study allowed for the long-term treatment of patients who were treated either with active UT-15 or vehicle in studies P01:03, P01: 04 or P01:05. In addition a total of 208 patients not previously enrolled into clinical studies were treated in an open-labeled manner.

4.1.2 Subject enumeration and exposure

As of the cutoff date, exposure was 476 subject-years, with 224 subjects treated for more than 1 year. This open-label study comprises the bulk of the exposure to UT-15. The exposure in this study is shown in Figure 1.

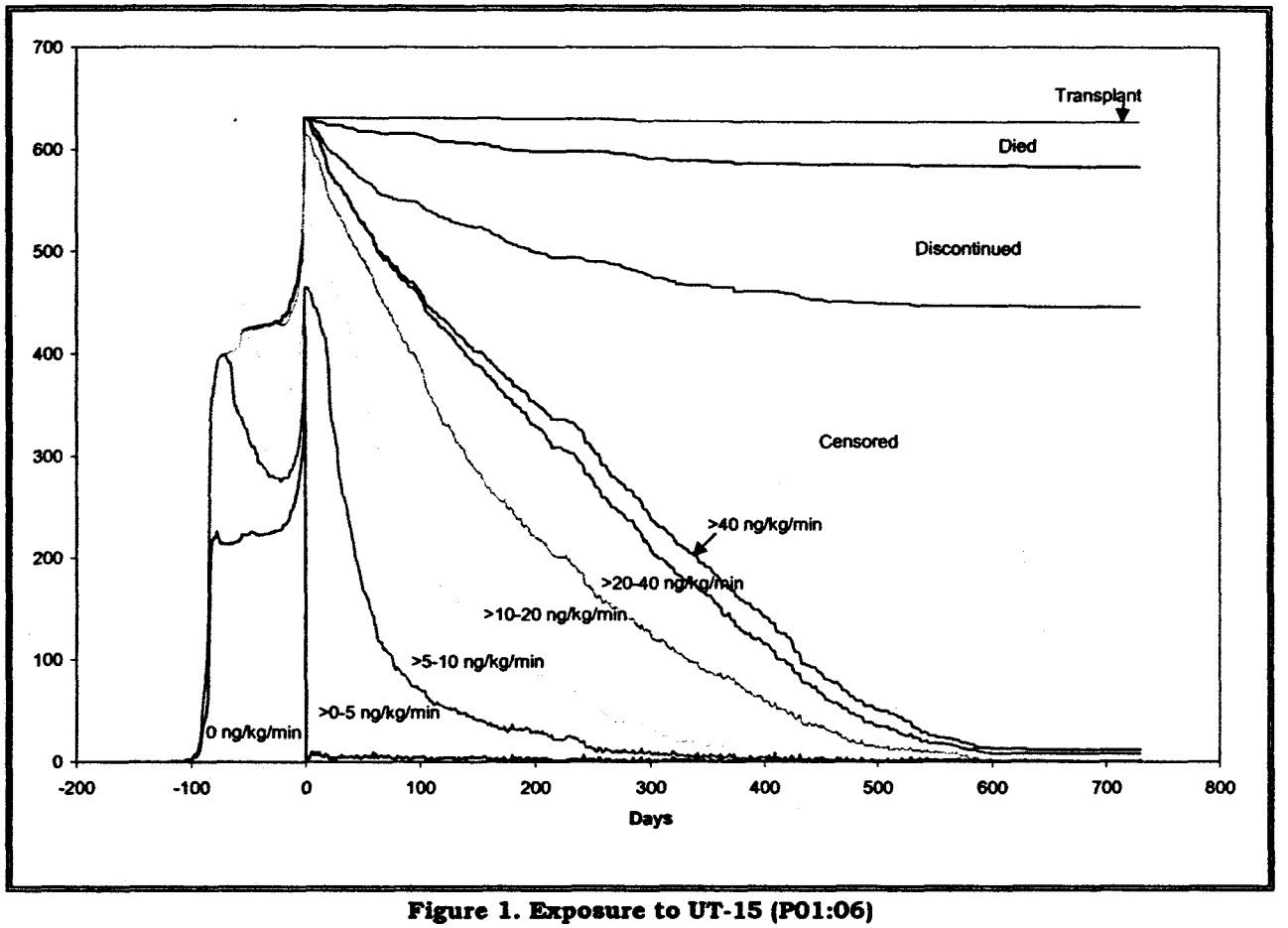

Figure 1. Exposure to UT-15 (P01:06)

Figure is a stacked bar chart in which each subject contributes in one of a number of states on each day after enrollment. Subjects entering from studies P01:03, P01:04, and P01:05 have dosing information prior to enrollment in P01:06. Data obtained from 120-day safety update.

The proportion of subjects who remained alive, in study, and on a non-zero dose of UT-15 is shown in Figure 2.

Figure 2. "Life-table" for remaining on UT-15 (P01:06)

Proportion of subjects remaining on a non-zero dose of UT-15 among subjects not censored by the reporting cutoff date. This is not a true life table, because subjects could go to a zero-dose and subsequently return on treatment.

For subjects in study P01:06 who remained on any non-zero dose, the proportion on various doses is shown in Figure 3.

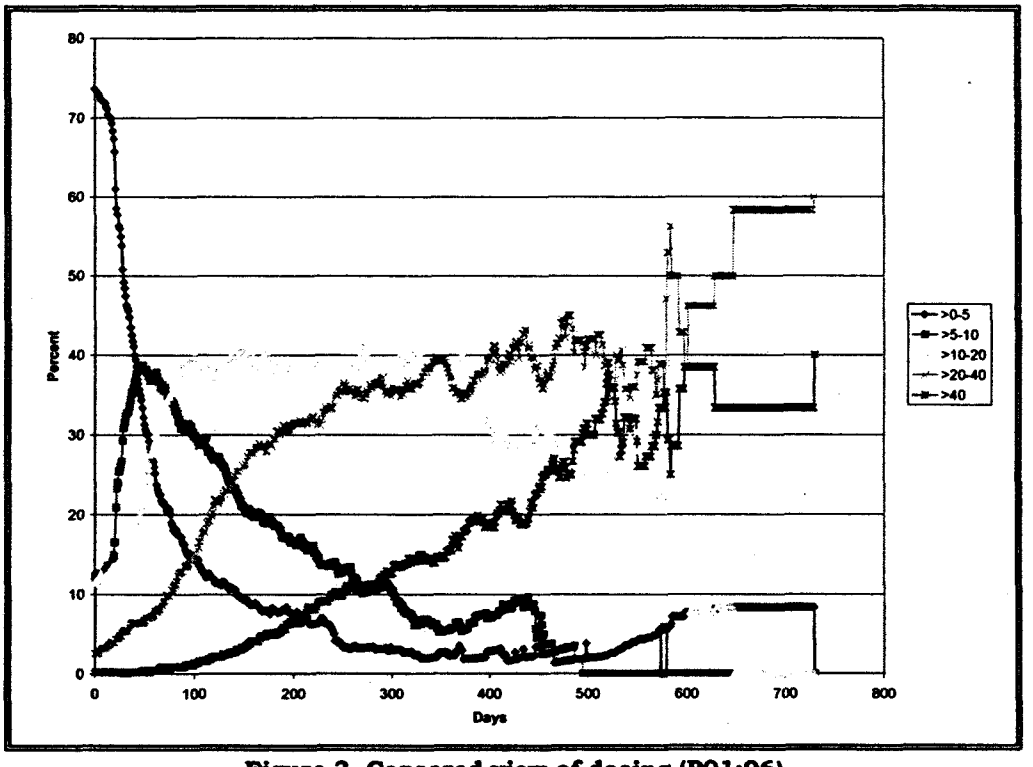

Figure 3. Censored view of dosing (P01:06)

The demoninator is the number of subjects on any non-zero dose. Data from 120-day safety update.

4.1.3 Demographics

There were few males, few non-Caucasians, and few subjects over age 65. No separate analyses were performed in these subgroups.

4.2 Secondary source data

4.2.1 Other studies

There are no other known studies with UT-15.

4.2.2 Post-marketing experience

There is no post-marketing experience with UT-15.

4.2.3 Literature

No publications were found that did not correspond with identified studies.

4.3 Adequacy of clinical experience

The development program appears to have been large enough to have reliably detected a reasonably sized treatment effect. The population studied contained relatively few males and relatively few representatives of racial minorities, but there are no data to suggest such groups respond differently to pulmonary hypertension or to treatments for pulmonary hypertension.

