Table 76. Hemodynamic results (P01:04-05)[101]

		Baseline		Week 12 change		
		Veh	UT-15	Veh	UT-15	P-val
Heart rate bpm	N mean±SE	234 82±1	228 82±1	215 -1±1	198 -1±1	0.5
Right atrial pressure mmHg	N mean±SE	231 10±0.4	228 10±0.4	211 1.4±0.3	195 -0.5±0.4	<0.001
Cardiac index L/min/m²	N mean±SE	232 2.2±0.05	225 2.4±0.06	209 -0.1±0.04	194 0.1±0.04	<0.001
Stroke index L/beat/m²	N mean±SE	231 28±0.7	222 30±0.9	208 -0.6±0.5	193 1.8±0.6	<0.001
Pulmonary systolic mmHg	N mean±SE	235 95±1.5	231 96±1.6	215 0.3±0.9	199 -2.7±0.8	0.02
Pulmonary diastolic mmHg	N mean±SE	235 40±0.8	231 43±1.0	215 0.6±0.6	199 -2.2±0.6	0.002
Pulmonary mean mmHg	N mean±SE	235 60±1.0	231 62±1.2	215 0.7±0.6	199 -2.3±0.5	<0.001
Pulm vasc resis index mmHg/L/min/m²	N mean±SE	203 25±0.9	204 27±1.0	187 1.2±0.6	163 -3.5±0.6	<0.001
Pulmonary cap wedge mmHg	N mean±SE	225 9.3±0.2	217 9.5±0.2	199 0.9±0.4	175 -0.1±0.3	0.08
Systemic systolic mmHg	N mean±SE	234 121±1.3	230 119±1.1	214 -0.4±0.8	198 -2.3±1.1	0.08
Systemic diastolic mmHg	N mean±SE	234 74±0.8	230 72±0.9	214 -0.4±0.1	198 -1.8±0.9	0.06
Systemic mean mmHg	N mean±SE	234 91±0.9	229 90±0.9	211 -1.0±0.9	197 -1.7±0.9	0.1
Syst vasc resis index mmHg/L/min/m²	N mean±SE	219 39±1.0	211 38±1.1	190 -0.8±0.9	175 -3.5±1.0	0.3
Mixed venous oxygen %	N mean±SE	215 60±0.8	215 62±0.7	182 -1.4±0.7	181 2.0±0.8	<0.001
Respiration rate min⁻¹	N mean±SE	227 19±0.3	225 19±0.3	205 -0.4±0.3	194 -0.6±0.3	<0.2

The table indicates that for this truncated population (i.e. completers), there were modest decreases in right atrial pressures, pulmonary artery pressures (mean, systolic and diastolic) and pulmonary vascular resistance. Cardiac index, stroke index and mixed venous oxygenation were increased.

[101] *The p-value is based on the treatment effect of the ANCOVA with baseline and treatment as the covariates.*

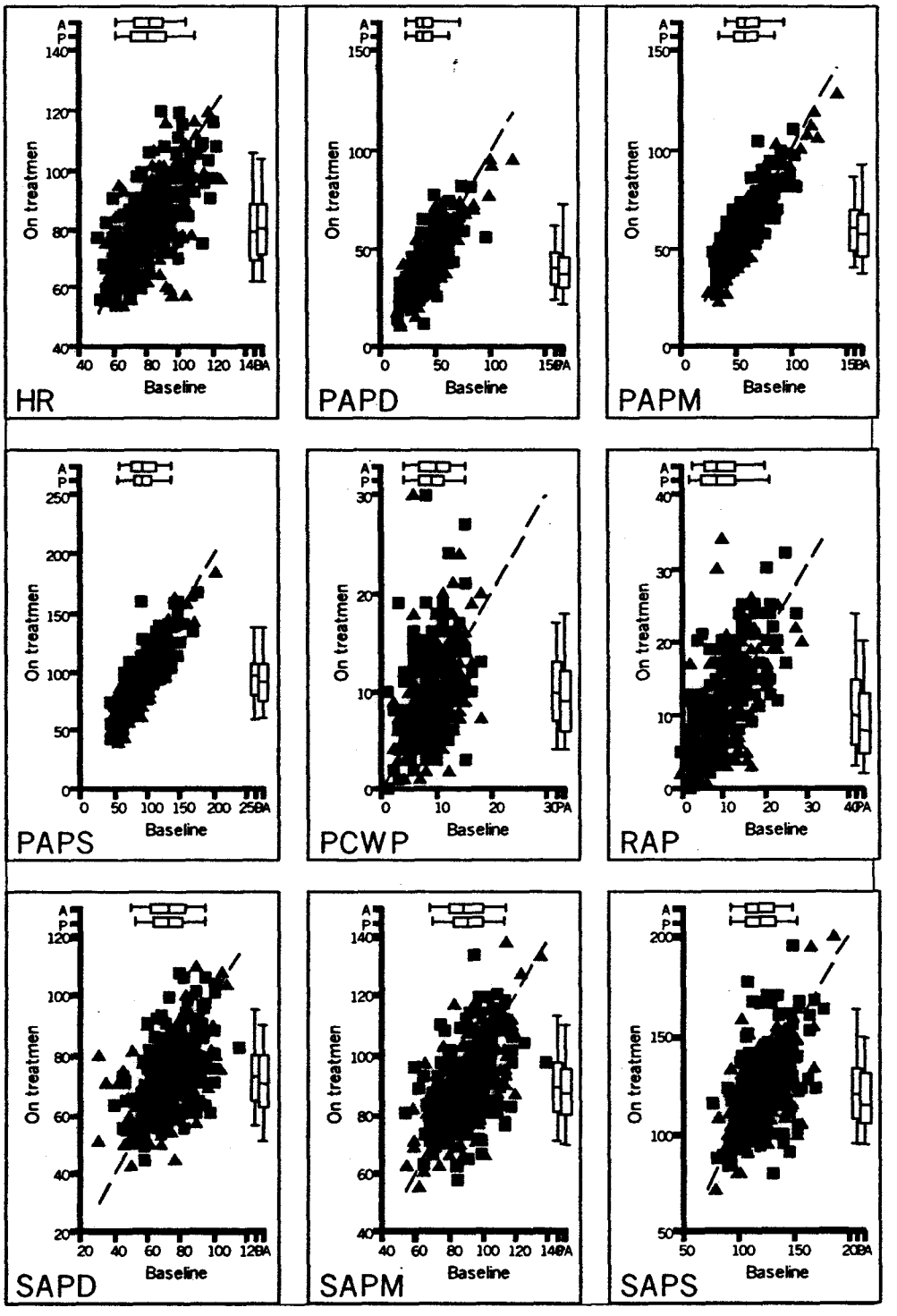

Figure 15. Hemodynamics scatter plots (P01:04-05)

Reviewers' analysis. Baseline and week-12 hemodynamic data are plotted for subjects on vehicle (P, square) and UT-15 (A, triangle). Marginal box-and-whiskers plots compare the distributions in the treatment groups at baseline and at 12 week.s. Panes are (HR) heart rate, (PAPD) pulmonary artery diastolic pressure, (PAPM) pulmonary artery mean pressure, (PAPS) pulmonary artery systolic pressure, (PCWP) pulmonary capillary wedge pressure, (RAP) right atrial pressure, (SAPD) systemic diastolic pressure, (SAPM) systemic mean pressure, and (SAPS) systemic systolic pressure.

The effect on hemodynamics, though statistically significant is in general small and of uncertain consequence. For cardiac index the net change (assuming that the data for those measured is consistent with the whole group) there was a net increase of 7.6%. There was an approximately 5% (3 mm Hg) decrease in mean pulmonary artery pressure. There was an approximately 18% decrease in pulmonary vascular resistance.

The sponsor was requested to analyze whether there was a correlation between hemodynamics (change in and % change in CI, PVR or PAPm) and walking distance, dyspnea fatigue rating or Borg-score. Among these 18 analyses only the correlation between PVR and walk distance was nominally significant (by Spearman-Rank correlation). Change in mixed venous oxygenation was correlated with walk and dyspnea fatigue index. The % change in mixed venous oxygenation was correlated with walk distance and dyspnea-fatigue index.

Oxygen saturation

Although prespecified as a secondary end-point, this metric was not measured. In fact it did not appear that this metric was collected. With the exception of those who were on oxygen, during catheterization, no oxygen saturation data was captured.

Other end points

The following end points are often considered in drugs for use in subjects with CHF due to left-sided systolic dysfunction. The outcomes would be reasonable to consider for subjects with pulmonary hypertension. They were not pre-specified as end-points for these studies.

Mortality

There did not appear to be a signal that mortality was altered by UT-15. There were a total of 19 subject who died during the course of the study. Nine in the UT-15 and ten in the vehicle group. Death occurred on treatment day (mean + SD) 42 $\pm$ 26 for UT-15 and on day 49 $\pm$ 35 for vehicle.

Of these deaths, six UT-15 (#4017, #9006, #10002, #23002, #51007, and #55005) and seven vehicle (#9012, #10001, #15003, #16003, #60006, #60015 and #65004) were listed as deaths. Four subjects, two in the UT-15 (subjects #54005 and #58001) and one vehicle subject (#65011) were listed as having deteriorated, these subjects died after the assessment of deterioration. There were two subjects, one UT-15 (#4503) and one vehicle (#52006) subject who were listed as adverse events who died. One subject in the vehicle group (#16006) was listed as having completed (the subject had the last cardiac catheterization) but died during the hospitalization.

Hospitalizations

This data was culled from Table 14.3.4.1, p 5609. That section of the submission contained narratives of all serious adverse events. These narratives should have captured all hospitalizations. There was no difference in the number of subjects hospitalized in comparing UT-15 to vehicle. There were 40 vehicle subjects and 38 UT-15 subjects who were hospitalized or had their duration of hospitalization increased. Capsular summaries for those hospitalized are available under safety. Two of the vehicle subjects who were hospitalized had actually inadvertently received UT-15 at the time of event that caused hospitalization.

With respect to the number of subjects who were hospitalized for cardiovascular events or worsening of pulmonary hypertension, any analysis would be highly subjective. This reviewer, however, counted those who died or appeared to be hospitalized for cardiovascular diseases as 25 in the vehicle group and 22 in the UT-15 group. Check marks next to the number in Table 82 on page 138 reflect this reviewer's judgement as to what was considered as a cardiovascular event.

Need for medication changes

With respect to subjects who required either pressor support or flolan, this reviewer counted 12 UT-15 subjects and 13 vehicle subjects who required pressors or flolan during the course of the study. Among those who were treated with pressors three vehicle subjects and no UT-15 subjects received flolan early on (day 2) of treatment for short duration (1 day). It seems that flolan in these subjects was used as a provocative test for pulmonary vascular responsiveness and not to treat worsening of status. Excluding these three subjects suggest 12 UT-15 and 10 vehicle subjects required inotropic or prostaglandin support during the study. There did not appear to be any differences in the need of pressors or flolan or pressors among the two treatments.

This reviewer also explored the need or increase of medications used for pulmonary hypertension. The data was contained in sponsor's Listing 16.2.4.7 of the NDA. This was not a pre-specified analysis, but has been used as support of medications that have been approved for the treatment of left-sided failure. Since this reviewer tabulated the data by hand and not by querying the database, the analysis is only be considered an approximation.

The metric used was the number of subjects who received treatment with an additional drug used to treat pulmonary hypertension or had one of these ongoing medications increased at the end of treatment relative to baseline. The drug classes that were considered in this analysis were those that might be increased in subjects whose pulmonary hypertension status was worsening. The drugs included loop diuretics, calcium channel blockers, vasodilators (including hydralazine, clonidine, nitrates), ACE inhibitors or angiotensin II blockers, oxygen, flolan, pressors, steroids, digoxin, aldactone or non-loop diuretics. Topical steroids used for the treatment of infusion site pain were not included in the sponsor's listing but captured in a subsequent listing 16.2.4.8. These topical steroids were not included in this count. This reviewer also did not consider changes in antithrombotics (e.g. coumadin and its derivatives, heparin) or antiplatelet drugs (e.g. ticlopidine) as a reflection of worsening disease but rather as responses to changing INR.

