started on flolan four-months post discontinuation and therefore after the 100 day window. Day 1 5 Six minute walk in meters 198 406 Dyspnea fatigue index score 2 5	This subject was censored with no LOCF, per analysis #3,. The sponsor suggests the deterioration was a consequence of discontinuing UT-15. This subject's carried forward value was extremely good. The six-week measurement was never performed although the time of discontinuation was within the window for this measurement.
01:04/ 2020 ADR UT-15	This was a 33-year old female subject with a six-month history of primary pulmonary hypertension. The subject received as their maximum dose 1.3 ng/kg/min. After a total of 5-weeks of therapy UT-15 was discontinued because of intolerable site pain. The subject elected to start intravenous flolan within one month. Day 1 9 Six minute walk in meters 264 347 Dyspnea fatigue index score 8 8	Worse outcome by analysis # 2. Although elected to start flolan it is possible to construe as a worse change in status. The sponsor claims the subject's status was improved. It is therefore, unclear why flolan was needed. The subjects discontinuation fell within the six week visit window. It is unclear why no exercise test was performed prior to discontinuation.

[90] *ADR = adverse drug reaction; WC = withdrew consent*

Study Subject Class[90] Arm	Description	Classification by reviewer
01:05/ 4503 ADR UT-15	This was a 36-year old female with primary pulmonary hypertension and NYHA Class III. The subject received a maximum infusion of 5.0 ng/kg/min. The subject became septic as a consequence of a chemical abortion. The subject was febrile. The subject arrested and died three days later. Day: 1 | 8 | 45 Six minute walk in meters: 375 | 340 | 362 Dyspnea fatigue index score: 6 | 3 | 5	Worst outcome by analysis #1.. This subject was treated as a Adverse Event and should be treated as a worse outcome since the subject died during the time window of the study.
01:04/ 5009 ADR UT-15	This was a 51-year old female Caucasian subject with NYHA Class III associated with a congenital systemic to pulmonary shunt. The maximum dose was 1.25 ng/kg/min. The subject discontinued after approximately 6 weeks due to continuous, moderate infusion site pain. The subject was not titrated upward and remained on the 1.2 ng/kg/min dose. The subject was alive approximately 1 month later. This subject did not receive flolan post discontinuation. Day: 0/1 | 9 | 42/43 Six minute walk in meters: 337 | 253 | 276 Dyspnea fatigue index score: 7 | 3 | 3	Worse outcome by analysis #2. The subject had a decrease in exercise performance and a marked worsening of the dyspnea fatigue index.
01:04/ 7004 ADR UT-15	This was a 44-year old Caucasian female, NYHA Class II as a consequence of systemic shunts The subject discontinued medication on study on day 25 due to infusion site pain. The subject was subsequently hospitalized due to hemoptysis. The maximum dose was 1.0 ng/kg/min. The subject was alive This subject did not receive Flolan. Day: 0/1 | 10 | 44/45 | 87 Six minute walk in meters: 345 | 393 | Too ill | 398 Dyspnea fatigue index score: 7 | 6 | 7 | 6	This subject had an off-treatment measurement at week 12. This value was used. by the sponsor. This subject did not fit into the categories for worst outcome but was too ill at last visit. This patient could have been treated as a worst outcome but was censored.
01:05/ 10507 ADR UT-15	This was a 45-year old female NYHA Class IV with her pulmonary hypertension secondary to Eisenmennger's syndrome. The subject was treated only 9 days due to infusion site pain. The subject was alive 30 days later. This subject received an elective transplant two months later. Day: 2 | 9 Six minute walk in meters: 183 | — Dyspnea fatigue index score: 1 | 3	Worse outcome by analysis #1. This subject was transplanted during the window of the study. The fact that it was elective is not prespecified as mitigating to worse outcome
01:04/ 11002 ADR UT-15	This was a 49-year old female subject with PPH and NYHA Class II. The subject received a maximum dose of 2.5 ng/kg/min. The subject discontinued on day 31 of treatment. The subject was alive one month after discontinuation. This subject received Flolan 2 months post –discontinuation. Day: 1/2 | 9 | 30 Six minute walk in meters: 370 | 381 | 229 Dyspnea fatigue index score: 4 | 4 | 3	Worse outcome by analysis # 3. The subject's exercise capacity deteriorated by day 30. The subject received flolan during the window of the study. The subject's exercise performance was going downhill.
01:04/ 11003 ADR UT-15	This was a 28-year old female with NYHA Class III and pulmonary hypertension secondary to Eisenmenger's syndrome. The subject was discontinued after 45 days. The subject was alive one month after discontinuation. The subject was started on Flolan 3 months after discontinuation, outside the window of the study. No statement re inotropic support was made. This subject did not have a six-minute walk performed at week 6.	Censored a LOCF analysis is appropriate. This subject was censored on day 45. I have concern as to why the subject did not have a six-minute walk test at week 6. The start of Flolan was outside the study window.