Long-term exposure in approximately 600 subjects or 500 subject-years is adequate to exclude, with 95% confidence, an incidence of unobserved adversity at the rate of about one per 150 exposed patients or one per 125 patient-years. This is rather less safety data than is frequently available for the evaluation of a new chemical entity.

4.4 Data quality and completeness

Case report forms were provided for all subjects who died or were withdrawn for medical reasons. A spot-check comparing values in the CRF with the sponsor's electronic data revealed no discrepancies.

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5 Integrated review of effectiveness

Studies P01:04 and P01:05 are the key pivotal studies[3]. The procedures and measurements for these two protocols were identical and the studies were analyzed both individually and as a single pooled study. Subjects who enrolled into these studies were symptomatic pulmonary hypertension subjects (NYHA Class II-IV), despite optimum concurrent therapies. The etiology of the pulmonary hypertension could be either primary disease or could be as consequence of either collagen vascular disease or left to right congenital shunts.

5.1 Six-minute walk

The primary end point was the change in walking distance from baseline at the end of week 12. For the pivotal analyses, missing values for those who discontinued were imputed. Those who discontinued either because of death, deterioration or transplantation received the worst rank or worst value. Those who discontinued due to adverse events had their last rank carried forward or their last metric for walk carried forward.

The primary method of analysis was a non-parametric analysis of the pooled studies. The database was to be considered demonstrating a benefit for UT-15 if either both studies were by themselves significant at the $p< 0.049$ or if one study was significant ($p< 0.049$) and the pooled studies had a p-value of less than 0.01.

By the sponsor's own analysis the database would not be considered successful. Neither of the studies demonstrated a p-value of < 0.049 ($p=0.06$ for both studies), although the pooled studies demonstrated an overall p-value of < 0.01 ($p=0.006$ for the pooled studies]. The magnitude of the change in median walking distance was small, ranging from 2 meters in study P01:04 to 19 meters in study P01:05. The fractional increase in walk distance over baseline for UT-15 patients relative to vehicle was between < 1% to a 6% increase for each or the studies and a pooled increase of approximately 3%.

Not only did the sponsor's analysis not meet the pre-specified criteria for considering the trials a success but also there was an inherent bias in the statistical approach employed in the analysis of the study. There was a clear imbalance in the number of subjects who discontinued for adverse events. Nearly all such discontinued subjects were treated with UT-15 and nearly all those who discontinued did so for infusion site pain or infusion site reaction.

There are several consequences that result from this algorithm for imputing data for discontinued subjects. First, those who discontinue due to adverse events could never be classified as worst outcomes even if they should subsequently die, deteriorate or receive a lung transplant. The fraction of subjects who discontinued for adverse events, therefore, was shielded from the worst imputed outcome values possible in this study.

Second, nearly all subjects that discontinued in the UT-15 group did so because of infusion site pain/ reaction. Since infusion site pain was ubiquitous in the UT-15 subjects, those who discontinued were possibly suffering from infusion site pain in conjunction with a worsening of their pulmonary hypertension. The attribution of cause and therefore the imputed value was markedly dependent on this attribution.

Third, the process of imputation presupposes the values at early times are reflective of the performance at the time of discontinuation. There are clearly subjects whose imputed value for walking distance does not reflect their status at the time of discontinuation. Subjects who discontinue for pain, whose discontinuation fell within

[3] *For a full description, see Section A.4 on page 82.*

the time-window of an exercise test and who did not undergo testing were imputed an earlier value, which would likely be better than their current status.

Lastly, there was an asymmetry in the need for pain medication that could alter vascular dynamics or mitigate some of the disease symptoms particularly those that are associated with pain.

In order to deal with the inherent biases due to the unequal rates of discontinuation for adverse events the data was analyzed in three additional ways. The first analysis included as worst outcomes three UT-15 and two vehicle subjects who died or were transplanted during the 100-day window of the study. The resulting p-values of the pooled database to 0.02 and that for the individual studies to >0.1.

The second analysis further includes as worst outcome, those subjects who discontinued for adverse events if Flolan® was started within one month of discontinuation and within the window of the study. There were six additional subjects. Two subjects were started on Flolan® either prior to or immediately upon discontinuation of UT-15. Two additional subjects were started within two weeks of discontinuation of UT-15 and two within one month of discontinuation of UT-15 therapy. None of these subjects obviously required Flolan® at baseline and the need for Flolan® upon discontinuation of UT-15 suggests that the subject's status had deteriorated. The p-values for the pooled and individual studies when treating those subjects started on Flolan® within 1 month of discontinuing UT-15 as well as those who died or required transplant as worst outcomes, no longer are significant. For the pooled data, the p-value was 0.082. For the individual studies the p value was > 0.2.

A third analysis also included all those who were treated with Flolan® during the window of the study as worst outcomes. In addition, there was one subject whose status at the time of discontinuation appeared to be inconsistent with the imputed measurement from week 1. The value for this subject was excluded. The p-values for this analysis for the pooled data was >0.1. The p-values for each of the individual studies were >0.2.

The above analyses presume that all subjects who discontinued UT-15 therapy and received Flolan® did so because they deteriorated. Some or all of these subjects, however, may have been started on Flolan® because no other options were available. An alternate analysis, performed by the sponsor imposes a last rank value for all those who discontinued prematurely, even if the reason was death, deterioration or need for transplantation. This analysis removes one source of the bias against the placebo in that no subject received a worst outcome. This analysis is sponsor's analysis # 4 in this review. The p-value for the pooled studies was 0.011 and that for the individual studies was between 0.07-0.08.

In summary, the study did not succeed by the pre-specified criteria of success. Neither study P01:04 nor P01:05 was by itself statistically significant by a method of analysis that biases results towards UT-15 treatment. Additional analyses that corrected for the asymmetry in adverse events completely eliminate any benefit even for the pooled studies.

5.2 Supportive metrics

Since the primary outcome of the study did not succeed by the pre-specified criteria, supportive measures of efficacy are more difficult to interpret. Nevertheless, there is a suggestion from the supportive information that UT-15 may have some effect on symptoms associated with severe pulmonary hypertension. The supportive symptoms were collected only among those who completed the study. Those who discontinued for any reason did not have any values imputed. In addition, the supportive symptoms

were administered by the treating physician who might have been aware, based on the nature of infusion site reaction the subject's treatment.

Subjects showed improvement in the composite of sixteen signs and symptoms of pulmonary hypertension. The metric that was used was a composite of all these symptoms. Subjects were assigned a "+1" for symptoms present at baseline and absent after 12-weeks, and a "-1" for symptoms that went from absent to present. Symptoms that were present at baseline and present at end of study, or absent at baseline and absent at end of study were assigned a value of "0". The net change for each subject was averaged over all those who approximately 1 unit for those treated with UT-15. The specific symptoms that were improved or were less frequently worsened in the UT-15 group were dizziness, palpitations, orthopnea and chest pain. The most troublesome symptoms of pulmonary hypertension, dyspnea and fatigue did not appear to be differentially resolve across groups.

A second metric that was prospectively collected as a supportive end-point was the dyspnea fatigue index. This metric consists of three components with values ranging from 0-4. The three components are "magnitude of task", "magnitude of pace" and "functional impairment". The higher the value, the less symptomatic the subject. There was a net increase of approximately 1.4 units in the overall symptom score among those treated with UT-15, approximately equally divided among the three components of this metric.

The quality of life metric was the Minnesota Living With Heart Failure questionnaire. This questionnaire consists of 21 questions and is divided in to 4 dimensions. This questionnaire was validated among subjects with CHF but not among patients with pulmonary hypertension, although the specifics of the questionnaire should be broadly applicable to patients with pulmonary hypertension. The questionnaire consists of a global and three components termed dimensions (i.e. physical, economical and emotional dimension). This questionnaire was not apparently administered to all subjects. Overall the global QOL did not differ between the two treatments. The physical dimension [portion of the questionnaire, however, was statistically favored the UT-15 group.

Each subject was asked to rank his or her degree of breathlessness after each six-minute walk by the Borg-dyspnea scale. This metric ranged from 1-10. The higher numbers suggest greater degrees of shortness of breath. The exercise coordinator performed this task and consequently is more likely to have been shielded from telltale signs suggesting active drug or vehicle use. Both the pooled studies and each of the individual studies were highly significant in improvement ($p<0.01$) of this metric. The magnitude was approximately 0.8 units.

5.3 End points related to the natural course of the disease

Despite modest effects on measurements of performance and symptoms, there does not appear to be any evidence that UT-15 alters the natural course of pulmonary hypertension. Deaths, hospitalizations, cardiovascular/pulmonary hypertension hospitalizations or need for new or increases in medications were no different between groups. The need for inotropic or Flolan® support during the 12-week study did not differ between the two treatments.