Based on this analysis, there were 165/233 subjects (70.8%) of those in the UT-15 group and 163/266 (69.1%) of the vehicle group who did not receive new medications and did not have baseline medications increased in doses (these patients could have medications changed i.e. decreased but were not counted). There did not appear to be an overwhelming signal that subject's status was sufficiently altered to require less concurrent medications.

Concomitant medications by class of drug, at the end of study and at screening are shown in table below (derived from sponsor's Table 11.2.2.12 and 11.4.5). There were slight increases in the number of subjects treated with each category of drug for both treatments. There were far more subjects treated with anticoagulants at the end of the study than at baseline-screening. Other classes of drugs were only slightly increased over baseline. There were more subjects on vehicle versus UT-15 subjects taking diuretics at the end of the study relative to baseline (28 versus 20), calcium channel blockers (4 versus 3), other vasodilators (0 versus 6) and digoxin (11 versus 9).

Table 77. Medication changes (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
Anticoagulants	Baseline	58 (52)	61 (54)	88 (82)	88 (73)	160 (68)	149 (64)
	Treatment	94 (85)	95 (84)	116 (92)	104 (87)	210 (89)	199 (85)
Calcium channel blockers	Baseline	50 (45)	49 (43)	48 (38)	48 (40)	98 (42)	97 (42)
	Treatment	52 (49)	50 (44)	49 (39)	51 (43)	101 (43)	101 (43)
Other vasodilators	Baseline	19 (17)	18 (16)	16 (13)	15 913)	35 (15	33 (14)
	Treatment	24 (22)	18 (16)	17 (14)	15 (13)	41 (17)	33 (14
Digoxin	Baseline	30 (27)	34 (30)	29 (23)	22 (18)	59 (25)	56 (24)
	Treatment	35 (32)	41 (36)	33 (26)	26 (22)	68 (29)	67 (29)
Diuretics	Baseline	54 (49)	69 (61)	75 (60)	57 (56)	129 (55)	136 (58)
	Treatment	71 (64)	82 (73)	86 (68)	74 (62)	157 (66)	156 (67)

Change in NYHA classification

This parameter was not measured after baseline. No change in subject NYHA status was available.

Dose response

There was no formal dose-response data available. Since subjects were forced titrated based on symptom improvement as well as tolerance to drug, any dose-related data is confounded by duration of time in the study. Dose response data could theoretically be defined by the walking effect at a given infusion rate of drug.

The relationship of infusion rate and walking distance at week 12 is shown in Figure 16. Both vehicle (P) and UT-15 (A) have positive non-zero slope effects. The intercepts of the two drugs differ. The intercept for vehicle is negative and significantly different from baseline.

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Figure 16. Change from baseline in walking distance (feet) by dose (studies P01:04, P01:05).
P=Vehicle; A=active treatment. Data derived from datasets for both studies combined, tables RANDCODE, WALK, and ODRUG. Horizontal line marks no change from baseline.

The data from the figure above were fitted to a straight line (linear least squares procedure) using JMP. The resulting fitted parameters and their confidence limits are shown in Table 78.

Table 78. Fit of change in walking distance (feet) by dose to y=m*DOSE+b.

	m±SD	P(m≠0)	b±SD	P(b≠0)
Vehicle	5.5±2.7	0.04	-106±52	0.04
UT-15	8.5±2.9	0.003	-28±30	0.4

Subgroup analysis based on baseline status

Dr. Lawrence, the FDA statistician analyzed the time-dependent effect of the various cohorts that were enrolled in this study .A linear mixed-effect model was used here as an exploratory analysis in order to see the treatment effect over time. This model assumes that those subjects who discontinued early, regardless of the reason for discontinuation, would have walking distances similar to those subjects who completed the study. Missing data can be predicted based on the performance of other subjects that have similar characteristics to the one with missing data.

Since each subject would theoretically have three measurements post-baseline, Dr Lawrence modeled the change from baseline as a quadratic function of time. The specific linear model that was used contained fixed-effects for treatment group, baseline distance walked, etiology, vasodilator use among secondary PH subjects, and time as a quadratic function. In addition, all two-way interactions between treatment group and the other variables as well as the two-way interactions between stratification (etiology/

vasodilator use) and time were included in the model. There were random effects for the intercept, slope, and the quadratic term for time. The strategy was to specify a complex model and let the data decide which terms were important. The curves for each stratification level at the average baseline walking distance are shown in Figure 13 on page 119.

From Figure 13, it appears that at Week 1, subjects in all strata in the vehicle group improved walking distance by an average of about 10 meters. Over the course of the trial, there was a gradual deterioration in the performance of all subjects, independent of origin. In the UT-15 group, the change at Week 1 was about 15 m in the SPH (no vasodilator) subgroup and about 20 m in the other two subgroups, but over the course of the trial, the improvement was maintained or increased slightly.

Kinetics

Pharmacokinetic measurements were collected on Days 2, week 1, week 6 and week 12. The kinetic data was not attached to this study report but was submitted separately as a biopharmaceutical report.

Tolerance

There is no information submitted that any effect of UT-15 lasts more than the 12-week duration of this study. No randomized withdrawal information of the study was performed to convincingly demonstrate a persistent drug effect. The concern that there may be tolerance arises from the large increase in dose of UT-15 in going from week 1 to week 6 or week 12 and the minimal change in walking distances over these dose increases. The doses are graphically displayed in Figure 12 on page 90. There were a greater than 4-fold increase in dose in going from the end of week1 1.2 ng/kg/min to week 6 (5.9 ng/kg/min). There was minimal change, however, in walking distance during the same period of time.

There does not appear to be adequate information available from pre-clinical, animal and biopharm data to rule out a potential of diminishing effect of long duration of UT-15 treatment. Mechanism of tolerance may include

- A decrease in the availability after long duration of infusion i.e. fibrosis at the infusion site may limit availability. Because infusion sites were rotated frequently, this is not likely.
- Metabolites may be produced that act in a counter-regulatory manner to the effect of UT-15 (the metabolic profile as well as the half-life of the known metabolites as well as the potential for the existence of uncharacterized metabolites remain a possibility.
- Down regulation of receptors or de-linking of receptors from regulatory proteins may have occurred.

A.4.4.8 Safety

A.4.4.8.1 Exposure

There were a total of 469 subjects who were randomized and received at least one dose of drug/vehicle. The mean (±SD) duration of exposure for those treated with UT-15 was 81.06 ± 17.1 days and for vehicle it was 82.83 ± 14.1 Days. There were 31 UT-15 and 16 vehicle subjects who were treated for less than 72 days (the lower limit of the window for the 12-week visit). Subjects were exposed to UT-15 for a total of 18,887 subject x days (51.75 subject x years) and to vehicle for 19,547 subject x days (53.55 subject x years). Exposure to vehicle was therefore 3.5% greater than that of UT-15 The mean dose of UT-15/vehicle are shown in Figure 12 on page 103.

The distribution of infusion rates for UT-15 and vehicle subjects are shown in Table 79. Approximately 50% of those treated with vehicle received doses of >20 ng/kg/min. For the UT-15 treated subjects the median dose was 9.3 ng/kg/min.

Table 79. Distribution of doses by week (P01:04-05)

Dose µg/kgmin	Week 1		Week 4		Week 8		Week 12	
	Veh N=231	UT-15 N=233	Veh N=228	UT-15 N=227	Veh N=221	UT-15 N=209	Veh N=217	UT-15 N=202
0 to 2.5	244	233	12	58	0	21	0	16
2.5 to 5.0	6	—	56	100	9	51	6	37
5.0 to 10	1	—	160	69	26	81	14	75
10 to 20	—	—	—	—	186	56	88	64
>20	—	—	—	—	—	—	109	10

More vehicle subjects were titrated upward and more UT-15 subjects were down titrated during the course of the study (Table 80). It should be noted that when doses were decreased, the usual reason was for either infusion site pain/reaction. There was no fixed dose decrease that was to occur in response to infusion site pain supervened. Trivial dose changes were often implemented as a consequence of infusion site pain. The reasons for dose decreases are shown in Table 81.

Table 80. Increases and decreases in dose (P01:04-05)[102]

	One or more increase		One or more decrease	
	Vehicle	UT-15	Vehicle	UT-15
Week 1-4	230	224	15	58
Week 5-8	226	203	19	70
Week 9-12	212	173	8	35

Table 81. Reasons for dose decreases (P01:04-05)

	Veh	UT-15		Veh	UT-15
Infusion site pain	1 (<1)	64 (27)	Headache	1 (<1)	9 (4)
Infusion site reaction	0 (0)	31 (13)	Vasodilation	0 (0)	9 (4)
Nausea	1 (<1)	11 (13)	Diarrhea	0 (0)	6 (3)
Pain	0 (0)	9 (4)	Vomiting	1 (<1)	6 (3)

Of the treated subjects who had dose reduction, 57 of the 64 UT-15 subjects with infusion site pain and 26 of the 31 subjects with infusion site reaction. For UT-15 infusion site pain and infusion site reaction were first noted at doses of 0- <2.5 ng/kg/min. Only six subjects had the onset of pain and 4 subjects with infusion site reaction had the onset of symptoms at doses > 2.5 ng/kg/min.

Approximately 65% of those treated with UT-15 complained of infusion site pain by the end of the first week of treatment. The percentage increased to approximately 90% complained of pain by the end of week 3. Nearly all subjects had infusion site pain by the end of week 12.

The fraction of subjects treated with opiates by the end of week 1 was 4%. This fraction increased to approximately 12% by the end of week 3 and 28% by the end of the study. The fraction of subjects treated with anti-inflammatory drugs was 16% at the end of week 1and increased to 28% at the end of week 3 and 44 % by the end of the 12-week

[102] *Sponsor's Table 12.1.2A*

study. The fraction of UT-15 who received either opiates opr anti-inflammatory drugs was 16% by the end of week 1, 32% by the end of week 3 and 52% by the end of the study.

It is, however, unclear whether the need for pain medication was continuous and therefore a necessary component of treatment or the pain medication as taken only on a PRN basis and therefore only an intermittent nuisance. Based on discussions with the sponsor, patients were offered a prescription and compliance and use of the pain medication was not further followed.

A.4.4.8.2 Deaths

There were a total of 19 deaths in or around the study. Nine of these deaths in people randomized to UT-15 and ten to vehicle. Subjects who died were: # 04/4017; #05/4503; #04/9006; #04/10002; #04/23002; #05/51007; #05/54005; #05/55005; and #05/58001 in the UT-15 group and 04/9012; #04/10001; #04/15003; #04/16003; #04/16006; #05/52006; #05/60006; #05/60015; #05/65004; #05/65011 in the vehicle group. The underlined subjects discontinued for reasons other than death but died during the 12-week window of the study. Capsular summaries are available in Table 82 below which contains the list of all subjects hospitalized.

A.4.4.8.3 Dropouts/discontinuations

There were 20 dropouts for adverse events or withdrawal of consent in the UT-15 group. One additional subject #4503 was listed as a dropout but died of sepsis.

A.4.4.8.4 Hospitalizations or prolongation of hospitalization:

There were 38 and 40 subjects, randomized to UT-15 and vehicle, respectively who were either hospitalized or whose hospitalization was prolonged. Two vehicle subjects were inadvertently administered UT-15 and were hospitalized after the cross-over while treated with active drug. Capsular summaries for those that were hospitalized, deteriorated or died are shown in Table 82.