Study Subject Class[90] Arm	Description	Classification by reviewer
	Day: -11, 1, 7, 36 Six minute walk in meters: 287, —, 323, — Dyspnea fatigue index score: —, 2, 2, 2	
01:04/ 14012 ADR UT-15	This was a 61-year-old female subject with NYHA class III with pulmonary hypertension as a consequence of systemic sclerosis. The subject received a maximum dose of 6.25 ng/kg/min. The subject was discontinued on day 58 due to severe infusion site pain. The subject developed shortness of breath after discontinuation. The subject was alive 1-month and apparently did not receive flolan. Six minute walk in meters (day): Day: 1/2, 9, 44, 58 Six minute walk in meters: 339, 345, 333, — Dyspnea fatigue index score: 6, 6, 6, 9	This subject could be considered a worse outcome because of the description of worsened shortness of breath and no statement as to the need for inotropic or flolan. The subject did not fit into the three analytic categories. He was treated as LOCF.
01:04/ 16006 Complete Vehicle	This was a 57-year old female with primary pulmonary hypertension and NYHA Class III The subject developed worsening status but was catheterized, with modest change in hemodynamics (PAPm increased to 104 from 96 mm Hg). O_2 saturation decreased to 43.5%. The subject was to be treated with Flolan but arrested and died prior to the start of Flolan. Day: 1, 7, 42/43, 81 Six minute walk in meters: 329, 312, 264, — Dyspnea fatigue index score: 4, 4, 4, —	Worse outcome by analysis #1. This subject had a 0 meters 6-minute walk as the final measurement, it would make no difference if a worse outcome was imputed.
01:04/ 19001 ADR UT-15	This was 54-year old female with PPH and NYHA Class III. This subject was discontinued from the UT-15 infusion due to infusion site pain on day 7. She subsequently restarted UT-15 after an approximately 2-week hiatus. After an additional two weeks she discontinued again due to infusion site pain. Approximately 2 months later she stared Flolan. Six minute walk in meters (day): Day: 1, 8, 41 Six minute walk in meters: 383, 383, — Dyspnea fatigue index score: 6, 6, 2	This subject could be considered a worse outcome but did not fit into the three analytic categories. He was treated as LOCF. The dyspnea fatigue index at the last time point had deteriorated. No exercise measurement was performed despite being in the window of the 6-week visit. The LOCF value clearly does not reflect status at termination. Flolan was not started till after the 100-day window.
01:04/ 19005 ADR UT-15	This was a 63-year old female with PPH and NYHA Class III. The maximum dose received was 5.0 ng/kg/min. The subject discontinued study after approximately 9 weeks due to infusion site pain with no improvement in symptoms of pulmonary hypertension. The subject was alive 1-month post discontinuation. Day: 1, 10, 45 Six minute walk in meters: 264, 276, 180 Dyspnea fatigue index score: 5, 6, 6	LOCF. Subject was censored on day 63. Flolan was started after the window of the study. The last exercise performance was two weeks prior to discontinuation.
01:04/ 19008 ADR UT-15	This was a 55-year old female with PPH and NYHA Class III symptoms. The maximum infusion the subject received was 5.0 ng/kg/min The subject discontinued after 6 weeks of therapy and was subsequently lost to follow up. Upon this reviewer's request, the subject was located. The sponsor claims the subject was doing well and not treated with Flolan.	LOCF. Assuming the sponsor is accurate, this subject could be censored. The was clearly no exercise benefit but a moderate worsening of the dyspnea fatigue index

Study Subject Class[90] Arm	Description	Classification by reviewer
	Day: 1 / 12 / 45 Six minute walk in meters: 315 / 343 / 355 Dyspnea fatigue index score: 7 / 5 / 5	
01:05/ 19502 ADR UT-15	This was a 69-year old female with Class IV CHF secondary to pulmonary hypertension in association with scleroderma. The subject received a maximum dose of 1.3 ng/kg/min. The subject discontinued after approximately 5 weeks due to site pain. Approximately 1-month post study she started on Flolan. Day: 1 / 8 / 45 Six minute walk in meters: 186 / 207 / 241 Dyspnea fatigue index score: 2 / 4 / 2	Worst outcome by analysis #2. Treated as worse outcome because of use of Flolan at approximately day 76.
01:05/ 52006 ADR Vehicle	This was a 46-year old female with NYHA Class III and PPH. This subject received vehicle at a maximum dose of 3.75 ng/kg/min. This subject was admitted to a hospital due to a viral infection. The subject subsequently died. Day: 1/2 / 9 Six minute walk in meters: 296 / 269 Dyspnea fatigue index score: 3 / 3	Worst outcome by Analysis #1. This subject is classified as an ADR but is clearly a worst outcome secondary to death.
01:05/ 52008 ADR UT-15	This was a 37-year old female with a history of primary pulmonary hypertension and NYHA Class III status. The maximum dose of UT-15 was 2.5 ng/kg/min. UT-15 infusion was stopped after 47 days due to infusion site pain and the subject was immediately started on Flolan. Day: 2 / 9 Six minute walk in meters: 260 / 273 Dyspnea fatigue index score: 2 / 2	Worst outcome by analysis #2. Flolan started within 100 day time window of study. Although an exercise test should have been scheduled at the time of discontinuation, none was performed. The subject was transplanted four months later (post window of study). A LOCF analysis clearly optimistically treats this subject's outcome
01:05/ 54011 ADR UT-15	This was a 54-year old female with a history of pulmonary hypertension and Eisenmengers syndrome. The maximum dose was titrated to 2.5 ng/kg/min but terminated infusion on approximately day 31. The subject was alive one-month post discontinuation. The subject did not receive Flolan. Day: 0 / 8/9 Six minute walk in meters: 288 / 235 Dyspnea fatigue index score: 3 / 6	Censored at day 31.
01:05/ 54012 ADR UT-15	This was a 62-year old female with a history of PPH and NYHA Class III status. The subject was stared on UT-15 and received a maximum dose of 2.5 ng/kg/min After approximately 1 week at this dose (day 16) the subject discontinued from the study due to infusion site pain. The subject started flolan "electively" five days later. Day: 1 / 9/10 Six minute walk in meters: 233 / 275 Dyspnea fatigue index score: 3 / 3	Worst outcome by analysis # 2. Due to inception of Flolan treatment.
01:05/ 54018 ADR UT-15	This was a 43-year old female with PPH and NYHA Class III. The subject received a maximum infusion rate of 3.75 ng/kg/min The subject discontinued on day 48 because of infusion site pain. Prior to final termination of UT-15, the subject was hospitalized to start Flolan infusion.	Worst outcome by analysis #2. Treated as worst outcome. Flolan started during course of study.

Study Subject Class[90] Arm	Description	Classification by reviewer
	Day 2 / 8/11 / 43/47 Six minute walk in meters: 335 / 380 / 325 Dyspnea fatigue index score: 3 / 11 / 6	
01:05/ 60005 WC UT-15	This was a 43 -year old female with primary pulmonary hypertension and NYHA Class III, who was discontinued from the study on day 38 of therapy with the final down titration on day 46 because of hemolytic anemia. The subject was alive 30 days later with no comment on whether this subject required inotropic or Flolan support during the on-going duration of study. Day: -2/0 / 8/9 / 44 / 87 Six minute walk in meters: 425 / 475 / 225 / 340 Dyspnea fatigue index score: 6 / 5 / — / —	Censored LOCF day 44 measurement.
01:05/ 60007 WC UT-15	This was 67-year old female with primary pulmonary hypertension and NYHA Class III status. The subject received UT-15 for a total of 16 days when she was requested withdrawal from the study. The subject was alive at 1-month post discontinuation. No information is supplied if the subject was alive at 100 days after the inception of therapy and whether the subject required inotropic or flolan support during the study duration Day: -1 / 9 Six minute walk in meters: 357 / 439 Dyspnea fatigue index score: 5 / 5	Censored LOCF. Poor follow-up, taking a more lenient position this subject was considered as censored in day 16

There were a total of 19 UT-15 subjects who discontinued due to ADRs these 18 had at least one post-baseline measurement. There were in addition two subjects who discontinued due to withdrawal of consent. One subject had no post-baseline measurement and nine subjects had no week 6 measurement. Values for these nine subjects were imputed for the 6-week visit.