There were a total of 19 subjects who died during the window of the study. Ten of these subjects were in the vehicle group and nine in the UT-15 group.

Hospitalizations were equivalent in both groups. There were 40 subjects who were hospitalized or had their hospitalizations prolonged among the vehicle group and 38 among the UT-15 group. Two of those hospitalized among those randomized to vehicle were hospitalized after accidentally receiving UT-15. The investigators at the various study sites did not adjudicate cause-specific hospitalizations. This reviewer, based on

the capsular summaries found 22 of those treated with UT-15 and 25 of those treated with vehicle had their hospitalizations prolonged or had a de novo hospitalization as a consequence of cardiovascular or pulmonary hypertension etiologies.

Subjects who status deteriorates may require new medications or increase in doses of ongoing medications. A difference in the need to alter medications may suggest a benefit of a given treatment. For the purposes of this assessment the following drug classes were considered: 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. The number of subjects who required no change in medication or no increase in medication comparing baseline to week-12 were similar in both groups.

There was no difference in the number of subjects who required Flolan® or inotropic support. This reviewer counted 12 subjects in the UT-15 group and 10 in the vehicle group that required one of these medications.

5.4 Hemodynamics

Among those who completed the study, there was a modest improvement in catheterized hemodynamics. Right atrial pressures, pulmonary artery pressures (mean, systolic and diastolic) and pulmonary vascular resistance were decreased. Cardiac index, stroke index and mixed venous oxygenation were increased. The effects on hemodynamics, though statistically significant were 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 8%. There was an approximately 5% (3 mm Hg) decrease in mean pulmonary artery pressure. There was an approximately 18% decrease in pulmonary vascular resistance.

5.5 Dosing

Dosing was predicated on improving symptoms of pulmonary hypertension while minimizing excessive pharmacologic effect or infusion related adverse events. It is therefore not possible to define either the initial, optimal or an appropriate dose range of use for UT-15 based on the data from this study or from the database as a whole.

Despite nearly an order of magnitude increase in mean infusion rate, there was minimal increase in walking distance among those treated with UT-15. The observed differences more reflect a worsening of the distance walked by the vehicle group than by an improvement among those taking larger and larger infusions of UT-15. There was no randomized withdrawal to ascertain a persistent (or any) benefit of UT-15. In fact among the handful of subjects who discontinued UT-15 acutely, no evidence of rebound was described. It is therefore unclear if there was any persistent beneficial effect of UT-15.

5.6 Comparison with Flolan

Flolan is approved for the treatment of patients with primary pulmonary hypertension Class III and IV. However, its use is difficult and inconvenient. The infusion of Flolan requires the insertion of an indwelling central catheter with the attendant risks of the inserting the catheter and the subsequent risk of catheter infection. Flolan has a rapid half-life and rapid dissipation of its hemodynamic effects. Any inadvertent interruption of the infusion is potentially life threatening. Flolan is chemically labile at room temperatures and must be reconstituted every 8 hours or kept at cold temperatures during the infusion. UT-15 was developed to avoid these problems and thereby delay the time till Flolan treatment becomes infusion.

There is no scientific rationale to concurrently use UT-15 with Flolan. There is also no empirical safety or efficacy information on the concurrent use of these drugs. UT-15 is intended as treatment of pulmonary hypertension solely to postpone starting Flolan. There is no study that randomized patients to Flolan or UT-15 that demonstrates

equivalent outcomes so that there may be unintended negative consequences in the delay of Flolan infusion. Comparing the labeling of Flolan to the likely labeling of UT-15 the mortality benefit for Flolan does not appear to be uniformly observed with UT-15. The current labeling of Flolan states:

> *"Survival was improved in NYHA functional Class III and IV PPH patients treated with FLOLAN for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period 8 of 40 patients receiving standard therapy alone died, whereas none of the 41 patients receiving FLOLAN died (P=0.003)."*

In the pivotal UT-15 studies (P01:04 and P01:05) the drug demonstrated no mortality benefit. The UT-15 study population consisted of predominantly (55%) primary pulmonary hypertension patients with the vast majority NYHA Class III and this portion of the population coincides with the population for which Flolan demonstrated a mortality benefit. There were 9 deaths among those randomized to UT-15 and 10 deaths among those randomized to vehicle during the 12-week study. Five of the 9 deaths on UT-15 were patients with primary pulmonary hypertension while 8 of the 10 deaths on vehicle were patients with primary pulmonary hypertension.

Performance benefit on the 6-minute walk for UT-15 patients was small, approximately 3% of the baseline walk distance. Performance among those with Flolan was approximately 35-50% of baseline walk distance. Admittedly, the basis of comparison is across studies with different designs. Nevertheless, the magnitude of effects a does give one pause before assuming equivalence between UT-15 and Flolan.

6 Integrated review of safety

6.1 Methodology

6.1.1 Mortality

Mortality was a primary end point in no studies. Most studies were of duration short compared with the lifetime of patients with pulmonary hypertension, so most mortality occurred in the 12-week studies P01:04 and P01:05 and the long-term open-label follow-on study P01:06.

This review contains narrative summary of all of the deaths developed from the sponsor's summaries and the case report forms.

6.1.2 Withdrawals

Case report forms were available for medically related withdrawals. There were also narrative summaries of these events.

6.1.3 Adverse events

Case report forms provided a mechanism for reporting adverse events and identifying their seriousness, severity, and relationship to study drug. The sponsor provided a summary narrative and case report forms for serious nonfatal adverse events.

Common adverse events were separately tabulated for studies of normal volunteers, placebo-controlled studies in pulmonary hypertension, and chronic studies of open-label administration.

6.1.4 Laboratory findings

The principal laboratory data of interest were obtained during placebo-controlled studies. The sponsor tabulated changes from baseline in mean laboratory values. Electronic datasets provided by the sponsor were used to construct baseline-vs.-on-treatment plots for data from continuous measurements. Such graphs show the relationship between baseline and on-treatment values with a 45-degree line of no effect for orientation and, in the margins, box-and-whiskers plots of the distributions in various treatment groups.

6.1.5 Vital signs

Vital signs were monitored as a conventional aspect of in-hospital patient care, and they were systematically collected for the first 8 hours of randomized treatment in placebo-controlled studies P01:04 and P01:05.

6.1.6 ECGs

ECGs were collected at baseline and at the end of active treatment in the placebo-controlled studies. These were analyzed much like the laboratory data from these studies.

6.2 Results

6.2.1 Exposure

The sponsor's Integrated Summary of Safety covers the period up to 31 May 2000 for deaths and serious adverse events, and up to 4 February 2000 for other safety data.

A summary of studies, exposure to study drug, deaths, and serious adverse events is shown in Table 2.

Table 2. Exposure to UT-15[4].

Study	N	Route	Duration	On UT-15		
				Deaths	With	SAE
Studies of clinical pharmacology in subjects with CHF						
P76:01	12/12	iv	—	—	—	—
P01:01	14/14	iv	1.5 h	0	/4	12
P01:02	25/25	sc, iv	4 h	0	10/10	
Studies of pharmacokinetics in normal volunteers						
P01:07	15/15	sc, iv	2.5 h	0	0	0
P01:08	29/29	sc	2 x 6 h	0	0	0
P01:09	14/14	sc	28 d	0	/8	0
P01:10	6/6	sc	8 h	—	—	—
Controlled studies in pulmonary hypertension						
P01:03	26/17	sc	56 d	0	2/2	4
P01:04	224/113	sc	84 d	4	17/17	40
P01:05	246/123	sc	84 d	5	16/14	
Uncontrolled studies in pulmonary hypertension						
P01:06	631/631[5]	sc	>819 d	36	150	170
P01:11	3/3	sc	240 d	0	0	1
P01:12	16/16	sc	10 d	—	—	—
Portopulmonary hypertension						
P02:01	9/9	sc	2.5 h	0	—/0	—
Peripheral vascular disease						
P03:01	8/—	iv	—	—	—	—

A brief description of these studies is given in the following paragraphs.

Study P01:01 was a two-period crossover study in which subjects were titrated to the maximum tolerated dose of Flolan and UT-15 and maintained for 90 minutes.

Study P01:02 was a parallel study in which subjects received UT-15 10 ng/kg/min for 1.25 h, followed by 5, 10, or 20 ng/kg/min for 2.5 h.

Study P01:03 was a parallel study in which subjects received placebo or UT-15 for 8 weeks.