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Table 82. Capsular summaries for those who died, were hospitalized or whose hospitalization was prolonged (P01:04-05)

Study/ Subject[103] Arm Event	Description
√04/2019 UT-15	This was a 37- year old Caucasian female with pulmonary hypertension and SLE and NYHA Class III status. She was hospitalized for an allergic reaction to Bactrim, prescribed for a UTI.
04/2022 UT-15	This was a 35-year old Caucasian Female with pulmonary hypertension and systemic sclerosis and NYHA class III. Concomitant medications included furosemide, isradipine, oxygen and warfarin. She was hospitalized for guaiac positive stools.
04/3009 UT-15	This was a 38-year old Caucasian female subject with pulmonary hypertension and SLE and NYHA Class III status. The subject was hospitalized for pneumococcal meningitis.
04/4017 UT-15 death	This was a 32-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. She was hospitalized on day 21 of the study for worsened heart failure and eventually died.
05/4503 UT-15 ADR Pt died	This was a 36-year old Hispanic female with primary pulmonary hypertension and NYHA Class III status. The subject became septic status post a medical termination of pregnancy. The subject treated with antibiotics but subsequently died.
04/5003 UT-15	This was a 71-year old Caucasian female with pulmonary hypertension and limited scleroderma and NYHA Class IV. Concomitant medications included digoxin, enalapril and warfarin. She was hospitalized for diarrhea, rectal bleeding and vomiting. Warfarin was withheld and the subject was rehydrated.
04/5009 UT-15 ADR	This was a 51-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. She was hospitalized on day 2 (one-day post-catheterization) for a right groin hematoma and a collection of blood in the pelvis. The subject was not taking anticoagulants at the time of the event.
04/7004 UT-15 ADR	This was a 44-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt. She was NYHA Class II. The subject was hospitalized twice, once for hemoptysis and a possible upper lobe infiltrate (on day 35) once again for hemoptysis (on day 43). Endobronchial embolization was performed. Concomitant medications included digoxin and furosemide. Coumadin was stopped on the day of the first event.
04/9001 UT-15	This was a 30-year old Caucasian female with pulmonary hypertension and mixed connective tissue disease and NYHA Class III who was admitted to the hospital for nausea, vomiting dehydration and hyponatremia (serum sodium 126). The subject was given iv fluids and recovered.
04/9002 UT-15	This was a 61-year old Caucasian female with pulmonary hypertension and mixed connective tissue disease who was admitted because of diarrhea, pancytopenia (Hemoglobin = 8.9 g/dL; platelets 44 x 10^3/uL; WBC = 3,74 x 10^3/uL) and hyponatremia (Na+ = 117 mEq/L). She had recently been treated with cyclophosphamide. She was treated with fluid restrictions, electrolytes, dobutamine, prednisone and platelet and RBC transfusions. She recovered.
04/9006 UT-15 death	This was a 29-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt (atrial septal defect) and NYHA Class III status. She developed lightheadedness and bilateral loss of vision on day 2. A paradoxical embolism was suspected. The study drug was stopped. The next day the drug was commenced, New symptoms (facial droop and dysarthria) were noted. Angiography and thrombolysis were undertaken and a bird's nest filter placed to intercept any emboli from the lower limbs. The subject subsequently suffered seizures, with increased intracranial pressure. The subject deteriorated to brain death and subsequently expired.
04/9017	This was a 53-year old Caucasian female subject with primary pulmonary hypertension NYHA Class III. The subject was hospitalized for an acute psychiatric disturbance.

[103] *√indicates non-fatal events the reviewer assess as cardiovascular in nature.*

Study/ Subject[103] Arm Event	Description
04/10002 UT-15 death	This was a 40-year old Caucasian female with pulmonary hypertension associated with mixed connective tissue disease and NYHA Class IV status. The subject was hospitalized on study day 57 with worsening right heart failure. Her condition deteriorated and she suffered an arrhythmia and died.
√04/10006 UT-15	This was a 46 year old Caucasian male with a history of primary pulmonary hypertension and NYHA Class III. The subject was hospitalized on day 22 for altered renal function (BUN was 99 increasing to 115, Creatinine was 1.7 and increased to 2.5 mg/dL). The subject was hydrated with correction of the BUN (to 85mg/dL). The subject was again hospitalized on days 38 and again on day 57 for fluid overload.
√04/12002 UT-15	This was a 71 year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III status. The subject sustained a CVA on day 52 of treatment but continued on therapy.
04/12007 UT-15	This was a 70-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 86 for a pneumothorax post 12-week catheterization.
04/13001 UT-15	This was a 58-year Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject administered an excess of UT-15 (a bolus of 1.5 mL or approximately 1500 ng). The subject had severe pain at the infusion site and removed the subcutaneous catheter. The symptoms, upon arriving at the emergency room, consisted of vomiting, headache, neck ache and leg pain. The study drug was restarted.
√04/14005 UT-15	This was a 40-year old Caucasian female with a history of pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III. After the 12-week catheterization the subject developed increasing dyspnea, chest pain and left shoulder pain and was hypoxemic. She was treated with supplemental oxygen improved over the next two days and was discharged.
√04/14009 UT-15	This was a 36-year old Hispanic female with pulmonary hypertension associated with a congenital systemic to pulmonary shunt. She was treated with digoxin, oxygen and warfarin. After heavy menstrual bleeding she was seen in the ER on day 69 with a complaint of lightheadedness and dyspnea. Her hemoglobin was 7.3 g/dL, the INR was 1.43. She was again hospitalized on day 79 with a diagnosis of acute right heart failure. She received transfusions as well as oxygen and diuretics.
05/14501 UT-15	This was a 41-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 48 an episode of acute hemolytic anemia.
√05/21501 UT-15	This was a 36-year old Hispanic female subject with primary pulmonary hypertension an NYHA Class III. The subject was hospitalized because she was hypoxemic associated with an acute flu syndrome. She recovered.
04/23002 UT-15 death	This was a 15-year old Native American female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class II status. The subject was found comatose, pulseless and hardly breathing. Attempted resuscitation was unsuccessful and the subject died.
05/24505 UT-15	This was a 49-year old Caucasian female with pulmonary hypertension as a consequence of a congenital systemic to pulmonary shunt. She was NYHA Class III. She was hospitalized on day 55 for dehydration.
05/50015 UT-15	This was a 52 year old Caucasian female with pulmonary hypertension and limited scleroderma and NYHA Class IV. The subject had a syncopal episode at cardiac catheterization on day 85 of the study. The event was attributed to a vasovagal event.
√05/50023 UT-15	This was a 37-year old Caucasian female with a history of pulmonary hypertension associated with mixed connective tissue disease and NYHA Class IV status. The subject had her hospitalization duration increased because of supraventricular tachycardia. On day 3 of treatment. The subject was again hospitalized on day 70 and 76 for worsening heart failure and pain at the infusion site.
05/51007 UT-15 death	This was a 28-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III status. The subject had a syncopal episode at the time of catheterization for week 12. The subject had an episode of bradycardia with loss of

Study/ Subject[103] Arm Event	Description
	consciousness. Intravenous atropine was administered. The subject developed A-V block and subsequently developed electromechanical dissociation and died. Autopsy revealed severe pulmonary hypertension with cor pulmonale. Inflammatory changes were noted in the myocardium.
√05/52001 UT-15	This was a 40-year old Caucasian male with primary pulmonary hypertension and NYHA Class III. The subject developed a recurrent event of atrial flutter and was treated with amiodarone.
05/53001 UT-15	This was a 48-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III. The subject complained of asthenia. The asthenia was attributed to malfunction of the infusion pump. The subject was admitted to the hospital for pump repair on day 17 and again on 26.
05/53020 UT-15	This was a 61-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was taking acenocoumarol and furosemide. The subject developed an episode of melena. The INR at the time was 4.0. The hemoglobin was 4.9 g/dL. The subject received three units of packed red blood cells. At gastroscopy an active area of hemorrhagic gastritis was noted.
√05/53022 UT-15 deteriorate	This was a 42-year old Caucasian male with a history of primary pulmonary hypertension and NYHA Class III. The subject was hospitalized on day 28 for worsening heart failure. Because of intolerable site pain in conjunction with the worsening of heart failure the subject was started on iv flolan.
√05/54005 UT-15 deteriorate	This was a 20-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject was admitted to the hospital on day 43 for worsening hypoxemia and unstable hemodynamics. The subject was suspected of having had a pulmonary embolism (the subject was not on any anticoagulant at the time of enrollment because of a history of menorrhagia). No ventilation-perfusion scan was performed. The subject had two cardio-respiratory arrests and died.
√05/54014 UT-15	This was a 44 -year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt. The subject was admitted to the hospital with asthenia and increasing dyspnea. The subject was diagnosed with adrenal insufficiency and was treated with intravenous then oral hydrocortisone.
05/55005 UT-15 death	This was a 32-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class IV. The subject had an episode of syncope and hypotension associated with chest pain. The subject was treated with pressors. There was no statement re EKG changes or cardiac enzymes. The subject developed VF and died.
√05/58001 UT-15 deteriorate	This was a 39-year old Caucasian male with primary pulmonary hypertension and NYHA class III status. The subject was treated with spironolactone and warfarin. The subject was admitted to the hospital because of hemoptysis and weakness. The INR at admission was 6.09. The subject's status deteriorated. The subject developed metabolic acidosis and his renal function deteriorated. Ventilation worsened. The subject improved slightly then deteriorated and died.
√05/58006 UT-15 deteriorate	This was a 53-year old Caucasian subject with primary pulmonary hypertension and NYHA Class III status. The subject suffered a syncopal episode with chest pain. The subject was hospitalized on day 17, 28 and 38 of treatment. The subject, however, was subsequently started on intravenous flolan.
05/59003 UT-15	This was a 48 year old Caucasian female with primary pulmonary hypertension and NYHA Class II status. The subject was taking concurrent digoxin, furosemide and warfarin. The subject was hospitalized on day 81 with melena and marked asthenia. Warfarin was withheld for one day when the INR was subsequently measured as 1.14. Endoscopy revealed features of acute petechial gastritis.
√05/60005 UT-15 withdrew consent	This was a 43 year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject was admitted to the hospital on day 28 for purpura associated with a low platelet count 68,000 x 10^3. The subject also developed hemolytic anemia (Hemoglobin dropped from 13.9 to 9.6 g/dL) associated with an elevated

Study/ Subject[103] Arm Event	Description
	reticulocyte count (29%) and bilirubin (2.2 ng/dL). This subject also became profoundly hypoxemic and was treated with O_2. The subject withdrew consent from the study.
√05/65006 UT-15 Withdrew consent	This was a 48-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject was admitted to the hospital on day 20 for bleeding at the infusion site. The subject was again hospitalized on day 64 for worsening pulmonary hypertension. Intravenous flolan was started.
√04/4001 Vehicle	This was a 33-year old Caucasian female with primary pulmonary hypertension and NYHA Class II. Shortly after the completion of the catheterization, when pressure was applied to the vascular access, she developed bradycardia (heart rate 27-30) that responded to atropine.
04/4009 Vehicle	This was a 34-year old female with pulmonary hypertension and systemic sclerosis and NYHA Class III status who was hospitalized for bronchitis. She was treated with vancomycin, Zosyn and azithromycin.
√05/7502 Vehicle	This was a 37-year old black female with pulmonary hypertension and SLE and NYHA Class III status. The subject was treated with hydrochlorothiazide and prednisone. She halted warfarin in anticipation of cardiac catheterization. The subject was hospitalized with pleuritic chest pain that was eventually diagnosed as a pulmonary embolism. A doppler ultrasound eventually showed a non-occlusive thrombus in popliteal and common femoral veins. She was discharged on warfarin and enoxaparin.
√04/8006 Vehicle deteriorate	This was a 50-year old Caucasian female with primary pulmonary hypertension and NYHA Class III. She was hospitalized on day 59 for increasing dyspnea, ascites and peripheral edema. She was discontinued from the study and iv flolan commenced.
√04/9012 Vehicle death	This was a 56-year old Caucasian male with primary pulmonary hypertension and NYHA ClassIV heart failure. The subject was admitted to the hospital on day 8 for worsening heart failure. The subject received inotropic support but deteriorated and died the same day.
04/9018 Vehicle	This was a 31-year old female Caucasian female subject with pulmonary hypertension associated with a congenital systemic to pulmonary shunt who suffered a right pneumothorax post catheterization.
04/10001 Vehicle death	This was a 65-year old male with pulmonary hypertension associated with a mixed connective tissue disease/CREST syndrome and NYHA Class IV. The subject was admitted to the hospital with acute respiratory distress after hematemesis. He was thought to have esophagitis and possible aspiration pneumonia. The subject was managed with mechanical ventilation and required vasopressors. The subject died 6 days later.
√04/12003 Vehicle	This was a 76-year old Caucasian female with primary pulmonary hypertension and NYHA Class III. The subject was hospitalized on day 87 for chest pain. Angioplasty and stenting of the circumflex artery was performed.
√04/14001 Vehicle	This was a 35-year old Asian female with pulmonary hypertension associated with mixed connective tissue disease with NYHA class III status. She was admitted to the hospital in right heart failure on day 12 of treatment. She required dobutamine and furosemide. She was discharged five day later. She was again hospitalized on day 74 for a syncopal episode. The subject had a history of syncope. At the end of the study she was started on flolan.
04/15003 Vehicle death	This was a 23-year old Caucasian female with pulmonary hypertension and SLE/mixed connective tissue disease and NYHA Class II status. The subject was hospitalized for increasing dyspnea on day 25 of treatment. A transthoracic ECHO demonstrated a large pericardial effusion with possible tamponade. A pericardiocentisis was performed with removal of 1200 cc of fluid. The subject arrested and died.
04/16003 Vehicle death	This was a 67-year old Caucasian female with pulmonary hypertension associated with limited scleroderma and NYHA Class III heart failure. The subject was hospitalized on day 48 due to dyspnea and cough. The subject was again hospitalized on day 85 for acute respiratory distress. The subject was intubated but subsequently vomited with aspiration. The subject became febrile. The subject died 4 days later.
04/16006	The subject was a 57-year old Caucasian female with a history of primary pulmonary