Reviewer's analysis #1

This was similar to the pivotal analysis mITT population, using a non-parametric method. Those who died, or were transplanted during the 100-day window of the study were treated as a worse outcome. There were five such subjects in the database [#4503 (UT-15), #10507 (UT-15), #58001 (UT-15), #16006 (vehicle), #52006 (vehicle)]. One vehicle subject (#16006) although completed the study was unable to walk at final visit and was assigned a walking distance of 0 feet. The p-value for treating these patients as worst outcome is shown in Table 62. The p-values for the individual studies was > 0.1. The p-value for the pooled study was 0.02.

Table 62. Results of reviewer's analysis #1[91] (P01:04-05)

	P01:04	P01:05	Total
P-value	0.10	0.10	0.02

Reviewer's analysis #2

[91] Nominal p-values include deaths and transplantation within the 100-day, mITT cohort, non-parametric analysis.

This analysis treated those who died, received transplantation within 100 days or were started on Flolan within 1 month of discontinuation as worst outcomes. Those subjects who were treated with flolan within 30 days of discontinuation (the time of flolan inception) are [#54018 (before discontinuation of UT-15); #52008 (immediately upon discontinuation of UT-15); #54012 (5 days post UT-15); #2006 (2 weeks post UT-15); #2020 (1 month post UT-15); #19502 (1 month post UT-15)]. The p-values are shown below. To the extent that some of those who started on Flolan had not decompensated but were started on treatment due to no viable alternative to therapy, this analysis unduly penalizes active treatment.

Table 63. Results of reviewer's analysis #2[92] (P01:04-05)

	P01:04	P01:05	Total
P-value	0.23	0.22	0.08

The result of this analysis even suggests the pooled data is no longer statistically significant. Each of the individual studies is far from significant.

Reviewer's analysis # 3

This analysis treated those who died, received transplantation or received Flolan during the window of the study or whose course was clearly downhill were treated as worse outcomes. This includes patient [#2001 (6-weeks); #11002 (2 months)] ; #5009 (markedly worse dyspnea/fatigue index). In addition, subject # 2016 this subject had an LOCF value based on week 1 measurements that was increased over baseline by 208 meters, yet upon discontinuation on day 47, this patient had evidence of shortness of breath. The LOCF value clearly does not reflect the value at the end of the study. This subject's value should be censored with no LOCF. The results are shown below. To the extent that some of those who started on flolan had not decompensated but were started on treatment due to no viable alternative to therapy, this analysis unduly penalizes active treatment.

Table 64. Results of reviewer's analysis #3[93] (P01:04-05)

	P01:04	P01:05	Total
P-value	0.27	0.22	0.11

There are other subjects whose histories suggest a worse performance at the time of discontinuation but did not fit into the three categories that formed the three analyses. Additional analyses could incorporate these subjects as worse outcomes. There are also subjects who discontinued treatment during the time window appropriate for the six-week exercise test. The test, however, was not performed prior to discontinuation. There was one additional subject who was apparently lost to follow-up. The status of this subject during the 12-week study period is unclear. Treating all these subjects as worst outcomes could have been rationalized, further degrading any p-value estimate.

Bias from concurrent medication. There is a second set of biases that resulted from the asymmetry of infusion site pain. Subjects treated with UT-15 were more likely treated with opiate agonists, anti-inflammatory drugs or other medications than were vehicle subjects. It is not inconceivable that these medications may have hemodynamic

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[92] *Nominal p-values include deaths and transplantation within the 100-day window as well as those treated with Flolan within 30-days of discontinuation as worse outcome, mITT cohort, non-parametric analysis.*

[93] *Nominal p-values include patients who died or were transplanted as well as those treated with Flolan within the 100-day window, mITT cohort, non-parametric analysis.*

effects on their own. The sponsor has submitted the following analyses to answer the question of the independent effect of opiates and anti-inflammatory drugs.

Table 65. Effect of opiates and anti-inflammatory drugs on walking distance (P01:04-05)

		Type of Analysis			
		No imputation		Imputation	
		No Drug	Yes Drug	No Drug	Yes Drug
Opiates	N	148	53	168	64
	Mean±SE	23±5	1±8	3±8	-14±14
Anti-inflammatory	N	121	80	134	98
	Mean±SE	21±6	11±6	1±9	-7±10
Any pain medication	N	55	146	64	168
	Mean±SE	22±11	15±5	-11±16	2±7

Those who need pain medication, either opiates, anti-inflammatory or any generally performed better than those who required none for the no-imputation analysis. The process of imputation has a slightly lesser effect on the subjects who received pain medications. For example imputing data for those who did not complete the study decreased the estimated 6-minute walk distance for those with any pain medication by 33 meters. For those who received some sort of pain medication the imputed value dropped by only 13 meters. The variability of the measurements, however, makes any conclusion highly speculative. There is, therefore, no convincing evidence that pain medication alters the 6-minute walk distance.

Sponsor's analysis at week 1 and 6

The sponsor's analysis shows minimal additional increase in 6-minute walk for the UT-15 group after week 1. The vehicle group, however, shows a gradual decline in the 6-minute walk distance at weeks 6 and 12, but at all points appears to be no worse than baseline. The net-difference between UT-15 and vehicle over time shows a small increase in walk distance.

The dose of UT-15 during this period of time was 1.2 ng/kg/min at week 1, 5.9 ng/kg/min at week 6 and 9.2 ng/kg/min at the end of week 12. The initial dose was predicated on having minimal activity. It is therefore, somewhat surprising that despite a nearly 8-fold increase in dose, there was little additional benefit in walking distance. The splaying of the difference between treatment and vehicle may in part or in total reflect the process of imputation as oppose to a real effect on walking distance.