Studies P01:04 and P01:05 were parallel studies in which subjects received placebo or UT-15 for 12 weeks.

Study P01:06 is an ongoing open-label study conducted among subjects previously enrolled in Studies P01:03, P01:04, or P01:05, and 208 subjects newly enrolled. As of the cutoff date, exposure was 476 subject-years, with 224 subjects treated for more than 1 year.

Study P01:07 was a two-period crossover study of bioavailability, comparing intravenous and subcutaneous administration of UT-15 15 ng/kg/min over 2.5 hours.

Study P01:08 was a two-period cross-over study of pharmacokinetics, comparing placebo with acetaminophen 1000 mg in subjects on sc infusions of UT-15 15 ng/kg/min for 7 days.

Study P01:09 was an open-label, forced titration study in which normal subjects received ascending doses of UT-15 2.5, 5, 10, and 15 ng/kg/min each for 7 days.

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[4] N=total enrollment / exposed to UT-15; With=withdrawals total/medical

[5] The study is ongoing. The numbers refer to the NDA cutoff date of 1 October 2000.

Study P01:11 was an open-label study of the transition to UT-15 of subjects receiving Flolan.

Study P02:01 was an open-label, baseline-controlled study with dosing at 10 ng/kg/min sc for 2.5 h.

Study P76:01 was a single-center, open label study in subjects NYHA III-IV CHF.

6.2.2 Deaths

Two subjects died subsequent to completion of study P01:02.

- Study P01:02 subject #02005 was a 47 year old, 72-kg, Caucasian female with a 4-year history of primary pulmonary hypertension, NYHA IV at baseline. She completed study with UT-15 without problems except intermittent backache[6]. The following day, she had a central venous catheter placed for Flolan administration, but she developed electromechanical dissociation and died despite CPR efforts, prior to Flolan administration. The investigator and sponsor regard the death as not reasonably attributable to UT-15.
- Study P01:02 subject #04004[7] was a 39 year old female with NYHA III primary pulmonary hypertension who completed study with UT-15 without incident. She remained in hospital for insertion of a central venous catheter and was discharged on Flolan 4 ng/kg/min. She was readmitted the following day (2 days after the last dose of UT-15) with syncope and dizziness, seized, had a brady-asystolic arrest, and died the same day despite CPR efforts. Death was attributed to decompensated cor pulmonale. The investigator and sponsor regard the death as not reasonably attributable to UT-15.

In studies P01:04 and P01:05, there were 9 deaths (3.8%) on UT-15 and 10 deaths (4.3%) on placebo.

Deaths on UT-15 are summarized in the paragraphs below:

- Study P01:04 subject 004017 was a 32 year old, 70-kg female with a 1-month history of PPH, NYHA III at baseline. She was having injection site pain and inject site reaction throughout treatment. She developed right heart failure on day 21 (UT-15 4 ng/kg/min). She was hospitalized and died, 3 days after decreasing the dose of study drug. Events were attributed to underlying disease.
- Study P01:04 subject 009006 was a 29-year-old, 55-kg female with congenital atrial septal defect, NYHA III at baseline. She had a stroke (pontine infarct with bilateral loss of vision) on day 2, several hours after Swan-Ganz removal. She received UT-15 1 ng/kg/min for about 9 hours. Thrombotic stroke was diagnosed by MRI and cerebral angiography, and she was treated with thrombolysis, but died 3 days after study drug administration. Events were attributed to catheterization and not to study drug.
- Study P01:04 subject 010002 was a 40-year-old, 114-kg female with mixed connective tissue disease, NYHA IV at baseline. She was hospitalized on day 57 of treatment (UT-15 7.5 ng/kg/min) with right

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[6] CRF is ambiguous as to whether this subject discontinued for backache.

[7] CRF was not provided.

heart failure, and treated with diuretics, inotropes, and increased UT-15 (12 ng/kg/min). On day 81 (apparently still on UT-15), she developed ventricular tachycardia that did not respond to resuscitation.

- Study P01:04 subject 023002 was a 15-year-old 40-kg female status post repair of ventricular septal defect, NYHA II at baseline. On day 52 of treatment with UT-15 4 ng/kg/min, she had respiratory arrest at home and died in the ER despite resuscitation attempts. Death was attributed to her underlying condition.
- Study P01:05 subject 004503 was a 36 year old, 49-kg Hispanic female with a 3-year history of primary pulmonary hypertension, NYHA III at baseline. She discontinued UT-15 5 ng/kg/min on day 49 to undergo medical termination of pregnancy. Her hospital course was complicated by low cardiac output, disseminated intravascular coagulopathy, oliguria, hypoxemia, and sepsis. She died 7 days after discontinuing UT-15. Death was attributed to sepsis.
- Study P01:05 subject 051007 was a 28 year old 58-kg Caucasian female with recent onset of primary pulmonary hypertension, NYHA II at baseline. At her week-12 cardiac catheterization (day 86 on UT-15 20 ng/kg/min), she had vasovagal syncope, followed by complete A-V block, electromechanical dissociation, and death.
- Study P01:05 subject 054005 was a 20 year old 40-kg Caucasian female with congenital left-to-right shunt, NYHA III at baseline. She was hospitalized on day 43 of treatment (UT-15 2.5 ng/kg/min) for worsening hemodynamics and hypoxemia, thought to be pulmonary embolus. She was treated with vasodilators and anticoagulation, but died 8 days after admission. It is unclear how long previously UT-15 was stopped. Death was attributed to pulmonary embolus and underlying condition and not to study drug.
- Study P01:05 subject 055005 was a 32 year old 87-kg female with a 9-month history of primary pulmonary hypertension, NYHA IV at baseline. She was receiving UT-15 1.25 ng/kg/min up to day 6, when she was hospitalized with recurrent syncope, chest pain, and hypotension. Myocardial infarction was suspected, but she developed intractable ventricular fibrillation prior to angiography. The investigator and sponsor disagree on the possible role of UT-15 in these events.
- Study P01:05 subject 058001 was a 39 year old, 83-kg Caucasian male with a 15-month history of primary pulmonary hypertension, NYHA III at baseline. He was receiving UT-15 1.5 ng/kg/min on day 17 when he was admitted to hospital for hemoptysis, hyponatremia, and hyperkalemia. Pulmonary embolus was suspected. Renal and respiratory function declined and he died on day 7 of admission (unclear whether still on UT-15) with bradycardia followed by cardiac arrest. These events were not attributed to UT-15.

Deaths on placebo are summarized in the paragraphs below.

- Study P01:04 subject 009012 was a 56 year old 80-kg Caucasian male with a 2-year history of primary pulmonary hypertension, NYHA IV at baseline. He died on day 9, one day after being admitted to

hospital for right heart failure. Events not considered related to study drug.

- Study P01:04 subject 010001 was a 65 year old 80-kg male with a 1-year history of mixed connective tissue disease, NYHA IV at baseline. On day 36, he was hospitalized with hematemesis and acute respiratory distress. Six days later, he developed bradycardia and cardiac arrest from which he could not be resuscitated. Events not considered related to study drug.
- Study P01:04 subject 015003 was a 23 year old 60-kg Caucasian female with a 3-year history of systemic lupus erythemetosis and mixed connective tissue disease, NYHA III at baseline. She was hospitalized on day 46 for dyspnea and hypoxemia attributed to right-to-left shunting through a patent foramen ovale. She arrested during a pericardiocentesis procedure and did not survive. Events were not attributed to study drug.
- Study P01:04 subject 016003 was a 67 year old 54-kg female with a 4-month history of scleroderma, NYHA III at baseline. She was hospitalized on day 85 for acute respiratory failure. Death 3 days later was attributed to progression of right heart failure.
- Study P01:04 subject 016006 was a 57 year old 45-kg female with a 5-year history of primary pulmonary hypertension, NYHA III at baseline. On day 74, she was hospitalized with a 3-day history of progressive right heart failure symptoms. She underwent 'week-12' right heart catheterization and the decision was made to start IV Flolan, but a few hours later she arrested and could not be resuscitated. Death was attributed to progression of right heart failure.
- Study P01:05 subject 052006 was a 46 year old 97-kg female with a 1-year history of primary pulmonary hypertension, NYHA III at baseline. On day 32, she was hospitalized with upper respiratory infection, fever, and heart failure symptoms. The blind was broken and study drug was discontinued. She died from cardiogenic shock the following day.
- Study P01:05 subject 060006 was a 17 year old 55-kg Caucasian female with an 11-year history of primary pulmonary hypertension, NYHA IV at baseline. On day 60, she was hospitalized with right heart failure. She died 2 days later following cardiac arrest.
- Study P01:05 subject 060015 was a 19 year old 60-kg Caucasian female with a 4-year history of primary pulmonary hypertension, NYHA III at baseline. On day 47, she was hospitalized for right heart failure. Despite treatment, she progressed to cardiogenic shock and died the following day.
- Study P01:05 subject 065004 was a 51 year old 64-kg Caucasian female with a 6-month history of primary pulmonary hypertension, NYHA III at baseline. On day 18, she was hospitalized for dyspnea and chest pain, and had a cardiac arrest from which she could not be resuscitated.
- Study P01:05 subject 065011 was a 59 year old 67-kg Caucasian male with a 1-year history of primary pulmonary hypertension, NYHA

III at baseline. On day 43, he was hospitalized for hypoxemia and was switched to Flolan. Thirty-one days later, he died suddenly. Autopsy revealed features of PPH and heart failure; death was attributed to arrhythmia.