Study/ Subject[103] Arm Event	Description
Vehicle Completed death	hypertension and NYHA Class III status. The subject developed ankle edema and acute dyspnea and was hospitalized on day 62. The subject was catheterized on day 75 of the protocol for the end of study hemodyanmics. The subject became hyposaturated, arrested and died 10 days later.
04/17006 Vehicle	This was a 60-year old Caucasian female with pulmonary hypertension associated with limited scleroderma , CREST syndrome and NYHA Class III status. The subject was hospitalized for pyrexia. All cultures were negative and the subject was discharged three days later. The subject subsequently developed hip pain. She was again hospitalized on day 14 of treatment for pyrexia. The pyrexia resolved three days later.
04/20006 Vehicle	This was a 36-year old Hispanic female with primary pulmonary hypertension and NYHA Class II status. She was treated with Acenocoumarol, chlorthalidone and oxygen. She was fatigued and had palpitations and experienced prolonged menorrhagia. Her hemoglobin on admission was 9.2 g/dL. She received two units of packed red blood cells with a rise in hemoglobin to 12.1 /dL and she was discharged.
√04/20007 Vehicle	This was a 42-year old Hispanic female subject with primary pulmonary hypertension and NYHA Class IV status. She developed worsening dyspnea and edema. She was admitted to the hospital where she was treated with diuretics, low dose dopamine and oxygen.
04/20010 Vehicle	This was a 19-year old Hispanic female with pulmonary hypertension and a systemic right to left shunt and NYHA Class III. On day 2, one-day post catheterization in which contrast was administered to confirm the presence of the PDA, her creatinine increased to 3.4 mg/dL. Baseline creatinine was 1.02 mg/dL. She was treated with hydration and her status improved after three days. Her creatinine was 1.4 mg/dL.
√04/22007 Vehicle	This was a 35-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III. The subject was hospitalized for dyspnea, cough, chest pain and abdominal bloating. A chest X-ray showed a right pleural effusion. The subject improved with intravenous diuretics.
05/22501 Vehicle	. This was a 63-year old Caucasian female with a history of pulmonary hypertension and systemic sclerosis and NYHA Class III status. She was admitted to the hospital on day 50 of treatment with increasing dyspnea. A focal infiltrate was observed on X-ray, possibly indicative of pneumonia. High resolution CT scan of the chest showed a right-sided pleural effusion and a small left-sided pleural effusion. She received oxygen and antibiotic. The subject was discharged from the hospital after 4 days.
05/22504 Vehicle died study P01:06	This was a 19-year old Caucasian female with primary pulmonary hypertension and NYHA Class II status. The subject was hospitalized at day 50 for worsening shortness of breath. The subject completed the study The subject was subsequently started on open-label UT-15 in Study P01:06 and did not improve. She was treated with iv flolan but died four days later.
√05/50003 Vehicle	This was a 35-year old Caucasian female with a history of primary pulmonary hypertension who was hospitalized on day 52 of treatment because of increased dyspnea and weight gain. She received increased diuretics, oxygen and diuretics.
√05/50014 Vehicle	This was a 50-year old Caucasian male with primary pulmonary hypertension and NYHA Class IV. The subject was hospitalized several times (on day 17, 35, 54 and 75) due to worsening heart failure. The subject required a dobutamine drip on day 81 of the study. The subject completed the study and was entered in Study P01:06. He died of a low cardiac output state two weeks later.
√05/50022 Vehicle	This was a 21-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III. The subject The subject was hospitalized due to worsening edema and hyponatremia on day 56 of treatment. The subject was discharged after three days. The subject was again hospitalized on day 72 for increasing edema and weight gain, She was discharged after 4 days.
05/52003 Vehicle	This was a 30-year old Caucasian female with pulmonary hypertension with a congenital systemic to pulmonary shunt and NYHA Class III. The subject was hospitalized on day 53 for diarrhea and vomiting. This subject was inadvertently administered UT-15.which was suspected since the infusion site was red and swollen.

Study/ Subject[103] Arm Event	Description
05/52004 Vehicle	This was a 27-year old Caucasian female with a history of primary pulmonary hypertension and NYHA Class III. The subject was taking bumetanide, diltiazem, phenprocoumon and sprionolactone at the time of the event. The subject was hospitalized on day 32 and 47. The subject developed epistaxis and anemia. The subject was hospitalized a second time for infusion site pain. The subject at some point had inadvertently been switched to UT-15.
05/52006 Vehicle ADR Died	This was a 49-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject developed cold and fever (39° C). She became dyspneic and weak and required assisted ventilation and pressor support. She subsequently developed lactic acidosis, acute renal failure, ischemic hepatitis and finally cardiogenic shock and died.
05/53014 Vehicle	This was a 61-year old Caucasian male with pulmonary hypertension and systemic sclerosis with NYHA Class III status. The subject was hospitalized on day 67 for gout. Concomitant medications included digoxin, fuosemide, isosorbide mononitrate, phenprocoumon and verapamil.
05/54007 Vehicle	This was a 37-year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject had a syncopal episode with passage of stool. The subject was discharged two days later.
05/54027 Vehicle	This was a 62-year old Caucasian male with a history of primary pulmonary hypertension and NYHA Class III status. The subject was admitted to the hospital on day 49 for edema and right heart failure. The subject was treated with intravenous furosemide.
√05/54028 Vehicle deteriorate	This was a 27-year old Caucasian female and primary pulmonary hypertension and NYHA Class III status. Her status deteriorated to NYHA Class IV. She was treated with oxygen and pressors. She was discharged on intravenous flolan.
√05/56003 Vehicle	This was a 66-year old Caucasian male with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 47 of treatment because of worsening heart failure. The dose of diltiazem was adjusted and the subject improved and was discharged.
05/60006 Vehicle death	This was a 17-year old Caucasian female with primary pulmonary hypertension and NYHA Class IV status. Concomitant medications included heparin and nifedipine. The subject was hospitalized on treatment day 27 for hemoptysis. The subject was hospitalized again on day 60 of treatment for worsening dyspnea. The subject arrested and died.
05/60013 Vehicle	This was a 52- year old male with primary pulmonary hypertension and NYHA Class II. The subject was hospitalized on day 51 with pneumonia and hemoptysis. X-rays showed lung consolidation. A white blood cell count was 17,000. The subject was discharged after 19 days.
05/60015 Vehicle death	This was a 19 year old Caucasian female with primary pulmonary hypertension and NYHA Class III status. The subject and marked worsening of status and was admitted to the hospital on day 47. The subject's status worsened and the subject died the following day.
√05/64003 Vehicle deteriorate	This was a 41 year old Caucasian male with pulmonary hypertension and a congenital systemic to pulmonary shunt NYHA Class III status The subject was admitted on day 18 because of hemoptysis. The investigator decided to unblind this subject. The subject was started on flolan. The subject was categorized as having deteriorated.
05/65001 Vehicle	This was a 25 year old Caucasian male with primary pulmonary hypertension and NYHA Class II status. The subject was hospitalized for a manic reaction on day 43 of treatment.
05/65004 Vehicle death	This subject was a 51-year old Caucasian male with primary pulmonary hypertension and NYHA Class III status. The subject was admitted to the hospital on day 18 for worsening pulmonary hypertension. His status worsened and he died.
√05/65011 Vehicle deteriorate	This was a 59-year old Caucasian male with primary pulmonary hypertension and NYHA Class III status. The subject was hospitalized on day 65.for worsening pulmonary hypertension. The subject was started on flolan. The subject died approximately 2 weeks later.

Study/ Subject[103] Arm Event	Description
05/66005 Vehicle	This was a 34-year old Caucasian female with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject awoke at night with a short episode of dyspnea that lasted approximately 45 minutes. The episode revolved. The subject was admitted to the hospital with a negative work up.
05/66008 Vehicle	This was a 47-year old Caucasian male with pulmonary hypertension and a congenital systemic to pulmonary shunt and NYHA Class III status. The subject was admitted to the hospital for the feeling of a swollen tongue and pruritis. An aphthous ulcer was present on the lower lip. The subject was treated with an antihistamine and discharged. The event was attributed to a possible viral syndrome.
05/66010 Vehicle deteriorate	This was a 72-year old Caucasian male with primary pulmonary hypertension and NYHA Class IV status. The subject sustained worsening of pulmonary hypertension. The subject was admitted to the hospital on day 45 of treatment. The subject was started on flolan and discontinued from the study.

A.4.4.8.5 Adverse events listed as severe

There were a total of 146 (61.9%) subjects on UT-15 and 47 (20.2%) subjects on vehicle who had adverse events labeled as severe. Table 83 contains those adverse events that were categorized as severe in at least two subjects in either treatment group.

Table 83. Severe adverse events with n≥2 in either group (P01:04-05)

Event	Veh	UT-15	Event	Veh	UT-15
Any	47 (20.2%)	146 (61.9%)			
Infusion site pain	4 (1.7%)	93 (39.4%)	Shock	1 (0.4%)	2 (0.9%)
Infusion site reaction	2 (0.9%)	90 (38.1%)	Overdose	0 (0%)	2 (0.8%)
Infusion site bleed/bruise	2 (0.9%)	10 (4.2%)	Insomnia	0 (0%)	2 (0.8%)
Rash	0 (0%)	10 (4.2%)	Hemolytic anemia	1 (0.4%)	2 (0.8%)
Headache	4 (1.7%)	8 (3.4%)	Diarrhea	0 (0%)	2 (0.8%)
Pain	2 (0.9%)	6 (2.5%)	Contact dermatitis	0 (0.8%)	2 (0.8%)
Heart failure	11 (4.7%)	6 (2.5%)	Epistaxis	0 (0%)	2 (0.8%)
Edema	0 (0%)	4 (1.7%)	Fever	2 (0.9%)	1 (0.4%)
Hypoxia	1 (0.4%)	4 (1.7%)	Chest pain	3 (1.3%)	1 (0.4%)
Pulmonary hypertension	4 (1.7%)	4 (1.7%)	Cough increased	3 (1.3%)	1 (0.4%)
Syncope	3 (1.3%)	4 (1.7%)	Dyspnea	5 (2.1)	1 (0.4%)
Vaodilatation	0 (0%)	4 (1.7%)	Anorexia	2 (0.9%)	1 (0.4%)
Nausea and vomiting	1 (0.4%)	3 (1.3%)	Asthenia	2 (0.9%)	1 (0.4%)
Vomiting	0 (0%)	2 (0.8%)	Hemoptysis	2 (0.8%)	0 (0%)
Anemia	1 (0.4%)	2 (0.8%)	Malaise	2 (0.8%)	0 (0%)

There were far more subjects with infusion site reaction in the UT-15 group whose intensity was labeled as severe. Severe symptoms of heart failure and dyspnea was more frequent in the vehicle group; edema and hypoxia was, however, more frequently in the UT-15 group

Other adverse events listed as severe in intensity in one subject in that treatment are listed below.