Table 66. Sponsor's analysis of 6-min walk at weeks 1-12 (P01:04-05)[94]

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Week 1	N	110	106	121	118	231	224
	Median	0	12	12	11	8	11
	25th-75th %ile	-17, 26	-9, 31	-9, 35	-9, 29	-12, 32	-9, 32
	P-value		0.22		0.86		0.27
Week 6	N	111	113	125	119	236	232
	Median	0	9	7	15	5	13
	25th-75th %ile	-38, 24	-20, 38	-23, 39	-21, 48	-29, 34	-20, 45
	P-value		0.16		0.14		0.03
Week 12	N	111	113	125	119	236	232
	Median	1	3	-3	16	0	10
	25th-75th %ile	-53, -31	-27, 67	-37, -35	-22, 37	-45, -33	-25, -48
	P-value		0.06		0.55		0.06

FDA statistician's analysis of time course

A linear mixed effect model was used as an exploratory analysis to define the treatment effects with respect to time dependent and disease etiology-dependent effects of treatment. The model assumes those who discontinued early, regardless of the reason, would have walked distances similar to those who completed. The model includes a quadratic term for time. Other parameters used in constructing the model include: treatment group, baseline distance walked, etiology, vasodilator use in the primary pulmonary hypertension subjects. The statistician's curves are shown in Figure 13.

This analysis shows all groups had an increase in walk distance at the 1-week (approximately day 7) measurement. There was a greater benefit initially among all subjects independent of disease etiology that was treated with UT-15 than vehicle. There was little alteration in effect at week 6 (approximately day 42). The major difference in outcome occurs at the end of the study measurement. The UT-15 group splays upward, the vehicle group splays downward. Since those who prematurely discontinued were presumed to maintain their rank at the last measurement, some component of the splay may be related to the asymmetry in discontinuations. There were nine subjects imputed values at week 6. Eighteen of the 19 subjects that had adverse event dropped out had values imputed for the week 12 measurement. The last subject #7004 who discontinued on day 25, nevertheless had a 12-week measurement performed off treatment. This value was used for this patient.

[94] *Derived from sponsor's table 11.4.1.1.4H; summary of change from baseline in six-minute walk test at Weeks 1, 6, and 12; non-parametric analysis of mITT group*

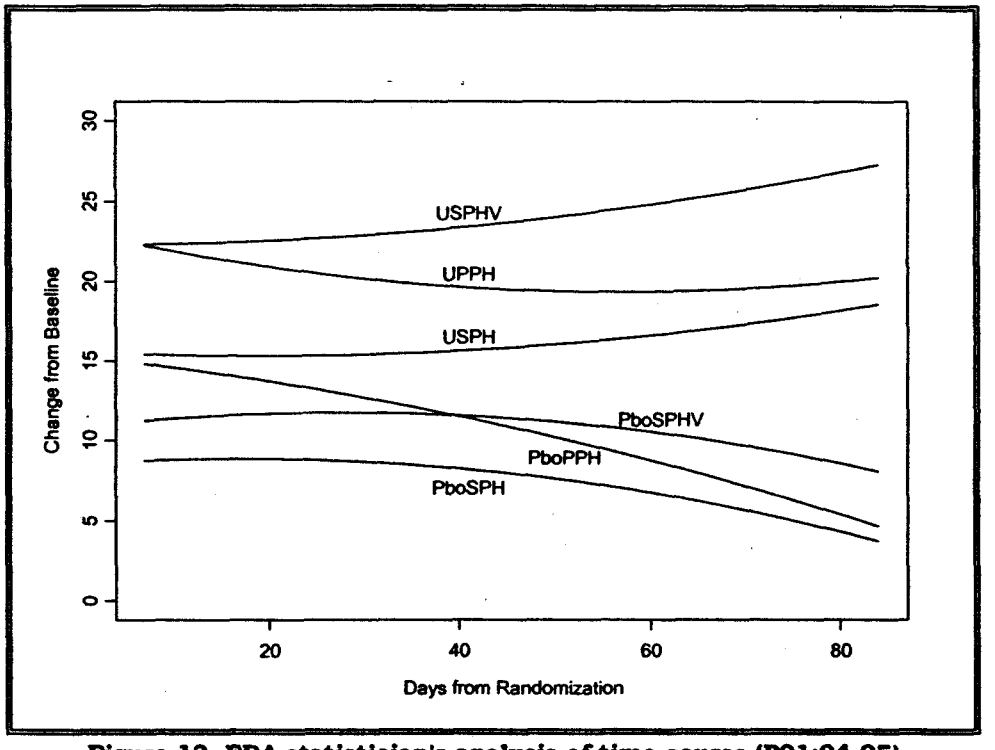

Figure 13. FDA statistician's analysis of time course (P01:04-05)

Fitted curves from linear mixed effects model at the average baseline value. USPHV=Uniprost, secondary PH, vasodilator use; VehiclePPH=Vehicle, PPH, etc.

Effect of baseline walking distance. The sponsor's Integrated Summary of Efficacy contains an analysis[95] suggestive that the effect of treatment with UT-15 was greater among subjects who were less able to walk at baseline. That analysis divided the population into quarters of the observed range of baseline walking distance (rather than quartiles of subjects). Estimates of the treatment effect in these subgroups are shown in Table 67.

Table 67. Treatment effect on walking distance by baseline distance (P01:04-05).

Baseline	UT15-Vehicle mean±SE	P-value
<150 m	51±16	0.0019
150 - 250 m	33±10	0.0005
250-350 m	16±7	0.03
>350 m	-2±12	0.87

As part of this review, the 416 subjects with both baseline and week 12 data (i.e., without imputation) were identified and the magnitude of treatment effect[96] was computed for successive blocks of 10 subjects, from the lowest baseline to the highest baseline value, using a moving bin technique. The results are shown in Figure 14.