The following deaths were reported with open-label follow-on study P01:06. None were considered reasonably attributable to study drug.

- P01:06 subject 302003 was a 44 year old Caucasian female, 75 kg, with a 3-year history of primary pulmonary hypertension, NYHA III at baseline. After 20 months on UT-15 (apparently at 37.5 ng/kg/min), she was hospitalized and died from a pulmonary hypertensive crisis.
- Study P01:06 subject 302013 was a 13 year old Caucasian female with a 3 month history of primary pulmonary hypertension, NYHA III at baseline. She died from pulmonary hemorrhage after 1 year on UT-15, most recently 18 ng/kg/min.
- Study P01:06 subject 402007 was a 58 year old 76 kg Caucasian female with a 2 year history of primary pulmonary hypertension, NYHA III at baseline. She died from hypotension after 1 year on UT-15, most recently 25 ng/kg/min.
- Study P01:06 subject 603604[8] was a 49 year old Caucasian male with a 4 month history of pulmonary hypertension associated with scleroderma, NYHA III at baseline. He was discharged from hospital on the day following initiation of UT-15, and then was readmitted on day 2 to day 5, and then again on day 6 to day 13. On day 14, he was found unresponsive at home and died the same day in the hospital ER, while receiving UT-15 2.5 ng/kg/min.
- Study P01:06 subject 404013 was a 67 year old Caucasian female, 59 kg, with a 2 year history of pulmonary hypertension associated with scleroderma, NYHA IV at baseline. She died of heart failure at 6 months, attributed to underlying disease, while receiving UT-15 24 ng/kg/min.
- Study P01:06 subject 409002 was a 61 year old Caucasian female, 45 kg, with a 2 year history of pulmonary hypertension associated with mixed connective tissue disease, NYHA III at baseline. She died at 6 months from sepsis, while receiving UT-15 31 ng/kg/min.
- Study P01:06 subject 409007 was a 36 year old Caucasian female, 95 kg, with a 6 month history of primary pulmonary hypertension, NYHA III at baseline. She completed a previous trial on active treatment. She died from cardiac arrest on day 5, while receiving UT-15 14 ng/kg/min.
- Study P01:06 subject 409019 was a 35 year old Caucasian male with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. He died a sudden death at month 3, while receiving UT-15 18 ng/kg/min.
- Study P01:06 subject 410005 was a 28 year old Caucasian female with a 6 month history of pulmonary hypertension associated with mixed connective tissue disease, NYHA III at baseline. She died of

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[8] *Adverse event pages of CRF are missing for this subject. Apparently, he was newly enrolled in Study P01:06.*

worsening pulmonary hypertension after 13 months, while receiving UT-15 3 ng/kg/min.

- Study P01:06 subject 410022 was a 35 year old Caucasian female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She died at 6 months, attributed to pulmonary hypertension and right heart failure, while receiving UT-15 6.5 ng/kg/min.
- Study P01:06 subject 410026 was a 32 year old Black female, 72 kg, with a 3 month history of primary pulmonary hypertension, NYHA III at baseline. She died at 5 months with pulmonary hypertension, while receiving UT-15 1.7 ng/kg/min.
- Study P01:06 subject 412005 was a 49 year old Caucasian female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She died a sudden death at 3 months, while receiving UT-15 19 ng/kg/min.
- Study P01:06 subject 414002 was a 46 year old Caucasian female, 103 kg, with a 2 year history of primary pulmonary hypertension, NYHA III at baseline. She had a sudden death at 2 months, while receiving UT-15 11 ng/kg/min.
- Study P01:06 subject 414011 was a 28 year old Caucasian female with a 7 month history of pulmonary hypertension associated with systemic lupus erythematosus, NYHA II at baseline. She received placebo during the previous study. She died on day 21 of cardiac arrest associated with progressive right heart failure, while receiving UT-15 2 ng/kg/min.
- Study P01:06 subject 420010 was a 19 year old Hispanic female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She received placebo during the previous study. She had sudden death at 3 months, while receiving UT-15 23 ng/kg/min.
- Study P01:06 subject 624603 was a 20 year old Hispanic female, 57 kg, with a 6 month history of primary pulmonary hypertension, NYHA III at baseline. She was newly recruited into this study, so there was no previous exposure to UT-15. She died on day 34, from cardiac arrest associated with severe pulmonary hypertension, while receiving an unknown dose of UT-15.
- Study P01:06 subject 550014 was a 51 year old Caucasian male, 81 kg, with a 4 year history of primary pulmonary hypertension, NYHA IV at baseline. He died at day 17 from low cardiac output, while receiving UT-15 2.5 ng/kg/min.
- Study P01:06 subject 550023 was a 38 year old Caucasian female with a 1 year history of pulmonary hypertension associated with mixed connective tissue disease, NYHA IV at baseline. She died on day 42 with progressive pulmonary hypertension, while receiving UT-15 9 ng/kg/min.
- Study P01:06 subject 552004 was a 27 year old Caucasian female, 59 kg, with a 5 month history of primary pulmonary hypertension, NYHA III at baseline. She died at 3 months from cardiac arrest and

right heart failure, while receiving UT-15 10 ng/kg/min.

- Study P01:06 subject 553011 was a 12 year old Caucasian female with pulmonary hypertension associated with a congenital left-to-right shunt, NYHA III at baseline. She received UT-15 in a previous study. She died from pneumonia and ARDS on day 9. The CRF in conflicted about whether she was receiving UT-15 (13 ng/kg/min) up to the time of death.
- Study P01:06 subject 554004 was a 20 year old Caucasian female with pulmonary hypertension associated with congenital left-to-right shunt, NYHA III at baseline. She had a sudden death at 4 months, while receiving UT-15 10 ng/kg/min.
- Study P01:06 subject 657601 was an 83 year old Caucasian male with a 5 year history of primary pulmonary hypertension, NYHA III at baseline. He had a sudden death at 2 months, while receiving UT-15 3.7 ng/kg/min.
- Study P01:06 subject 559008 was a 35 year old Caucasian male, 68 kg, with a 7 year history of primary pulmonary hypertension, NYHA III at baseline. He previously received placebo. He died on day 7 with progressive right heart failure, while receiving UT-15 2.5 ng/kg/min.
- Study P01:06 subject 560002 was a 38 year old Caucasian female, 50 kg, with a 3 year history of primary pulmonary hypertension, NYHA III at baseline. She died from decompensated right heart failure at 4 months, while receiving UT-15 13 ng/kg/min.
- Study P01:06 subject 560014 was a 56 year old Caucasian female, 60 kg, with a 6 month history of primary pulmonary hypertension, NYHA III at baseline. She died from right heart failure at 4 months, while receiving UT-15 7 ng/kg/min.
- Study P01:06 subject 565014 was a 57 year old Caucasian female, with a 4 month history of pulmonary hypertension associated with scleroderma, NYHA III at baseline. She died on day 47 with progressive right heart failure, while receiving UT-15 5 ng/kg/min.
- Study P01:04 subject 04018 was a 65 year old Caucasian female, 54 kg, with primary pulmonary hypertension, NYHA III at baseline. She died of right heart failure on day 196 while receiving UT-15 28 ng/kg/min.
- Study P01:04 subject 05010 was a 61 year old Caucasian female, 82 kg, with lupus, NYHA IV at baseline. She died with right heart failure on day 315 while receiving UT-15 6 ng/kg/min.
- Study P01:04 subject 20005 was a 21 year old Hispanic female, 53 kg, with primary pulmonary hypertension, NYHA II at baseline. She died on day 294 with sepsis and pneumonia, while receiving 38 ng/kg/min.
- Study P01:05 subject 22501 was a 64 year old Caucasian female, 50 kg, with systemic sclerosis, NYHA III at baseline. She died with acute exacerbation of respiratory failure, on day 290, while receiving UT-15 23 ng/kg/min.
- Study P01:05 subject 53003 was a 61 year old Caucasian female, 74

kg, with primary pulmonary hypertension, NYHA IV at baseline. She died, with progressive right heart failure, on day 530, while receiving UT-15 46 ng/kg/min.