Adverse events labeled as severe in a single subject that occurred in the UT-15 group were

Abdominal pain; Ascites; Cellulitis; Drug level decreased; Injection site reaction; Injection site pain; Injection site reaction; Sepsis; Viral infection; Atrial flutter; Bradycardia; Embolus; Hypotension; Migraine; Supraventricular tachycardia;

vascular disorder; Hematemesis; Hemorrhagic gastritis; Melena; Nausea; Rectal Hemorrhage; Adrenal cortical insufficiency; Pancytopenia; Dehydration; Gout; Peripheral edema; Myalgia; Myasthenia; Abnormal gait; Acute brain syndrome; Anxiety; Cerebral hemorrhage; Cerebral infarct; Dizziness; Hemiplegia; Psychosis; Speech disorder; Thinking abnormal; Withdrawal syndrome; Sweating; Visual field defect; Pruritis and Dysuria.

Adverse events labeled as severe that occurred in one subject in the vehicle group were:

Flu syndrome; Viral infection; Bradycardia; Congestive heart failure; Heart arrest; Hypotension; Pericardial effusion; Esophagitis; Nausea; Coagulation time increased; Myeloma; Gout; Hyponatremia; Peripheral edema; Convulsion; Depression; Dizziness; Manic Reaction; Paresthesia; Respiratory Apnea; Pruritis; Cute kidney Failure and Kidney failure;

A.4.4.8.6 Overall adverse events[104]

Adverse events of any intensity were fairly frequent. 231/233 or (99.1 %) of those in the UT-15 group and 218/236 (92.3%) of those in the vehicle group. The most common system involved was skin and appendages, with 222/233 (95.2%) and 155/236 (65.8%) subjects in the UT-15 and vehicle groups, respectively, had adverse events listed. The difference in the event rate reflects the irritating effect of the active treatment.

There was an increase adverse event rate among UT-15 subjects for "body as a whole", "digestive", "metabolic", "nutritional" and "nervous system". The specific adverse events increased in the UT-15 versus vehicle groups were "jaw pain" (13% versus 5%); "diarrhea" (25% versus 15%), "anorexia" (5 % versus 2%); and "nausea and vomiting" (3% versus 0.9%). With respect to the "Nutritional and Metabolic system", "edema" (9% versus 3%) was increased in the UT-15 group. With respect to "Nervous system", "vasodilatation" was increased (11% versus 5%).

"Chest pain" (9% versus 4%), "dyspnea" (8% versus 3%), "cough" (8% versus 35); and "infusion site bleeding" (44 versus 34) was more frequent in the vehicle group than in the UT-15 group.

[104] *From sponsor's Table 14.3.2.1.2A.*

Table 84. Adverse events (P01:04-05)[105]

	Veh N=236	UT-15 N=233		Veh N=236	UT-15 N=233
Any	218 (92%)	231 (98%)			
Body as a whole	131 (56%)	129 (55%)	Nervous	71 (30%)	51 (22%)
Headache	54 (23%)	64 (27%)	Vaodilatation	25 (11%)	11 (5%)
Jaw Pain	11 (5%)	31 (13%)	Dizziness	21 (9%)	19 (8%)
Pain	25 (11%)	28 (12%)	Insomnia	14 (6%)	8 (3%)
Infection	20 (9%)	21 (9%)	Anxiety	9 (4%)	11 (6%)
Flu syndrome	9 (4%)	11 (5%)			
Asthenia	7 (3%)	11 (5%)			
Chest pain	20 (9%)	10 (4 %)			
Abdominal pain	10 (4%)	8 (3%)			
Back pain	12 (5%)	6 (3%)			
Fever	11 (4%)	6 (3%)			
Cardiovascular	60 (26%)	46 (20%)	Respiratory	59 (25%)	79 (34%)
Hypotension	5 (2%)	9 (4%)	Pharyngitis	13 (5%)	21 (9%)
Heart failure	17 (7%)	7 (3%)	Epistaxis	10 (4%)	4 (2%)
Hemorrhage	13 (6%)	7 (3%)	Dyspnea	8 (3%)	19 (8%)
Syncope	12 (5%)	7 (3%)	Cough Increased	7 (3%)	19 (8%)
Digestive	74 (32%)	105 (45%)	Skin and Appendages	222 (94%)	155 (67%)
Diarrhea	36 (15%)	58 (25%)	Infusion site pain	200 (85%)	62 (27%)
Nausea	41 (18%)	52 (22%)	Infus site reaction	196 (83%)	62 (27%)
Vomiting	14 (6%)	12 (5%)	Infus site bleed/bruise	79 (34%)	102 (44%)
Anorexia	4 (2%)	11 (5%)	Rash	32 (14%)	26 (11%)
Nausea, vomiting	2 (1%)	7 (3%)	Pruritis	19 (8%)	14 (6%)
Melena	0 (0%)	5 (2%)			
Endocrine	2 (0.9%)	1(<1%)	Special Senses	3 (1%)	7 (3%)
Hematol, lymphatic	33 (14%)	19 (8%)	Urogenital	14 (6%)	11 (5%)
Ecchymosis	27 (12%)	9 (4%)			
Metabolic and	30 (13%)	47 (20%)			
Nutritional	6 (3%)	21 (9%)			
Edema	16 (7%)	11 (5%)			
Peripheral edema	0 (0%)	5 (2%)			
Hypokalemia					
Musculoskeletal	14 (6%)	10(4%)			

Relationship of dose to adverse events. There was no parallel dose group. No conclusions related to dose related events can definitively be made. Table 1.46 contains events occurring in greater than 10 subjects in any group as well s the dose at which onset of the event was noted. The percentages reflect the number of events divided by the number of subjects who received that dose.

Most adverse events, however, were evident at the lowest infusion rate (0-2.5 ng/kg/min). In particular, infusion site reaction and infusion site pain occurred in most subjects 72-75% of the UT-15 group at the lowest dose. The likelihood is that this origin with a low dose is a surrogate for early onset of events.

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[105] The sponsor treats those who inadvertently received UT-15 but were randomized to the Vehicle group as UT-15 patients. Clearly this is inaccurate. This reviewer, however did not modify the fractions.

Table 85. Adverse events by dose (P01:04-05)[106]

		Dose level (ng/kg/min)						Tot
		0	0-2.5	2.5-5.0	5.0-10	10-20	>20	al
Receiving dose	UT-15	31	236	213	162	81	11	236
	Veh	12	233	228	219	199	111	233
Body as a whole								
Headache	UT-15	1 (3%)	35(15%)	11 (5%)	11 (7%)	2 (2%)	1 (9%)	61
	Veh	0	27 (12%)	10 (4%)	8 (4%)	6 (3%)	3 35)	54
Jaw Pain	UT-15	1 (3%)	15(6%)	7 (3%)	6 (4%)	1(15)	0	30
	Veh	0	4 (2%)	1 (<1%)	3(1%)	2 (1%)	1 (1%)	11
Pain	UT-15	2 (6%)	14 (6%)	6 (3%)	4 (2%)	2(2%)	0	28
	Veh	0	8 (3%)	6 (3%)	3 (1%)	7 (4%)	1 (1%)	25
Infection	UT-15	0	9 (4%)	5 (25)	4 (2%)	1(1%)	1 (9%)	20
	Veh	0	6 (3%)	7(3%)	5 (2%)	2 (1%)	0	20
Asthenia	UT-15	0	5 (2%)	4(2%)	1 (<1%)	1(1%)	0	11
	Veh	0	2 (1%)	1(<1%)	2 (1%)	2 (1%)	0	7
Flu Syndrome	UT-15	0	8 (3%)	1 (<1%)	0	2 (2%)	0	11
	Veh	0	0	2 (1%)	3 (1%)	4 (2%)	0	9
Chest Pain	UT-15	0	4 (2%)	4 (2%)	1 (<1%)	1 (1%)	0	10
	Veh	0	4(2%)	4 (2%)	3 (1%)	9 (5%)	0	20
Back pain	UT-15	0	4 (2%)	2 (1%)	0	0	0	6
	Veh	0	4(2%)	2 (1%)	3 (1%)	2 (1%)	0	11
Abdominal pain	UT-15	0	5 (2%)	2 (1%)	0	1 (1%)	0	8
	Veh	0	6 3%)	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)	10
Fever	UT-15	0	2 (1%)	1 (<1%)	2 (1%)	0	0	5
	Veh	0	3 (1%)	3 (1%)	0	4 (2%)	0	10
Cardiovascular								
Heart Failure	UT-15	0	3 (1%)	2 (1%)	2 (1%)	0	0	7
	Veh	0	2 (1%)	3(1%)	3 (1%)	8 (4%)	1(1%)	17
Hemorrhage	UT-15	0	4 (2%)	2 (1%)	0	1 (1%)	0	7
	Veh	0	4 (2%)	2 (1%)	6 (3%)	1 (1%)	0	13
Syncope	UT-15	0	2 (1%)	2 (1%)	1 (1%)	2 (2%)	0	7
	Veh	0	2 (1%)	4 (2%)	3 (1%)	3 (2%)	0	12
Digestive								
Diarrhea	UT-15	0	22 (9%)	22 (10%)	10 (6%)	3 (3%)	0	57
	Veh	0	17 (7%)	7 (3%)	8 (4%)	4 (2%)	0	36
Nausea	UT-15	0	25 (11%)	13 (6%)	8 (5%)	4 (4%)	0	50
	Veh	0	19 (8%)	8 (4%)	10 (5%)	4 (2%)	0	41
Vomiting	UT-15	1 (3%)	6 (3%)	3 (1%)	2 (1%)	0	0	12
	Veh	0	6 (3%)	4 (2%)	1 (<1%)	3 (2%)	0	14
Anorexia	UT-15	0	5 (2%)	2 (1%)	4 (2%)	0	0	11
	Veh	0	3 (1%)	0	1(<1%)	0	0	4
Hematologic and lymphatic								
Ecchymosis	UT-15	0	8 (3%)	1 (<1%)	0	0	0	9
	Veh	0	5 (2%)	12 (5%)	5 (2%)	2 (1%)	2 (2%)	26
Metabolic and nutritional								
Edema	UT-15	1 (3%)	9 (4%)	8 (4%)	2 (1%)	0	0	20
	Veh	0	3 (1%)	1 (<1%)	2 (1%)	0	0	6
Peripheral edema	UT-15	0	7 (3%)	3 (1%)	0	1 (1%)	0	11
	Veh	0	1(<1%)	8 (4%)	4 (2%)	3 (1%)	0	16
Nervous								
Dizziness	UT-15	0	12 (5%)	2 (1%)	5 (3%)	2 (2%)	0	21

[106]Adverse events occurring in at least 10 subjects in either group and the dose at onset and percentage of those at the dose who had the event