[95] *Sponsor's Integrated Summary of Efficacy, Table 8.7.7B on page 140.*

[96] *{Dist(UT-15, Week 12) - Dist(UT-15, Baseline) } - { Dist(Veh, Week 12) - Dist(Veh, Baseline) }*

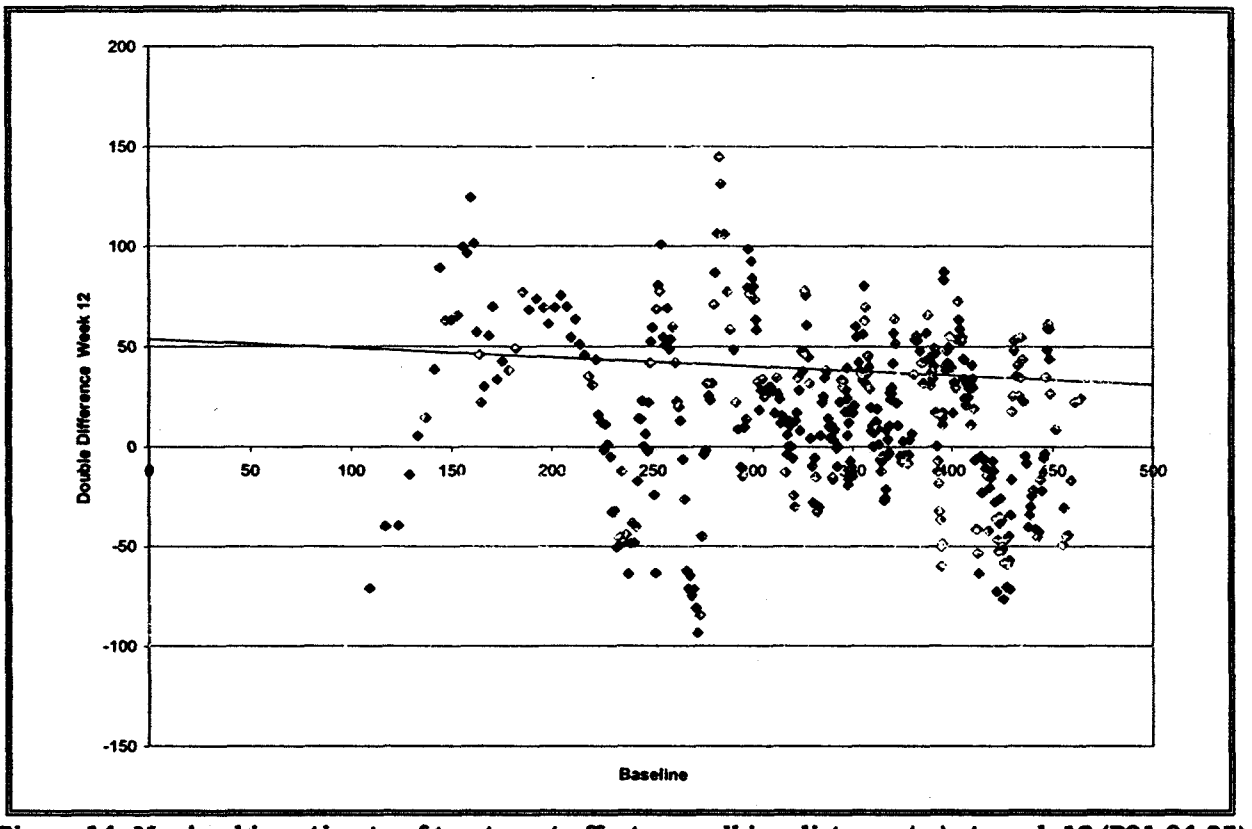

Figure 14. Moving-bin estimate of treatment effect on walking distance (m) at week 12 (P01:04-05)

Analysis described in text. The line is a linear least-sqaures line fit using JMP. The fitted line has intercept 176±28 feet and slope -0.111±0.025 , both significantly different from zero ($p < 0.0001$). The correlation coefficient, r^2, was 0.05.

This analysis is weakly supportive that the treatment effect is larger in subjects with lower baseline walking distances.

A.4.4.7.2 Secondary outcome measures

Signs and symptoms of PAH.

Table 51 shows the 16 signs and symptoms that were assessed. Subjects may or may not have had abnormalities or they may not have been asked about that particular sign or symptom at baseline or at subsequent visits. Each of these signs and symptoms were graded as shown in Table 68.

Table 68. Grading of signs and symptoms (P01:04-05)

Sign/Symptom	Grades
Fatigue	+1 to + 4
Dyspnea	Mild to moderate exertional dyspnea Paroxysmal nocturnal dyspnea Increasing exertional dyspnea Nocturnal cough/ Dyspnea at rest
Orthopnea	1 pillow 2 pillows 3 pillows Bed on blocks Sleeps in chair
Jugular venous distention	0 to ≤ 6 cm > 6 cm
Edema	Feet and ankles Lower legs and thighs Sacrum
Syncope	Some of the time Most of the time All of the time
Dizziness	
Palpitations	
Chest pain	
Loud P2 sound	No grades
Third heart sound	
Fourth heart sound	
Right ventricular heave	
Systolic murmur	Grade 1-6
Diastolic murmur	
Herpatomegaly	0-3 below RCM > 3 and < 6 below RCM

Despite the grading system, the value of each symptom was collapsed into a single metric. A "+1" was assigned for any sign that was present at baseline but absent at 12-week evaluation, and "–1" for any sign that was absent at baseline but present at baseline and a "0" for each sign and symptom that was present or absent at both time points. The overall change in score was the sum of these values over all signs and symptoms, provided at least eight of these 16 signs were assessed both at baseline and follow up. Subjects who did not complete the study were censored at the time of discontinuation.

The specifics at baseline of the signs and symptoms of pulmonary hypertension are shown in Table 69. There were somewhat more subjects with right ventricular heave and edema in the vehicle group and more subjects with dizziness and palpitations in the UT-15 group.