- Study P01:05 subject 53009 was a 56 year old Caucasian female, 64 kg, with primary pulmonary hypertension, NYHA III at baseline. She died on day 265 with sepsis, renal failure, and pneumonia, while receiving UT-15 17 ng/kg/min.
- Study P01:05 subject 64005 was a 54 year old Caucasian female, 61 kg, with primary pulmonary hypertension, NYHA III at baseline. She had a sudden death attributed to cor pulmonale on day 162, while receiving UT-15 19 ng/kg/min.
- Study P01:06 subject 14601 was a 73 year old Caucasian female, 65 kg, with primary pulmonary hypertension, NYHA IV at baseline. She died a sudden death on day 115, about 6 weeks after a myocardial infarction, while receiving UT-15 18 ng/kg/min.
- Study P01:06 subject 51601 was a 53 year old Caucasian female, 74 kg, with primary pulmonary hypertension, NYHA III at baseline. She died with pulmonary edema on day 147, while receiving UT-15 21 ng/kg/min.
- Study P01:06 subject 59603 was a 33 year old Caucasian female, 50 kg, with primary pulmonary hypertension, NYHA III at baseline. She died with right heart failure on day 37, while receiving UT-15 8 ng/kg/min.

A total of 116 subjects discontinued UT-15 in studies P01:04, P01:05 and (to the original cutoff date for) P01:06. In 40% of these the dose of UT-15 was apparently terminated abruptly. Half of the subjects who terminated UT-15 went on to receive Flolan. There were 15 deaths in the first 30 days after termination of UT-15 in study P01:06, 9 among subjects discontinued for deterioration. Five deaths occurred in the first 24 hours after discontinuing UT-15.

- Study P01:05 subject 550013 was a 34 year old Indian female with primary pulmonary hypertension, NYHA III at baseline. She discontinued from UT-15 2 ng/kg/min at 6 weeks because of infusion site pain. Other complaints were increased breathlessness and fatigue. The following day, she died a sudden death, attributed to progressive pulmonary hypertension.
- Study P01:06 subject 409001 was a 30 year old Caucasian female with primary pulmonary hypertension, NYHA II at baseline. She discontinued at 4 months (17 ng/kg/min) for pain. Her death in the emergency room, 12 hours later, was attributed to severe right heart failure.
- Study P01:03 subject 02010 was a female with primary pulmonary hypertension, NYHA III at baseline. After 3 months on UT-15, finally at 18 ng/kg/min, she developed sepsis and worsening pulmonary hypertension and she was discontinued to initiate Flolan. Death 2 days later was attributed to sepsis.
- Study P01:05 subject 58009 was a 39 year old female, 55 kg, with congenital left to right shunt, NYHA III at baseline. After 170 days on UT-15, up to 6 ng/kg/min, she was hospitalized with syncope and

aspiration pneumonia. Five weeks later, UT-15 was discontinued and Flolan was started, but she developed sepsis and complete A-V block and died the following day.

- Study P01:06 subject 61609 was a 31 year old female, 57 kg, with primary pulmonary hypertension, NYHA IV at baseline. She developed severe dyspnea and hypoxia on day 10, discontinued UT-15 5 ng/kg/min and started Flolan. She died the following day with hypoxia.

The other ten deaths occurred 2, 3, 3, 6, 8, 8, 9, 10, 13, and 17 days after discontinuation of UT-15.

6.2.3 Withdrawals

Essentially all of the withdrawals were medically related. The most common reason for withdrawal among normal volunteers was injection site pain and injection site reaction. Among subjects with pulmonary arterial hypertension of various etiologies, the most common reasons for withdrawals were plausibly related to disease progression.

6.2.4 Adverse events

6.2.4.1 Serious

There was one serious adverse event in study P01:01 with no plausible relationship to UT-15.

- Study P01:01 subject 03001 discontinued during screening because of vasovagal reaction. This event took place before exposure to study drug.

There one serious adverse event in study P01:02 with no plausible relationship to UT-15.

- Study P01:02 subject #09002 developed respiratory distress subsequent to a hematoma of the neck during cardiac catheterization prior to study drug administration. Subject went on to receive protocol-specified exposure to UT-15 without incident.

There was one serious adverse event among 3 subjects in study P01:11 (transition from Flolan to UT-15).

- Study P01:11 subject 1102001[9] was a male of unknown age or history enrolled to switch from Flolan to UT-15 because of recurrent cerebral emboli. During the transition, he had a cerebral vascular accident that was attributed to the Flolan catheter.

Eight subjects are described as having had overdoses of UT-15 during studies P01:04 and P01:05 or follow-on study P01:06. The highest reported dose was a 1.5 mg bolus. Symptoms were headache, nausea, vomiting, and diarrhea. Some of these cases were dispensation errors among subjects randomized to placebo. Others were errors flushing the catheter or programming the infusion pump.

There were two cases of hemolytic anemia among subjects receiving UT-15 in studies P01:04 and P01:05. Both cases resolved during continued exposure to a lower dose of UT-15. A cause was not identified in either case.

6.2.4.2 Common

6.2.4.2.1 Normal volunteers

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[9] *CRF not provided.*

Common adverse events among normal volunteers in acute studies are listed in Table 3.

Table 3. Common adverse events in acute studies with normal volunteers (Studies P01:07 and P01:08).

	Incidence (%) N=44		Incidence (%) N=44
Headache	59	Infusion site pain	14
Nausea	32	Pain	11
Vomiting	16	Jaw pain	11
Dizziness	16	Vasodilation	11

Headache, nausea, and dizziness were more common with iv dosing than with sc dosing.

Thirteen of 14 normal volunteers in 28-day study P01:09 reported adverse events, the most common of which are listed in Table 4.

Table 4. Common adverse events with chronic dosing among normal volunteers (study P01:09).

	Incidence (%) N=14		Incidence (%) N=14
Infusion site pain	86	Pain	43
Infusion site reaction	86	Infusion site bleed	36
Headache	79	Myalgia	29
Nausea	50	Akathesia[10]	21
Dizziness	43	Arthralgia	21

Infusion site pain and reaction were reported on low-dose UT-15, i.e., early in the study. No other events appeared to be related to dose.

6.2.4.2.2 Subjects with pulmonary hypertension

Eighty-three percent of subjects in acute studies of UT-15[11] reported at least one adverse event. The most common events are listed in Table 5.

Table 5. Common adverse events in acute studies of PAH (studies P01:01, P01:02, and P02:01).

	Incidence (%) N=48		Incidence (%) N=48
Headache	48	Jaw pain	10
Flushing	42	Vasodilation	8
Nausea	27	Vomiting	8
Back pain	17	Chest pain	8

None of the events appeared to be related to the dose of UT-15.

Common adverse events during longer-term exposure to UT-15 are shown in Table 6.

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[10] *Restlessness (literally, cannot sit still).*

[11] *Studies P01:01, P01:02, and P02:01.*

Table 6. Common adverse events in chronic studies of PAH (studies P01:03, P01:04, P01:05, and P01:06)[12].

	Incidence (%) N=481		Incidence (%) N=481
Infusion site pain	83	Jaw pain	16
Infusion site reaction	81	Pain	15
Infusion site bleed	29	Dizziness	12
Diarrhea	27	Rash	11
Headache	25	Pharyngitis	11
Nausea	22	Vasodilation	11

Injection site pain and reaction were the most common causes of reductions in the dose of UT-15.

Common adverse events during the placebo-controlled studies (P01:04 and P01:05) are listed in Table 7.

Table 7. Incidence of adverse events in placebo-controlled studies of PAH (studies P01:04 and P01:05)[13].

	Placebo N=233	UT-15 N=236		Placebo N=233	UT-15 N=236
Infusion site pain	27	91	Edema	3	9
Infusion site reaction	27	90	Anorexia	2	6
Headache	25	33	Epistaxis	2	5
Diarrhea	16	29	Nausea and vomiting	<1	3
Nausea	18	26	Hypokalemia	—	2
Jaw pain	5	16	Melena	—	2
Vasodilation	5	14			

None of these events was evidently related to the dose of UT-15.