		Dose level (ng/kg/min)						Tot
		0	0-2.5	2.5-5.0	5.0-10	10-20	>20	al
	Veh	0	8 (3%)	3 (1%)	4 (2%)	4 (2%)	0	19
Vasodilation	UT-15	1 (3%)	15 (6%)	5 (2%)	3 (2%)	1 (1%)	0	25
	Veh	0	6 (3%)	4 (2%)	0	0	1 (1%)	11
Insomnia	UT-15	0	9 (4%)	4 (2%)	0	1 (1%)	0	14
	Veh	0	2 (1%)	2 (1%)	3 (1%)	1 (1%)	0	8
Respiratory								
Pharyngitis	UT-15	0	5 (2%)	4 (2%)	3 (2%)	0	0	12
	Veh	0	8 (3%)	4 (2%)	2 (1%)	6 (3%)	1(1%)	21
Epistaxis	UT-15	0	5 (2%)	3 (1%)	2 (1%)	0	0	10
	Veh	0	0	0	1 (<1%)	0	0	1
Cough increased	UT-15	1 (3%)	2 (1%)	3 (1%)	1 (1%)	0	0	4
	Veh	0	4 (2%)	4 (2%)	5 (2%)	4 (2%)	2 (2%)	19
Dyspnea	UT-15	1 (3%)	3 (1%)	3 (1%)	1 (1%)	0	0	8
	Veh	1 (8%)	4 (2%)	3 (1%)	8 (4%)	2 (1%)	1 (1%)	19
Skin and appendages								
Infusion site pain	UT-15	2 (6%)	171 (72%)	17 (8%)	7 (4%)	0	0	197
	Veh	0	27 (12%)	13 (6%)	17 (8%)	5 (2%)	0	62
Infusion site reaction	UT-15	0	176 (75%)	8 (4%)	5 (3%)	4 (4%)	0	193
	Veh	0	26 (11%)	15 (7%)	14 (6%)	6 (3%)	1(1%)	62
Infusion site bleed/bruise	UT-15	0	36 (15%)	19 (9%)	19 (12%)	5 (5%)	0	79
	Veh	0	35 (15%)	26 (11%)	26 (12%)	14 (7%)	1(1%)	102
Rash	UT-15	1 (3%)	24 (10%)	4 (2%)	2 (1%)	0	0	31
	Veh	0	13 (6%)	2 (1%)	4 (2%)	3 (2%)	2 (2%)	24
Pruritis	UT-15	0	10 (4%)	7 (3%)	1 (1%)	0	1 (9%)	19
	Veh	0	4 (2%)	2 (1%)	1 (<1%)	5 (3%)	1 (1%)	13

A.4.4.8.7 Overdose

The sponsor lists eight subjects who had an adverse event that was classified as either overdose or drug excess. The most common organs effected by drug excess were skin (infusion site pain, infusion site reaction), gastrointestinal (vomiting, diarrhea, nausea, abdominal cramps), musculoskeletal (neck and leg aches), and vasodilatation (headache, flushing and near syncope).

Subject #13001: Developed symptoms of headache, leg aches, neck aches and vomiting after inadvertently flushing of her tubing prior to changing tubing.

Subject #52003: Inadvertently was given UT-15 at a dose of 10 ng/kg/min. Subject had been on vehicle up to that time. The subject developed vomiting and diarrhea. The dose was decreased to 8.5 ng/kg/min and the symptoms resolved..

Subject #52004: Inadvertently was given UT-15 at a dose of 8.5 ng/kg/min. This subject had been on vehicle up to that time. The subject developed pain at the infusion site. The dose was decreased to 6.25 ng/kg/min and the symptoms resolved.

Subject #53011:This subject's adverse event was classified as "excess UT-15". The dose of UT-15 was 15 ng/kg/min. This, however, was the appropriate dose for this subject. The symptoms included headache, nausea, diarrhea and abdominal cramps. Symptoms resolved upon lowering the dose to 12.5 ng/kg/min.

Subject #3006: This subject received 11 ng/kg/min inadvertently. The dose should have been 5 ng/kg/min. Symptoms included nausea, diarrhea and flushing, with improvement of symptoms with decrease in dose.

Subject #53004: Listed as having drug overdose due to inadequate bolus delivery. No additional information was supplied with the summary.

Subject #19501: This subject flushed the line with a bolus of 50 μg. The symptoms were nausea, vomiting and near syncope.

Subject #2004: Inadvertently was crossed over to UT-15 at a dose of 15 ng/kg/min. Symptom included gastrointestinal upset, leg cramps and redness at the infusion site.

A.4.4.8.8 Discontinuations without down-titration

There is little data with respect to the consequence of abruptly terminating UT-15 therapy. Although there were 25 subjects who discontinued UT-15 therapy, fifteen were down titrated as per protocol. Of the other ten subjects, six were started on Flolan. Four of these subjects were immediately started on Flolan. The two subjects who discontinued UT-15 and were not immediately started on Flolan apparently had no sequelae to the discontinuation of UT-15. One of these subjects actually discontinued UT-15 twice, with the highest dose at the time of discontinuation of 5 ng/kg/min. No sequelae were noted either the first or second time the subject discontinued treatment.

There were four subjects who discontinued UT-15 therapy and did not start Flolan. For three of the subjects the dose at which discontinuation occurred was very low, 2.5 ng/kg/min (2 subjects), and 1.25 ng/kg (1 subject). No sequelae were noted. The fourth subject discontinued from a dose of 5.0 ng/kg/min with no sequelae.

In summary, there were few subjects who abruptly discontinued from significant doses of UT-15 without immediate flolan therapy. Among the few who did no sequelae were noted.

A.4.4.8.9 Hemolytic anemia/ pancytopenia

Two subjects treated with UT-15 had hemolytic anemia. These subjects #60005 and #14501 are described in Table 82. One subject discontinued treatment and the other remained in the study on a lower dose. One additional UT-15 subject had pancytopenia (pt #9002). This subject is also described in Table 82. This subject also continued on therapy. Given the rechallenge, the relationship to UT-15 is unclear.

A.4.4.8.10 Vital signs

Vital signs were routinely measured during the first dose (a really low dose) of UT-15 or vehicle. Over the first 8 hours there was a drop in systolic/diastolic blood pressures of 4.5/1.2-mmHg in the UT-15 group and a drop of 5.8/4.6-mm Hg in the vehicle group. Heart rates were decreased 1.2 BPM in the UT-15 group and decreased 1.2 BPM in the vehicle group, at the end of the 8-hour period. These results are not adequate to rule out hemodynamic changes with credible doses of UT-15.

A.4.4.8.11 Orthostatic effects

Despite the association of prostacyclin agonists with changes in hemodynamics vital signs were not collected when infusion rates were increased. No standing measurements were performed, so no orthostatic values were available.

A.4.4.8.12 Laboratory

Laboratory values were collected at baseline and week 12 or at termination if less than 12 weeks. A central laboratory assayed all laboratory specimens, with the exception of coagulation profiles, which were assayed at the local site. The following chemistry, hematology and other laboratories were measured:

Chemistry: sodium, potassium, chloride, bicarbonate, CO_2, calcium, albumin, BUN/urea, total bilirubin, LDH, ALT/SGPT, AST/SGOT, creatinine.

Hematology: RBC count, hemoglobin, hematocrit, plactelet cout, WBC count/differential.

Other labs: coagulation times,urinalysis, β-hCG pregnancy test.

Any abnormalities in the values of chemistry and hematology must be interpreted in the context of the large number of concurrent therapies used in the studied population. In particular, diuretics were frequently used in this population and abnormalities in electrolytes and other laboratory values are to be expected i.e. changes in BUN/creatinine. Anticoagulants were frequently administered and consequently bleeding with drops in hemoglobin and hematocrit would be anticipated. There was also an asymmetry in the use of anti-inflammatory drugs, which were more frequently administered to the UT-15 group that could potentially alter predispose to bleeding i.e. a decrease in hematocrit.

Chemistry

Serious adverse events associated with abnormalities in chemistry. There were several subjects who were hospitalized in association with serious events associated with changes in chemistries. Capsular summaries of these subjects follow:

UT-15

#04/9001 had hyponatremia in association with vomiting and diarrhea;

#04/9002 had hyponatremia associated with diarrhea;

#04/10006 had elevated BUN associated with worsened renal function

#05/58001 had metabolic acidosis associated with deteriorated renal function

#05/60005 had hyperbilirubinemia associated with hemolytic anemia

Vehicle

#04/20010- had elevated creatinine associated with dye-induced renal failure

#05/52006- had lactic acidosis associated with renal failure

#05/53014 was hospitalized for gout

#05/50022- was hospitalized for worsening edema and hyponatremia.

Chemistry associated adverse events of any severity. The chemistry events listed as an adverse event is shown in Table 86.

Table 86. Chemistry abnormalities considered adverse events (P01:04-05)

	Vehicle	UT-15		Vehicle	UT-15
Liver damage	1 #50019	0	Alkalosis	0	1 #15007
Adrenal cortical insufficiency	0	1 #54014	BUN increased	0	1 #03012
Hypokalemia	0	5 #10025 #15005 #50009 #10002 #52004	Electrolyte abnormality	0	1 #50009
Gout	1 #53014	3 #10022 # 58009 #17003	Creatinine increased	1 #0210	0
Hyperkalemia	0	3 #58001 #9001 #10002	Kidney failure abnormal	0	1 #10006
Hyponatremia	2 #50022 #50014	2 #9001 #9002	Acute kidney failure	1 #20010	0
SGOT increased	2 #23001 #19503	0	Kidney failure	1 #9012	0
Bilirubenemia	2 #50020 #60013	1 #60009			

There were five subjects with hypokalemia and three with hyperkalemia, all in the UT-15 treated subjects. The other laboratory adverse events were randomly scattered between the two treatments.

Baseline, week 12 data and change from baseline information are shown in Table 87. The ranges that are shown are expanded to cover the normal range for the whole study population and are expanded to include the age ranges (> 8-75 years) and both genders who enrolled into the study. The data below reflect the pooled studies.

Table 87. Chemistry findings (P01:04-05)

Parameter Norm range		Baseline		Week 12 change		
		Veh	UT-15	Veh	UT-15	P-value
Albumin 2.9-4.9 g/dL	N x±SE	223 4.0±0.03	225 3.9±0.03	203 -0.04±0.02	186 0.02±0.03	0.14
Alk phosphatase 31-385 U/L	N x±SE	220 91±3	223 97±4	202 3.7±1.6	178 0.0±2.9	0.186
Total bilirubin 0.2 –1.2 mg/dL	N x±SE	223 1.0±0.04	225 1.0±0.05	202 0.12 ±0.03	185 -0.10±0.03	<0.0001
SGPT 6-43 U/L	N x±SE	223 29±2	224 27±1	203 -2.6±1.2	185 -2.8±1.2	>0.5
SGOT 9-40 U/L	N x±SE	223 31±1	224 30±1	203 -1.1±0.9	185 -1.4±1.0	0.35
LDH 53-325 U/L	N x±SE	211 245±5	221 248±5	191 4.4±3.8	175 -22±4	<0.0001
BUN/Urea 4-24 mg/dL	N x±SE	224 16±1	225 17±1	206 1.2±0.3	187 -0.3±0.7	0.0003
Creatinine 0.3-1.3 mg/dL	N x±SE	224 0.9±0.02	225 0.9±0.02	206 0.01±0.01	187 -0.01±0.02	0.12
Sodium 132-147 mEq/L	N x±SE	224 140±0.3	223 140±0.2	206 -0.4±0.3	185 -0.3±0.3	>0.5
Potassium 3.4- 5.4 mEq/L	N x±SE	211 4.2±0.03	220 4.1±0.04	191 -0.05±0.04	175 -0.01±0.04	>0.5
Calcium 8.4-10.3 mg/dL	N x±SE	224 9.0±0.04	224 9.1±0.04	205 -0.01±0.04	186 -0.10±0.04	0.25
Chloride 94-112 mEq/L	N x±SE	224 104±0.3	223 103±0.3	206 -0.2±0.3	185 0.0±0.3	>0.5
Bicarbonate 17.0-30.6 mEq/L	N x±SE	221 22±0.2	225 23±0.2	201 0.5±0.2	186 0.1±0.2	0.16

There were decreases in group means in the UT-15 group relative to Vehicle for total bilirubin, LDH and BUN/urea. The sponsor attributes the change to a decrease in hepatic congestion.

Shift tables for those measurements that were altered are shown in Table 88.