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Table 69. Signs and symptoms at baseline (P01:04-05)[97]

	P01:04		P01:05		Pooled	
	Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Dyspnea	109 (98)	113 (100)	125 (100)	120 (100)	234 (99)	233 (100)
Loud P2	109 (98)	109 (97)	117 (94)	111 (93)	226 (96)	220 (94)
Fatigue	97 (87)	106 (94)	107 (86)	105 (88)	204 (96)	211 (91)
Systolic murmur	80 (72)	77 (68)	71 (57)	70 (58)	151 (64)	147 (63)
Right ventricular heave	83 (75)	79 (70)	63 (50)	53 (44)	146 (62)	132 (57)
Jugular venous distension	61 (55)	68 (60)	71 (57)	64 (53)	132 (56)	132 (57)
Dizziness	54 (49)	58 (51)	53 (42)	64 (53)	107 (45)	120 (52)
Palpitations	50 (45)	60 (53)	50 (40)	61 (51)	100 (42)	121 (52)
Edema	53 (48)	52 (44)	58 (46)	44 (37)	111 (47)	96 (41)
Chest pain	43 (39)	46 (41)	48 (39)	49 (41)	91 (39)	95 (41)
Orthopnea	35 (32)	44 (39)	38 (30)	32 (27)	73 (31)	76 (33)
Hepatomegaly	22 (20)	24 (21)	35 (28)	29 (24)	57 (24)	53 (23)
Fourth heart sound	36 (32)	34 (30)	24 (19)	20 (17)	60 (25)	54 (23)
Third heart sound	14 (13)	15 (13)	21 (17)	15 (13)	35 (15)	30 (13)
Diastolic murmur	18 (16)	14 (12)	11 (9)	12 (10)	29 (12)	29 (12)
Syncope	7 (6)	13 (12)	10 (8)	7 (6)	17 (7)	20 (9)

Nearly all subjects had had dyspnea, and fatigue as the most common symptom. A loud P2 sound was the most frequent sign. The groups were relatively well balanced, although right ventricular heave and edema were more frequent in the vehicle group. Dizziness and palpitations were more frequent in the UT-15 group.

Sponsor's analysis. There are no data submitted as to the average number of signs and symptoms per subject at baseline. Consequently, the change in baseline signs and symptoms of PAH cannot easily be understood. Scores could range from –16 for a subject that had symptoms at baseline for each component to –1 for someone who had only one symptom. The analysis presumes that subject's are balanced at baseline.

Table 70. Change in signs and symptoms score (P01:04-05)[98]

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Week 1	N	110	111	123	119	233	230
	Change	0.7±0.2	0.9±0.2	0.5±0.1	0.8±0.2	0.6±0.1	0.8±0.1
	P-value	0.72		0.19		0.25	
Week 6	N	107	107	120	109	227	216
	Change	0.4±0.2	1.2±0.2	0.3±0.2	0.8±0.2	0.3±0.1	1.0±
	P-value	0.02		0.12		0.005	
Week 12	N	103	97	114	104	217	201
	Change	-0.1±0.2	0.9±0.3	0.0±0.2	1.0±0.2	-0.1±0.2	0.9±0.2
	P-value	0.01		<0.001		<0.001	

The data above demonstrate a benefit in the treatment group relative to vehicle at week 6 and 12. A more careful view of the data show that the effect on symptoms for the UT-15 group shows that maximal effect was seen at week1. The attainment of statistical significance more reflects deterioration in the relative status of the vehicle group.

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[97] *Data from sponsor's table 11.2.2.5.*

[98] *mITT group; from sponsor's table 11.4.1.2.1A.*

Comment. The data first should be interpreted in the context of who assigned values. In this case the treating physician based on interviews with the subject completed the dyspnea-fatigue index. It is this reviewer's impression that the treating physician was likely aware as to the treatment group based on the presence of severe infusion site pain. The assignment of values is likely to be subjectively confounded by knowledge of therapy.

There are several ways to interpret the above study. The sponsor's analysis would suggest that there is a persistent benefit to UT-15 therapy. There was however, a large drop out preferentially in the UT-15 group. An alternative interpretation to the data would be that there was a differential dropout was due to worsening in signs and symptoms in that population who discontinued. As a thought experiment, if the 33 subjects who were enrolled who did not contribute to the 12-week measurement had an average score of "–3 to -4", that is three or four of the sixteen metrics were worse at week 12 in these dropouts. The net effect would disappear. This sort of analysis is clearly an over correction since it assumes no vehicle subject including patients who died had such values imputed.

There is, therefore, probably some signal here; the magnitude, however, is unclear.

A shift table on the individual signs and symptoms that contributed to the dyspnea fatigue index is shown below. The symptoms that improved are dizziness, palpitations, chest pain and orthopnea. Of note there was no convincing benefit to the UT-15 for the three most common signs and symptoms of pulmonary hypertension i.e. dyspnea, fatigue and loud P2. Other metrics (See under Dyspnea-fatigue index and Borg index), however, appears compatible with an improvement in the most bothersome symptoms of pulmonary hypertension.

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Table 71. Subjects with baseline symptoms improved or worsened (P01:04-05)[99]