During open-label Study P01:06, 95% of subjects reported at least one adverse event and 27% had at least one reported serious adverse event, but only 4% had events considered possibly or reasonably attributable to study drug. The most common adverse events in P01:06, without regard to attribution, are shown in Table 8.

Table 8. Incidence (%) of common adverse events (P01:06)

	Incid		Incid
Any	95%	Headache	21
Infusion site pain	83	Jaw pain	16
Infusion site reaction	76	Pain	15
Diarrhea	29	Pharyngitis	12
Infusion site bleed/bruise	26	Dizziness	11
Nausea	23	Rash	11

Treatment-emergent serious adverse events with an incidence of at least 1% in the open-label study and without consideration of attribution were heart failure (5%), syncope (2%), pneumonia (2%), pulmonary hypertension (2%), and hypoxia (1%).

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[12] The table lists events without consideration of attribution. Most events were attributed to study drug.

[13] The table lists events without regard to attribution. Only events more common on UT-15 are shown.

6.2.5 Adverse events of special concern

6.2.5.1 Hemorrhage

In controlled studies (P01:03, P01:04, and P01:05), 242 subjects on placebo experienced 162 hemorrhagic adverse events (0.67 per subject) and 253 subjects on UT-15 experienced 140 hemorrhagic events (0.55 per subject). The most common sites were the infusion site, ecchymosis, and epistaxis, only the latter of which was more common on UT-15 (12 vs. 4 events).

6.2.5.2 Infusion site pain/reaction

The most common and most clearly treatment-related adverse events were infusion site pain and infusion site reaction. There was no apparent relationship between infusion site pain or reaction and dose of UT-15.

During open-label administration in Study P01:06, 91% of subjects were on concomitant medications, the most common of which were analgesics, including local anesthetics (19%), topical pain medications (25%), opioids (35%), and other analgesics (45%).

6.2.6 Dose escalation

The dose of study drug rose progressively with time on open-label UT-15, as shown in Figure 4.

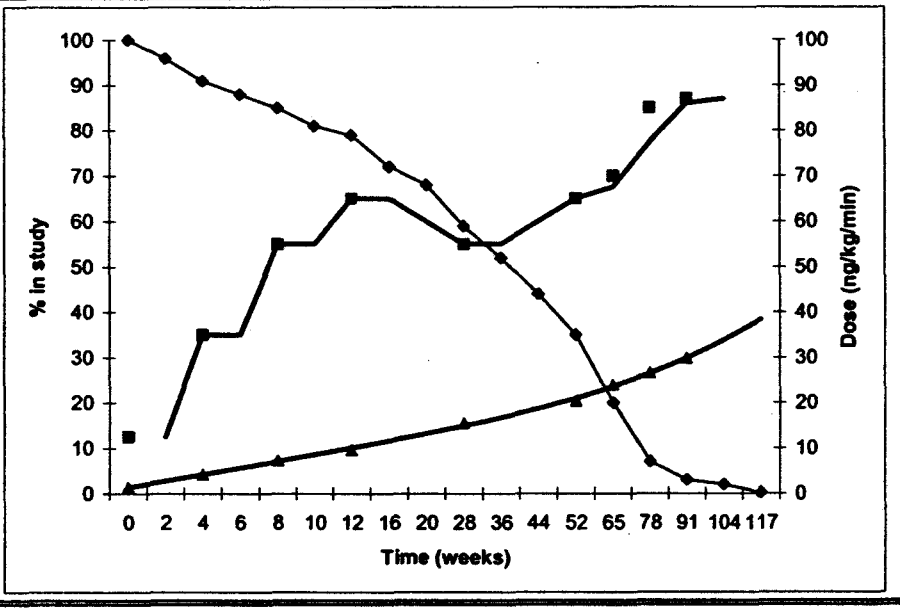

Figure 4. Proportion of subjects in study and UT-15 dosing (study P01:06).

Percentage of subjects followed in Study P01:06 as a function of time (diamonds; data from sponsor's 120-day safety update Table 12.1.1A) and the mean (triangles) and maximum (squares) dose of UT-15 in the same study (triangles; data from sponsor's 120-day safety update Table 12.1.1B).

Note that Figure 4 does not describe attrition during study P01:06. This study is ongoing. As of the cutoff date of 1 October 2000, 631 subjects had been enrolled, of whom 445 (71%) remained on study drug, 36 (6% had died, 136 (22%) had discontinued because of adverse events or need for rescue therapy, and 14 subjects had left for other reasons[14].

[14] Four transplants, 7 withdrawals of consent, and 3 lost to follow-up (all of whom were known to be alive at some later date).

The sponsor's analyses of dose escalation during study P01:06 demonstrate similar escalation among subjects originally randomized to placebo and UT-15.

Progressive dose escalation was also seen in studies P01:04-5, as shown in Table 9[15] .

Table 9. Dose escalation (studies P01:04 and P01:05).

	Placebo	UT-15
Baseline	1.2	1.2
Week 1	2.3	2.0
Week 6	10.0	5.9
Week 12	19.1	9.3

There is a much weaker case for tolerance in the studies supporting the approval of Flolan. There, doses trended upwards by less than a factor of two on average.

6.2.7 Laboratory findings

Mean changes in selected laboratory parameters are shown in Table 10. There were no significant shifts for these parameters, or for other hematological and urinalysis parameters.

Table 10. Baseline to on-treatment changes in mean laboratory parameters (Studies P01:04, P01:05)[16]

	Placebo			UT-15			Δ²
	BL	OT	Δ	BL	OT	Δ	
Chemistry							
Albumin	39.7	39.3	-0.4	40.0	39.7	-0.3	0.1
Alk phos	89	92	3	97	95	-2	-4
Bicarbonate	22	23	<1	23	23	<1	<1
Bilirubin (tot)	17	19	2	17	15	-2	-4
BUN	5.9	6.5	0.5	6.0	5.8	-0.2	-0.7
Calcium	2.2	2.2	<0.1	2.3	2.2	<0.1	<0.1
Chloride	104	103	<1	104	104	<1	<1
Creatinine	80	82	1	76	75	-2	-3
LDH	246	252	6	246	227	-19	-24
Potassium	4.2	4.1	<0.1	4.1	4.1	<0.1	<0.1
SGPT	29	27	-3	25	23	-2	<1
SGOT	31	30	-1	28	27	-1	<1
Sodium	140	139	<1	140	139	<1	<1
Hematology							
Hematocrit	0.46	0.46	<0.01	0.47	0.45	-0.02	-0.02
Hemoglobin	151	152	<1	153	148	-4	-5
Platelets	207	209	2	208	220	12	10
RBC	5.1	5.2	<0.1	5.4	5.3	-0.1	-0.2
WBC	7.3	7.8	0.5	7.3	7.2	-0.1	-0.6

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[15] Sponsor's analysis of doses in studies P01:04 and P01:05 together; includes subjects who remained on study but off study drug, so it underestimates the actual doses in use.

[16] Table derived from query "lab del2": "SELECT [lab blot del act].TESTNAME, [lab blot del pcbo].MBL AS PBL, [lab blot del pcbo].MOT AS POT, [lab blot del pcbo].DEL AS PDEL, [lab blot del act].MBL AS ABL, [lab blot del act].MOT AS AOT, [lab blot del act].DEL AS ADEL, [ADEL]-[PDEL] AS DEL2 FROM [lab blot del act] INNER JOIN [lab blot del pcbo] ON [lab blot del act].TESTNAME = [lab blot del pcbo].TESTNAME;". Column headings are BL=baseline, OT=on-treatment, D=on-treatment minus baseline, D2=double difference from baseline and placebo.

Comparisons of baseline and on-treatment values for individual subjects' selected lab tests are shown in Figure 5 to Figure 8.