Table 88. Selected chemistry shifts (P01:04-05)[107]

			Week 12					
			Low		Normal		High	
			Veh	UT-15	Veh	UT-15	Veh	UT-15
LDH 53-325 U/L	Baseline	Low	0 (0%)	3 (2%)	8 (4%)	5 (3%)	3 (1%)	1(<%)
		Normal	6 (3%)	12 (6%)	157 (75%)	151 (77%)	14 (7%)	8 (4%)
		High	1 (<1%)	0 (0%)	9 (4%)	14 (7%)	11(5%)	2 (1%)
SGOT 9-40 U/L		Low	0 (0%)	0 (0%)	1 (<1%)	7 (4%)	0 (0%)	0 (0%)
		Normal	4 (2%)	3 (2%)	162 (78%)	149 (76%)	12 (6%)	12 (6%)
		High	1 (<1%)	1 (>1%)	11(5%)	14 (7%)	18 (9%)	10 (5%)
Total bilirubin 0.2 –1.2 mg/dL		Low	0 (0%)	0 (%)	1 (<1%)	6 (3%)	0 (0%)	0 (0%)
		Normal	5 (2%)	3 (2%)	140 (67%)	134 (68%)	19 (9%)	7 (4%)
		High	1 <1%)	2 (1%)	5 (2%)	16 (8%)	38 (18%)	28 (14%)
BUN/Urea 4-24 mg/dL		Low	0 (0%)	0 (0%)	0 (0%)	5 (3%)	0 (0%)	1 (<1%)
		Normal	3 (1%)	4 (2%)	172 (82%)	152 (77%)	17 (8%)	11 (6%)
		High	0(0%)	0 (0%)	5 (2%)	17 (9%)	12 (6%)	6 (3%)
Creatinine 0.3-1.3 mg/dL		Low	0 (0%)	0 (0%)	0 (0%)	5 (3%)	0 (0%)	1 (<1%)
		Normal	3 (1%)	3 (2%)	185 (89%)	172 (8%)	7 (3%)	3 (2%)
		High	0 (0%)	0 (0%)	3 (1%)	7 (4%)	11 (5%)	5 (3%)

For the UT-15 group, 14/16 those with high LDH at baseline, normalized at the end of 12-weeks. For the vehicle group 10/21 subjects had their LDH normalized. Among those with normal or low LDH at baseline for the UT-15 group, 15/180 subjects had low LDH at 12-weeks. For the vehicle group among those with low or normal LDH at baseline, 6/188 subjects had low values.

With respect to SGOT, the only notable observation is that among the 25 subjects with high SGOT at baseline 15 were in the low or normal range at the end of the study. For the vehicle group among the 30 subjects with high SGOT at baseline, 12/30 subjects were either in the low or normal range at the end of 12 weeks.

Total bilirubin, particularly, those with high values at baseline were normalized at 12 weeks with UT-15 treatment.

With respect to BUN and creatinine, the decrease in group means at 12 weeks seems to be related the number of subjects with high baseline measurements who normalize.

Specific subjects with abnormal values at end of treatment that this reviewer would find of concern (the sponsor lists approximately 700 line listings of subjects who had values outside the normal range for a given laboratory at either/or baseline and 12 weeks. This reviewer has listed in Table 89 several of the more extreme values at end of study.)

[107] *Adapted from Sponsor's Table 14.3.5.3A.*

Table 89. Outlier subjects for clinical chemistry (P01:04-05)

	Vehicle			UT-15		
	Subject	Base	Wk 12	Subject	Base	Wk 12
SGOT	04/6001	40	78	04/4003	26	105
	04/9019	20	60	05/50005	24	79
	05/7502	15	48			
SGPT	04/6001	40	86	05/53019	38	91
	04/9019	18	62	04/9002	8	55
	05/50001	159	185	05/59011	NA	73
	05/22504	18	87			
Albumin	04/7006	3.3	2.5	04/2022	3.4	2.8
	04/20007	3.1	2.5	05/52003	4.4	5.4
Alk phosphatase				04/9002	194	455
				05/59014	380	454
Calcium	04/2017	9.2	8.3	04/4011	9.3	10.5
	04/6002	9.4	7.3	04/7008	8.3	7.9
	04/20010	8.6	8.2	04/10022	9.1	8.0
	05/24506	9.6	10.5	04/20002	8.4	7.8
	05/51004	9.1	7.8	05/4505	9.4	8.2
	05/54013	8.7	7.9	05/19503	9.3	8.3
	05/56003	8.4	11.2	05/51005	8.8	7.0
	05/57001	9.1	7.6	05/52003	9.4	10.5
	05/59013	8.9	8.3	05/54023	8.9	8.3
	05/65001	9.2	8.2	05/53011	8.0	7.8
				05/58010	9.2	7.7
				05/59006	9.0	8.0
				05/61006	9.2	7.2
				05/64005	9.2	8.3
				05/65009	8.5	8.1
				05/66002	8.8	8.1
Creatinine	04/5005	0.9	1.3	04/3012	1.3	3.4
	04/10007	0.8	1.8	04/10006	1.7	2.9
	05/51004	1.3	1.6			
LDH	04/6001	225	447	04/10021	230	355
	04/12003	336	442	05/2501	276	372
	04/21004	NA	443			
	05/16502	248	532			
	05/50024	229	478			
	05/54027	216	402			
	05/60014	NA	463			
Bicarbonate	04/6002	27.7	15.1	04/3013	26.5	33.0
	04/19002	20.0	15.3	04/14002	NA	31.5
	05/16502	21.3	35.5	05/2501	22.9	16.2
	05/22504	26.3	33.3	05/53009	19.1	14.5
	05/50004	32.0	34.8	05/60008	19.3	16.6
	05/50020	NA	16.2	05/61006	19.6	14.5
	05/51002	20.0	14.8	05/64001	18.7	15.4
	05/65014	19.4	14.1			
Chloride	04/8010	109	116	04/10006	97	88
	05/16502	109	81	05/54014	96	83
	05/56003	107	92	05/61006	106	83
Potassium	04/3005	4.5	5.7	04/4016	3.3	2.7
	04/10005	4.4	3.2	04/2021	3.7	3.3
	04/20006	4.0	3.2	04/4016	3.3	2.7
	05/54028	NA	5.9	04/4018	3.5	2.2
	05/16502	4.5	3.1	04/8004	4.5	3.3
				04/10020	3.9	2.6
				04/12001	4.3	3.2

	Vehicle			UT-15		
	Subject	**Base**	**Wk 12**	**Subject**	**Base**	**Wk 12**
				04/19007	3.7	2.8
				05/52004	4.0	3.1
Sodium	04/2011	146	131	04/10006	134	127
	05/50014	125	117	05/61006	141	112
Bilirubin	04/5005	0.5	1.4	05/6009	2.1	3.7
	04/5011	1.1	1.7	04/23001	0.7	1.3
	04/7002	0.4	1.9			
	04/7005	1.6	2.3			
	04/7006	1.0	1.6			
	04/10015	2.5	3.5			
	04/14011	0.5	1.5			
	04/14007	1.4	2.3			
	05/4502	1.8	2.4			
	05/17502	0.6	1.3			
	05/17502	1.1	2.2			
	05/50011	NA	3.1			
	05/50019	1.2	2.5			
	05/50020	NA	2.3			
	05/53008	2.9	3.3			
	05/53017	1.5	2.8			
	05/60011	0.8	2.0			
	05/60012	0.9	1.6			
	05/61010	0.6	1.3			
	05/61002	1.4	2.3			
	05/61008	1.4	2.4			
	05/61012	1.2	2.0			
	05/65015	1.2	1.9			
	05/66003	2.1	2.9			
BUN	04/10009	22	43	04/3012	22	80
	04/22007	39	45	04/10006	65	135
	05/51004	20	40			

There appear to be more subjects in the UT-15 group whose calcium decreased by a substantial amount or was outside the normal range than for the vehicle group.

As the group means and shift tables would suggest more vehicle subjects had elevated bilirubin and LDH than UT-15 treated subjects.

Two UT-15 treated subjects had substantial increases in creatinine. The largest increase was from 1.3 to 3.4 mg/dL.

There were more subjects with substantial drops in K+ among those treated with UT-15.

Hematology

Serious adverse events associated with hematologic parameters. Several subjects had serious adverse events associated with altered hematology. Those subjects whose adverse events are associated with bleeding, whether the hematologic parameters were abnormal are also included. Any interpretation is confounded by the concurrent anti-coagulation that may predispose to bleeding as well as the asymmetry in the need for anti-inflammatory drugs that might also lead to bleeding.

UT-15

#04/5003- hospitalized for diarrhea, rectal bleeding and vomiting.

#04/5009- hospitalized with a right groin hematoma shortly after catheterization.

#04/ 7004- hospitalized several times for hemoptysis.

#04/9002- hospitalized for pancytopenia, (hemoglobin 8.9 g/dl; platelets 44,000/uL; WBC 3,740/uL). She recovered and completed.

#04/14009- Subject was admitted for anemia (hemoglobin 7.3 g/dL). The sponsor attributed the fall in hemoglobin to heavy menstrual bleeding. The INR at the time of the event was 1.43.

#05/14501- for an episode of hemolytic anemia.

#05/53020: This subject had an episode of melena. The INR was 4.9 the hemoglobin was 4.9 g/dL.

#05/58001- hospitalized due to hemoptysis and weakness.

#05/59003- hospitalized due to melena and marked asthenia.

#05/60005- hospitalized with a low platelet count (68,000) and low hemoglobin (9.6g/dL) associated with a high reticulocyte count (29%).

#05/65006- hospitalized for bleeding at the infusion site.

Vehicle

#04/10001- hospitalized for respiratory distress and hematemesis.

#04/20006- hospitalized for palpitations and prolonged menorrhagia.

#05/52004- epistaxis and anemia.

#05/60006- hospitalized for hemoptysis.

#05/60013- hospitalized for pneumonia. The WBC count was 17,000/L.

#05/64003- hospitalized because of hemoptysis.

Hematologic/bleeding events that were considered as adverse events are shown in Table 90.

Table 90. Hematologic adverse events (P01:04-05)

	Vehicle	UT-15
Injection site hemorrhage	0	2 #50021; #57002
Hemorrhage	13 #20010; #54002; #54003; #54006; #54016; #54024; #54026; #54028; #9018; #52007; #54007; #54025; #17501	7 #52004; #54018; #10020; #19003; #19005; #20005; #20002
Embolus	0	1 #9006
Melena	0	5 #03012; #10002; #53010; #58006; #53020
Rectal hemorrhage	0	3 #03012; #19502; #05003
Gastrointestinal hemorrhage	0	2 #09006; #59003
Gum hemorrhage	0	2 #20005; #65013
Hemorrhagic gastritis	0	2 #53010; #53020
Hematemesis	0	1 #5003
Bloody diarrhea	1 #20001	0
Ecchymosis	27 #01001; #04002; #04004; #04005; #04006; #5007; #6002; #20001; #20004; #20006; #20007; #20008; #20010; #20503; #08006; #14003; #50001; #500020; #65001; #65002; #65005; #65007; #65008; #65011; #65015; #66001; #4001	9 #20005; #20501; #65003; #20504; #65009; #65013; #04012; #20002; #20009
Anemia	3 #17502; #52006; #20006	3 #58006; #14009; #52004
Petechia	2 #20004; #20008	2 #20002; #20005
Hemolytic anemia	0	2 #60005; #14501
Purpura	0	2 #60009; #60005
Thrombocytopenia	0	2 #19503; #20502
Eosinophilia	0	1 #60010
Pancytopenia	0	1 #9002
Coagulation time increased	1 #9012	0
Hypochromic anemia	1 #54024	0
Myeloma	1 # 50011	0
Cerebral hemorrhage	0	1 #9006
Cerebrovascular accident	0	1 #12002
Hemoptysis	5	4

	Vehicle	UT-15
	#50013; #60006; #61008; #60013; #64003	# 20005; #20504; #58001; #07004
Epistaxis	4 # 20003; #22006; #61007; #61010	10 #2004; # 2012; #15007; #15501; #23003; #53022; #0312; #22005; #54004; #52004

Table 91. Selected hematology findings (P01:04-05)[108]

Parameter Norm range		Baseline		Week 12 change		
		Veh	UT-15	Veh	UT-15	P-value
Hemoglobin 11.2-18.1 g/dL	N x±SE	220 15±0.2	224 15±0.1	200 0.02±0.09	188 -0.46±0.09	<0.0001
Hematocrit 34%-54%	N x±SE	218 47±0.5	224 47±0.5	198 -0.1±0.3	188 -1.7±0.3	0.0002
Platelet count 130-400 /nL)	N x±SE	213 210±5	217 206±5	194 0.9±2.8	178 13.6±3.3	0.0007
WBC count 3.8-13.62 /nL	N x±SE	220 7.5±0.2	224 7.7±0.2	200 0.3±0.1	188 -0.2±0.1	0.027
Eosinophil count 0-6.8%	N x±SE	220 1.3±0.08	224 1.4±0.1	200 0.17±0.08	188 0.36±0.09	0.046

There were statistically significant drops in hemoglobin, hematocrit and WBC in the UT-15 group relative to vehicle. Neither lymphocytes nor neutrophil percentages significantly changed. Eosinophils were increased (data not shown). Platelet counts were increased.