		Improved			Worsened		
		Veh	UT-15	P-value	Veh	UT-15	P-value
Dyspnea	Pooled	4 (2)	8 (3)	0.25	1 (0)	0 (0)	>0.99
	P01:04	0 (0)	1 (1)		1 (1)	0 (0)	
	P01:05	4 (3)	7 (6)		0 (0)	0 (0)	
Loud P2 sound	Pooled	5 (2)	7 (3)	0.56	8 (3)	7 (3)	>0.99
	P01:04	2 (2)	4 (4)		1 (1)	3 (3)	
	P01:05	3 (2)	3 (3)		7 (6)	4 (3)	
Fatigue	Pooled	12 (5)	17 (7)	0.25	12 (5)	5 (2)	0.14
	P01:04	5 (5)	9 (8)		4 (4)	2 (2)	
	P01:05	4 (6)	8 (7)		8 (6)	3 (3)	
Systolic murmur	Pooled	15 (6)	10 (4)	0.42	19 (8)	19 (8)	0.87
	P01:04	11 (6)	7 (6)		13 (12)	11 (11)	
	P01:05	3 (6)	3 (3)		6 (5)	8 (6)	
Right ventricular heave	Pooled	14 (6)	20 (9)	0.28	25 (11)	25 (11)	0.76
	P01:04	11 (10)	12 (11)		16 (14)	17 (15)	
	P01:05	3 (2)	8 (7)		9 (7)	8 (7)	
Jugular venous distension	Pooled	21 (9)	33 (14)	0.06	30 (13)	19 (8)	0.17
	P01:04	11 (10)	15 (13)		17 (15)	11 (10)	
	P01:05	10 (8)	18 (15)		13 (10.)	8 (7)	
Dizziness	Pooled	35 (15)	55 (24)	0.006	33 (14)	27 (12)	0.68
	P01:04	20 (18)	25 (22)		18 (16)	18 (16)	
	P01:05	15 (12)	30 (25)		15 (12)	9 (8)	
Palpitations	Pooled	25 (11)	46 (20)	0.003	22 (9)	27 (12)	0.36
	P01:04	10 (9)	21 (19)		9 (8)	13 (16)	
	P01:05	15 (12)	25 (21)		13 (10)	14 (12)	
Edema	Pooled	23 (10)	36 (16)	0.04	29 (12)	18 (8)	0.17
	P01:04	13 (12)	18 (16)		13 (12)	16 (14)	
	P01:05	10 (8)	18 (15)		16 (13)	2 (2)	
Chest Pain	Pooled	37 (16)	48 (21)	0.09	30 (13)	8 (3)	0.0005
	P01:04	15 (14)	26 (23)		15 (14)	5 (4)	
	P01:05	22 (18)	22 (18)		15 (11)	3 (3)	
Orthopnea	Pooled	14 (6)	29 (12)	0.01	30 (13)	17 (7)	0.09
	P01:04	7 (6)	19 (17)		16 (14.)	10 (9)	
	P01:05	7 (6)	10 (8)		14 (11)	7 (12)	
Hepatomegaly	Pooled	18 (8)	26 (11)	0.15	18 (8)	11 (5)	0.34
	P01:04	9 (8)	16 (14)		7 (6)	7 (6)	
	P01:05	9 (7)	10 (8)		11 (9)	4 (3)	
Fourth heart sound	Pooled	24 (10)	14 (6)	0.17	26 (11)	19 (8)	0.43
	P01:04	13 (11)	9 (8)		14 (13)	12 (11)	
	P01:05	11 (9)	5 (4)		12 (10)	7 (6)	
Third heart sound	Pooled	15 (6.)	7 (3)	0.19	12 (5)	12 (5)	>0.99
	P01:04	6 (5)	4 (4)		5 (5)	6 (5)	
	P01:05	9 (7)	3 (3)		7 (6)	6 (5)	
Diastolic murmur	Pooled	8 (3)	5 (2)	0.58	10 ()	4 (2)	0.18
	P01:04	6 (5)	4 (4)		5 (5)	2 (2)	
	P01:05	2 (2)	1 (1)		5 (4)	2 (2)	
Syncope	Pooled	10 (4)	15 (6)	0.30	7 (3)	1 (0)	0.07
	P01:04	4 (4)	8 (7)		2 (2)	1 (1)	
	P01:05	6 (5)	7 (6)		5 (4)	0 (0.)	

[99] Based on sponsor's Table 11.4.1.2.1C and 11.4.1.2.1D. P-value from Fisher's exact test. P-values not corrected for multiple comparisons.

The percentages of improved or worsened reflect those who improved relative to the total number of subjects at baseline. The true metric should be based on those with the symptom at baseline. Subjects who discontinued for adverse events were censored. The percentage for those that worsened could therefore be higher.

There are some suggestions from the data that UT-15 may alter some symptoms such as chest pain, palpitation, dizziness and edema. The more frequent and bothersome symptom of dyspnea and fatigue do not apparently change with UT-15 infusion. Some of the symptoms lack specificity in their description. Was the chest pain cardiac in nature? Others symptoms that improved may overlap and are therefore double-counted i.e. were palpitations and dizziness independent symptoms.

It is difficult to amalgamate the entirety of these symptoms into an overall benefit. No global question was asked "Are you feeling better or worse since you enrolled?". The sponsor's attempted to conglomerate the sum of the symptoms by summing all better or worse outcomes for the 16 symptoms. This analysis weighs all symptoms the equivalently. There are clearly more pertinent and disease related symptoms than others. In particular, dyspnea and fatigue were apparently not altered.

Some additional comments are appropriate. Week 12 data were predicated on censoring of subjects. The fact that subjects who discontinued did not have their symptoms assessed, biases the results towards UT-15 in allowing fewer subjects to potentially worsen. Conversely, it biases against improvement since fewer subjects are potentially available for improvement. This analysis assumes that any negative effect on symptoms at the time of discontinuation was not pertinent to the decision to discontinue. This is clearly an invalidated assumption.

There are clearly additional problems with this set of data. The physician, who was aware of the presence and intensity of infusion-site pain, completed the symptom assessment. Since infusion pain was so much more common in the treatment group, there may have been subtle bias in the assessment of this pain.

The overall pattern of symptom benefit is perplexing. If the mechanism of action of UT-15 is to decrease pulmonary artery resistance and pulmonary artery pressures, the particular benefit should be on hepatomegaly, ascites and edema. In fact more subjects on UT-15 reported edema as an adverse event than vehicle subjects (9% versus 3%). If the drug were particularly effective, then dyspnea and fatigue should also be affected. None of these parameters were convincingly altered.

On the other hand it is unclear how mechanistically one would interpret a benefit on orthopnea. This symptom would in general be attributed to left-sided cardiac failure. Since those who enrolled were precluded from having left-sided cardiac disease, the origin of the orthopnea is unclear, consequently, the mechanism of benefit is unclear. The effect on chest pain could reflect a decrease on right-sided ischemia, but the description of chest pain is unclear

There was a clear imbalance in the use of pain medications. More UT-15 subjects, because of infusion site pain, were taking opiates and/ or anti-inflammatory drugs than vehicle subjects. The sponsor compared the effect on symptoms of those who were treated with opiates to those who were not so treated. The sponsor found no statistical difference between those who were treated with opiates and those who were not. Any effect of opiate antagonists on signs and symptoms may exist but is small.

Dyspnea Fatigue Index

The dyspnea fatigue rating scale consists of three categories of performance (see Table 1.7). The metrics defines the magnitude of the task, the magnitude of the pace and the functional impairment of the subject. Each category contains 5 possible values that ranging from 4 to 0, with 4 indicating minimal compromise and 0 severe compromise.

The treating physician based on the subject's report completed the dyspnea-fatigue questionnaire.

The analysis below is based on only the actual data. There was no imputation of values for those who discontinued for death, deterioration or transplant. Missing values for those who discontinued for adverse events were also not imputed.