The baseline hemoglobin/hematocrit values at baseline are particularly high for a predominantly female population. Not infrequently, subjects had baseline hemoglobin greater than 17 and hematocrit greater than 55. The high baseline value might reflect a secondary polycythemia in response to chronic hypoxia. In actuality, a greater fraction of the vehicle subjects had a shift from high to normal or low for hemoglobin than UT-15 subjects. For hematocrits an equivalent number of subjects whose value was high at baseline shifted to normal or low for both groups.

The shift table for hematologic values are shown in Table 92.

[108] *Derived from sponsor's Tables 14..3..5..5 to 14.3.5.6 (A-C) Mean ± SE at baseline end of treatment and change from baseline. P -values from Wilcoxon rank statistic comparing UT-15 to Vehicle. using rank changes scores.*

Table 92. Selected hematology shifts (P01:04-05)[109]

			Week 12					
			Low		Normal		High	
			Veh	UT-15	Veh	UT-15	Veh	UT-15
Hemoglobin 1.2-18.1 g/dL	Baseline	Low	3(10%)	3 (2%)	6 (3%)	7 (4%)	1 (<1%)	2 (1%)
		Normal	8 (4%)	5 (3%)	164 (79%)	164 (84%)	8 (4%)	2 (1%)
		High	0 (1%)	0 (0%)	7 (3%)	6 (3%)	12 (6%)	27(4%)
Hematocrit 34-54%		Low	1 (<1 %)	2 (1%)	7 (3%)	6 (3%)	1 (<1%)	2 (1%)
		Normal	6 (3%)	4 (2%)	163 (78%)	156 (80%)	8 (4%)	3 (2%)
		High	2 (1%)	1 (>1%)	8 (4%)	10 (5%)	13 (6%)	12 (6%)
Platelet count 130-400 /nL)		Low	17 (8%)	19 (10%)	15 (7%)	21 (10%)	0 (0%)	0 (0%)
		Normal	10 (5%)	6 (3%)	162 (78%)	144 (74%)	2 (11%)	2 (1%)
		High	0 (0%)	0 (0%)	3 (1%)	1 (< 1%)	0 (18%)	3 (2%)
WBC count (3.8-13.6 /nL)		Low	3 (1%)	.4 (2%)	4 (2%)	9 (5%)	0 (0%)	0 (0%)
		Normal	10 (5%)	1 (<1%)	190 (91%)	177 (90%)	1 (<1%)	1 (<1%)
		High	0(0%)	0 (0%)	0 (0%)	3 (2%)	1 (<1%)	1 (<1%)
Eosinophils 0-6.8%		Low	1 (<1%)	0 (0%)	5 (2%)	7 (4%)	0 (0%)	0 (0%)
		Normal	8 (4%)	1 (<1%)	182 (87%)	184 (94%)	4 (2%)	3 (2%)
		High	0 (0%)	0 (0%)	7 (3%)	0 (0%)	2 (1%)	1 (<1%)

Specific values that were marked changes are shown in Table 93.

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[109] *Adapted from Sponsor's Table 14.3.5.7A.*

Table 93. Outlier subjects for hematology findings (P01:04-05)

	Vehicle			UT-15		
	Subject	**Base**	**Wk 12**	**Subject**	**Base**	**Wk 12**
Hematocrit Change >±6	04/2013	46	55	04/2008	53	63
	04/2017	50	40	04/2012	39	46
	04/5005	45	52	04/2022	43	37
	04/5010	53	44	04/3012	39	33
	04/7007	52	45	04/4003	52	44
	04/7010	55	46	04/7004	74	64
	04/9011	45	52	04/9002	31	44
	04/10007	41	34	04/9013	41	49
	04/14008	40	50	04/12002	47	54
	04/16001	33	40	04/14006	55	46
	04/20006	35	43	04/15001	52	45
	04/20007	52	45	04/16008	53	46
	05/7503	40	48	04/20009	57	50
	05/22504	38	45	04/22004	40	33
	05/24506	50	60	04/23001	42	52
	05/52007	64	53	05/12502	48	41
	05/54022	50	43	05/53009	67	56
	05/54025	42	49	05/53010	36	50
	05/54028	42	34	05/53011	69	51
	05/56003	35	44	05/53012	58	47
	05/57004	49	42	05/54001	44	37
	05/60012	60	51	05/54023	45	33
	05/61001	55	39	05/58009	76	64
	05/65001	52	44	05/58010	58	43
				05/59003	51	37
				05/59006	51	41
				05/64002	46	39
				05/66002	54	44
				05/66004	45	38
Hemoglobin Change >±1.5	04/2013	15.9	17.6	04/2008	17.2	19.5
	04/2017	15.3	13.1	04/2022	12.9	11.3
	04/4005	18.1	15.6	04/4003	16.6	14.0
	04/5010	15.9	13.7	04/4007	12.8	14.6
	04/7010	18.2	15.7	04/4012	22.8	20.1
	04/9003	12.9	14.8	04/4013	14.2	12.7
	04/9019	15.0	17.9	04/4018	16.0	13.6
	04/10007	13.6	10.2	04/7004	20.3	17.7
	04/10023	13.5	16.3	04/8002	17.4	15.5
	04/14008	12.1	16.1	04/9002	9.1	13.4
	04/16001	10.3	15.4	04/9010	14.7	11.9
	04/17001	18.9	16.4	04/9017	15.7	13.7
	04/20006	10.8	14.9	04/10021	16.2	18.3
	04/20007	14.8	13.1	04/10022	18.3	16.6
	05/5502	16.4	14.3	04/14006	17.1	15.2
	05/7503	13.8	15.5	04/15007	14.0	16.6
	05/16501	16.7	15.1	04/19003	15.2	13.5
	05/17502	11.8	10.1	04/22004	13.6	10.8
	05/22501	15.7	13.5	04/23001	13.3	17.1
	05/22504	12.9	14.8	05/12502	16.3	14.5
	05/24504	13.9	15.7	05/52004	14.2	11.5
	05/24506	16.7	19.4	05/53009	21.6	17.8
	05/50001	14.8	15.8	05/53010	11.8	15.8
	05/50019	17.4	19.4	05/53011	18.6	15.6
	05/51001	13.1	14.9	05/53012	18.4	16.8
	05/51002	13.9	16.0	05/54001	14.5	12.6
	05/52007	19.6	17.9	05/54004	20.6	18.1
	05/53006	12.8	14.7	05/54018	18.3	16.1

	Vehicle			UT-15		
	Subject	Base	Wk 12	Subject	Base	Wk 12
	05/54025	12.8	14.7	05/54023	15.3	11.9
	05/54028	13.6	11.2	05/58008	15.2	18.0
	05/56003	12.6	14.7	05/58010	16.5	14.2
	05/57003	18.8	20.4	05/59003	16.8	12.4
	05/57004	15.0	13.0	05/61005	16.8	15.1
	05/60012	17.8	15.2	05/64002	15.7	13.6
	05/61008	14.7	16.6	05/64005	17.2	15.1
	05/61012	18.1	16.4	05/65006	13.6	11.0
	05/65001	16.7	14.8	08/65002	15.8	13.4
	05/65005	12.1	10.5			
	05/65010	12.0	9.8			
	05/65012	14.9	16.6			
	05/65014	16.7	14.8			
	05/65015	17.0	15.4			
Platelets	04/10019	122	89	04/2022	105	213
Change >±75/nL	04/14001	180	107	04/4008	255	331
	04/17007	182	259	04/8004	309	173
	04/19006	117	79	04/9002	120	200
	04/21004	204	280	04/9010	166	89
	05/8501	432	348	04/10013	221	299
	05/10505	456	323	04/12004	270	351
	05/53015	195	273	04/20005	93	66
	05/54002	421	304	05/2501	296	209
	05/56003	207	111	05/9501	196	287
	05/60004	176	269	05/19504	283	359
	05/60013	214	136	05/20502	58	107
	05/60014	109	208	05/21501	360	269
	05/66006	274	190	05/22502	217	372
				05/24505	464	274
				05/53010	336	201
				05/59006	107	86
				05/60010	231	344
				05/64002	248	3540
Neutrophil count	04/10027	2.52	0.34	05/20502	NA	0.17
Change >±25%	05/20505	0.97	0.73	05/60008	1.39	1.07

Coagulation

Coagulation measures were collected on the CRF at baseline and week 12. . The results are not easily interpretable with respect to any kinetic interaction between UT-15 and warfarin. Changes in anti-coagulation (including other medications aside from warfarin) were allowed during the course of the study. Undoubtedly, coagulation measurements were required in response to the frequent changes in anticoagulation medications but these measurements were not captured on the CRFs. Of note is that most subjects in this study were inadequately anticoagulated. The prespecified goal was to have INRs between 1.5 to 2.5 among those receiving anticoagulation. Median values at the end of the study were 1.3 for the pooled studies. Subjects in study P01:05 were more likely than those in P01:04 to have INRs in the proposed range.

Table 94. INR data (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh	UT-15	Veh	UT-15	Veh	UT-15
Baseline	N	106	112	104	102	210	214
	Median	1.2	1.2	1.5	1.3	1.2	1.2
	25th -75th %ile	1.0-1.4	1.1-1.4	1.1-2.2	1.1-2.1	1.1-1.7	1.1-1.5
Week 12	N	96	95	100	92	196	187
	Change	1.2	1.2	1.6	1.4	1.3	1.2
	25th -75th %ile	1.1-1.4	1.1-1.4	1.2-2.5	1.1-2.0	1.1-1.8	1.1-1.7

Urinalysis

Table 95 contains those who had findings on urinalysis in comparing baseline and week 12 for UT-15 and vehicle. There were more subjects with urinalysis abnormalities in the vehicle group than in the UT-15 group at baseline. The number of subjects with blood in the urine of +1 to +3 in magnitude, decreased in the UT-15 group. The effect was marginal in the vehicle group. There was also a decrease in subjects with +3 protein in the urine for 16 to 9 in the UT-15 group. Overall the number of subjects with any degree of proteinuria was the same for the UT-15 group, comparing baseline to week 12.

Table 95. Selected urinalysis results (P01:04-05)

		Baseline		Week 12	
		Veh	UT-15	Veh	UT-15
Blood	Trace	12 (5%)	6 (3%)	18 (8%)	13 (6%)
	1+	19 (8%)	12 (5%)	12 (5%)	9 (4%)
	2+	7 (3%)	7 (3%)	6 (3%)	2 (1%)
	3+	5 (2%)	7 (3%)	8 (3%)	3 (1%)
Protein	Trace	28 (12%)	23 (10%)	24 (10%)	22 (9%)
	1+	30 (13%)	17 (7%)	16 (7%)	21 (9%)
	2+	22 (9%)	17 (7%)	18 (8%)	20 (9%)
	3+	8 (3%)	16 (7%)	11 (5)%	9 (4%)

ECG

ECGs were performed at baseline and at the end of week 12. The specifics of the ECGs are summarized in Table 96.