Table 72. Change in dyspnea-fatigue index (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Baseline		4.7±2.0	4.3±2.0	4.2±2.0	4.2±1.9	4.4±2.0	4.3±1.9
Week 1	N	110	111	123	118	233	229
	Change	0.1±1.4	0.2±1.6	-0.1±0.9	0.2±1.0	0.0±1.1	0.2±1.2
	P-value	0.4		0.01		0.02	
Week 6	N	107	108	120	110	227	218
	Change	0.1±1.8	0.9±1.9	0.3±1.5	0.7±1.7	0.2±1.6	0.8±1.8
	P-value	0.002		0.02		0.0001	
Week 12	N	102	97	114	104	216	97
	Change	-0.2±2.1	0.8±1.8	-0.1±1.6	1.3±2.0	-0.1±1.8	0.8±1.8
	P-value	0.002		<0.0001		<0.0001	

The effect of UT-15 on the components of the Dyspnea-Fatigue rating for the pooled data base show an improvement in all three categories, i.e. magnitude of the task, magnitude of the pace and functional impairment, as shown in Table 73.

Table 73. Effect of treatment on components of the dyspnea fatigue index (P01:04-05)

	Level	Baseline		Week 12	
		Veh N=236	UT-15 N=233	Veh N=216	UT-15 N=201
Magnitude of task	0	8	10	11	6
	1	109	111	96	48
	2	107	105	92	112
	3	10	7	15	34
	4	2	0	2	1
	Average	1.53	1.47	1.54	1.88
Magnitude of pace	0	10	8	10	5
	1	103	119	99	50
	2	109	92	88	108
	3	12	14	18	38
	4	2	0	1	0
	Average	1.55	1.48	1.54	1.89
Functional impairment	0	43	46	47	21
	1	90	88	78	59
	2	84	83	74	86
	3	16	15	15	33
	4	3	1	2	2
	Average	1.35	1.30	1.29	1.68

The pooled data indicate that there is an improvement of approximately 0.38-0.41 units for each of the components of the dyspnea fatigue index for the treatment group. For the vehicle group there was minimal effect on the magnitude of task and magnitude of pace of task, there was, however some deterioration in the functional impairment in the vehicle group. The results would suggest approximately 1/3 of the subjects had a unit change in each of the components.

There were more subjects who discontinued in the UT-15 group than in the vehicle group. Assuming all such subjects received a "0" for each component, and the vehicle subjects who discontinued were censored, the magnitude of the effect would be only 0.18 units for the sum of the three components of the metric.

Quality of life

The Quality of Life (QOL) questionnaire was administered at baseline, week 6 and end of week 12. The specifics of the QOL questionnaire are shown in Section A.4.3.8 which begins on page 89. The QOL is divided into four components. The sponsor's chooses to analyze only three of these components. The questionnaire was not validated for a pulmonary hypertension population.

In this study the population for which data was available was a truncated population. At baseline only 371 of the 469 enrolled subjects had available data. At the 12-week time, the number of subjects was only 325. Not all subjects who completed the study were queried with respect to this questionnaire. Those who discontinued for adverse events as well as those who died, deteriorated or were transplanted were also not analyzed. The global QOL was no different between treatments. Only the physical dimension at the 12-week time study point nominally differed between the two treatments, as shown in Table 74.

Table 74. Quality of life assessments (P01:04-05)[100]

			P01:04		P01:05		Pooled	
			Veh	UT-15	Veh	UT-15	Veh	UT-15
Global	Baseline	N	71	76	113	111	184	187
		Mean±SE	56.5±2.6	54.9±2.6	53.4±2.0	52.7±2.0	54.6±1.6	53.6±1.6
	Week 6	N	67	69	112	93	179	162
		Change	-5.1±2.1	-3.7±2.7	-5.8±1.6	-6.9±1.9	-5.5±1.3	-5.5±1.6
	Week 12	N	69	65	104	92	173	157
		Change	-1.2±2.3	-5.0±2.5	-2.9±1.9	-7.7±2.1	-1.9±1.4	-6.6±1.6
Physical	Baseline	N	71	76	113	111	184	187
		Mean±SE	25.6±1.1	25.5±1.1	25.2±0.9	24.4±0.8	25.4±0.7	24.9±0.7
	Week 6	N	67	69	112	93	179	162
		Change	-2.9±1.0	-3.5±1.2	-2.5±0.8	-3.7±0.8	-2.6±0.6	-3.6±0.7
	Week 12	N	69	65	104	92	173	157
		Change	-1.4±1.1	-4.3±1.2	-2.2±0.9	-4.7±0.9	-1.9±1.4	-4.5±0.7
Emotional	Baseline	N	71	76	113	111	184	187
		Mean±SE	13.5±0.8	12.8±0.9	11.4±0.7	11.6±0.7	12.2±0.5	12.1±0.6
	Week 6	N	67	69	112	93	179	162
		Change	-1.5±0.7	-0.5±0.9	-1.5±0.5	-1.9±0.6	-1.5±0.4	-1.3±0.5
	Week 12	N	69	65	104	92	173	157
		Change	-0.8±0.7	-1.1±0.7	-0.2±0.6	-1.5±0.6	-0.3±0.5	-1.3±0.5

Borg Dyspnea Score

This metric was not part of the pivotal measurements. The Borg-Dyspnea scale was administered immediately after each of the exercise tests. The instructions are described on page 94.

[100] *Mean ± SE; from sponsor listing 14.2.9.2A-C.*

Table 75. Borg Dyspnea score (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Baseline	N	111	113	123	119	234	232
	Mean±SE	4.3±0.2	4.4±0.2	4.4±0.2	4.2±0.2	4.4±0.2	4.4±0.2
Week 1	N	106	105	118	116	226	221
	Change	-0.2±0.2	-0.4±0.1	0.1±0.2	-0.1±0.1	-0.1±0.1	-0.3±0.1
Week 6	N	106	104	113	109	219	213
	Change	0.1±0.2	-0.9±0.2	-0.1±0.2	-0.5±0.2	-0.2±0.1	-0.7±0.1
Week 12	N	99	97	108	103	207	200
	Change	0.0±0.2	-0.9±0.2	-0.2±0.2	-1.0±0.2	-0.1±0.1	-0.9±0.1

The comparison of the treatment groups at 12 weeks had a nominal p-value < 0.01 for the individual studies and the pooled studies. There was a benefit in Borg dyspnea scale. The pooled study shows a decrease in subjective symptoms of approximately 0.81 units.

Hemodynamics

Hemodynamic parameters were collected at baseline and at end of study. Table 76 lists the baseline value as well as the change from baseline for hemodynamic parameters for the pooled studies. The individual studies are not shown but are substantially in the same direction. A scatter plot of baseline versus end of study for all hemodynamic parameters is shown as Figure 15.

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