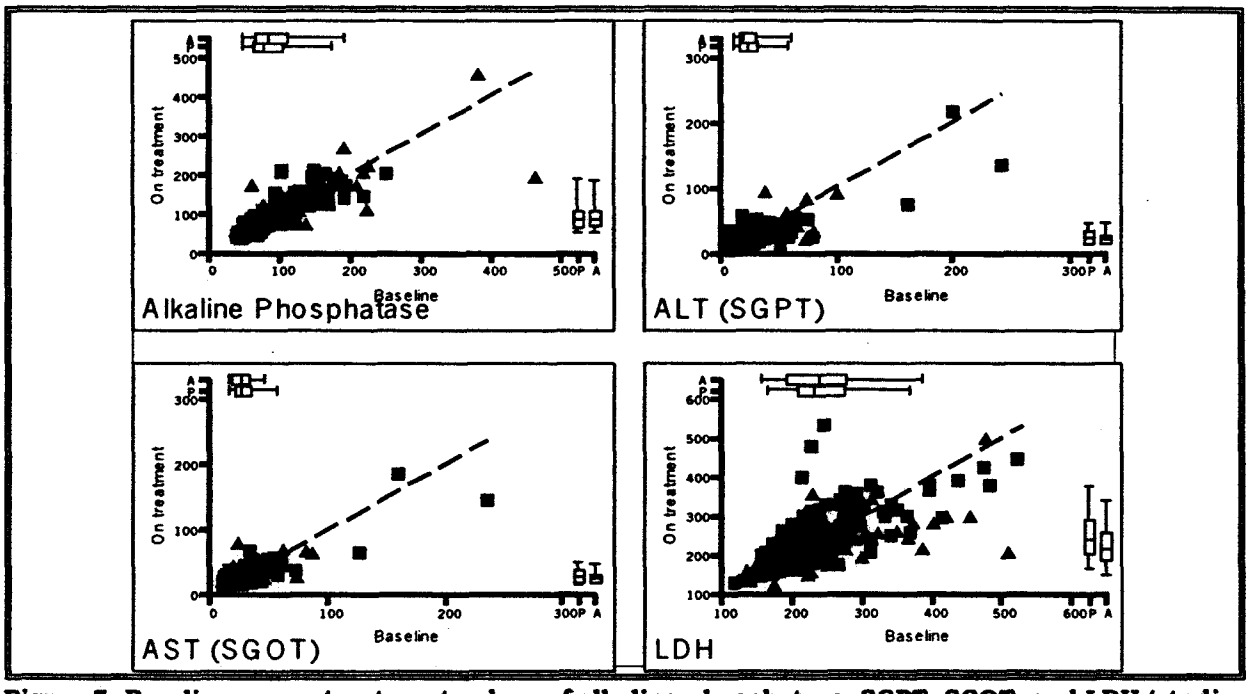

Figure 5. Baseline vs. on-treatment values of alkaline phosphatase, SGPT, SGOT, and LDH (studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

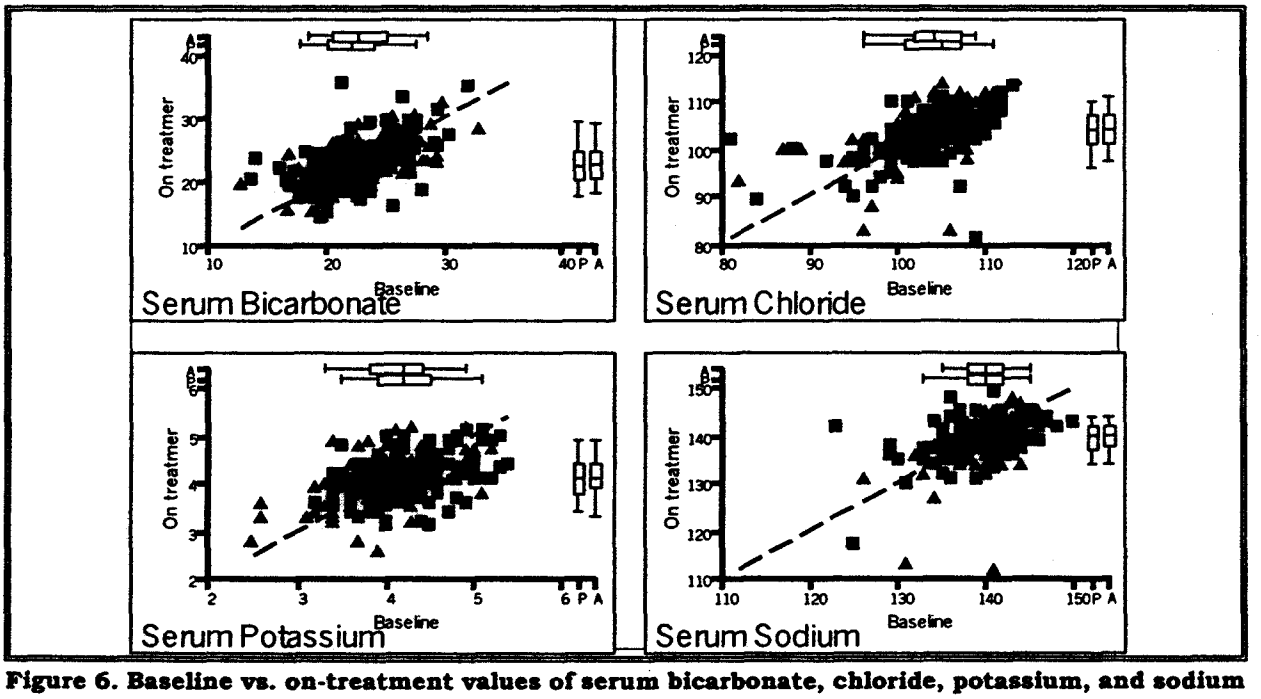

Figure 6. Baseline vs. on-treatment values of serum bicarbonate, chloride, potassium, and sodium (studies P01:04 and P01:05).

Analysis by reviewer. Data from stusdies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

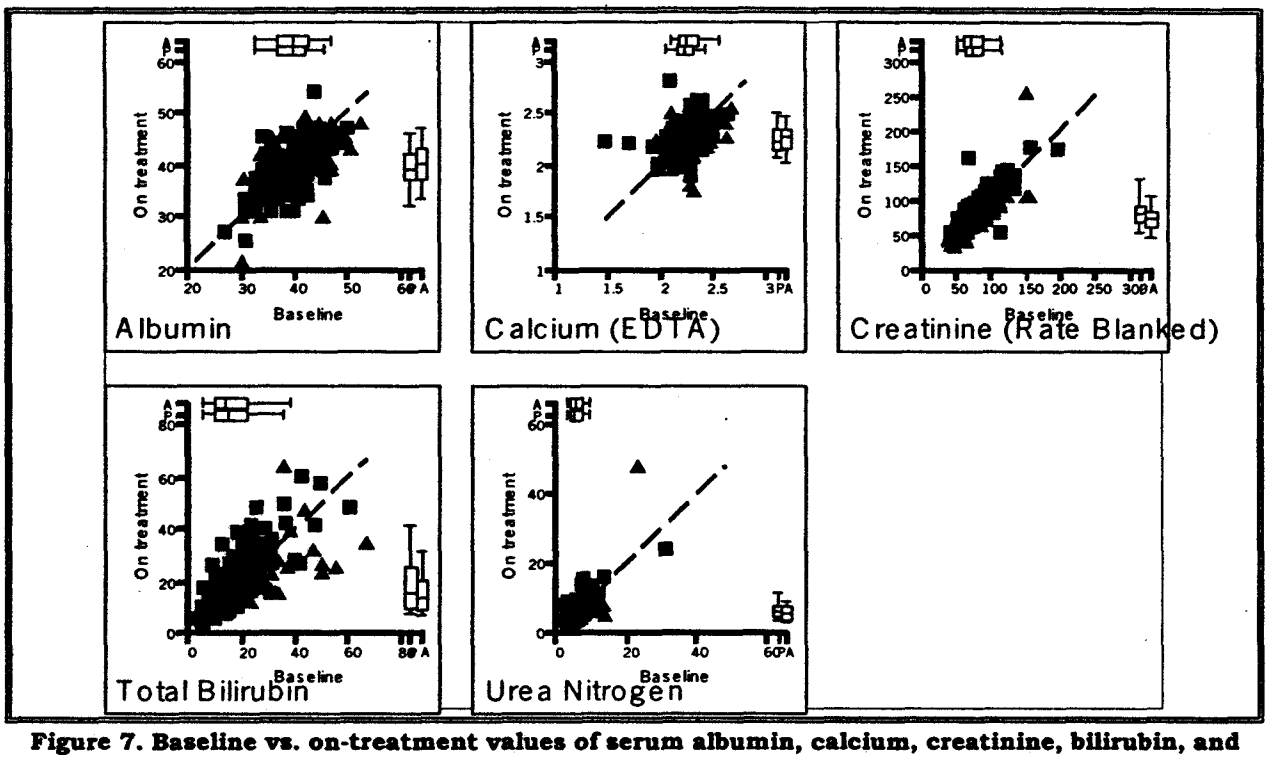

Figure 7. Baseline vs. on-treatment values of serum albumin, calcium, creatinine, bilirubin, and BUN (studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

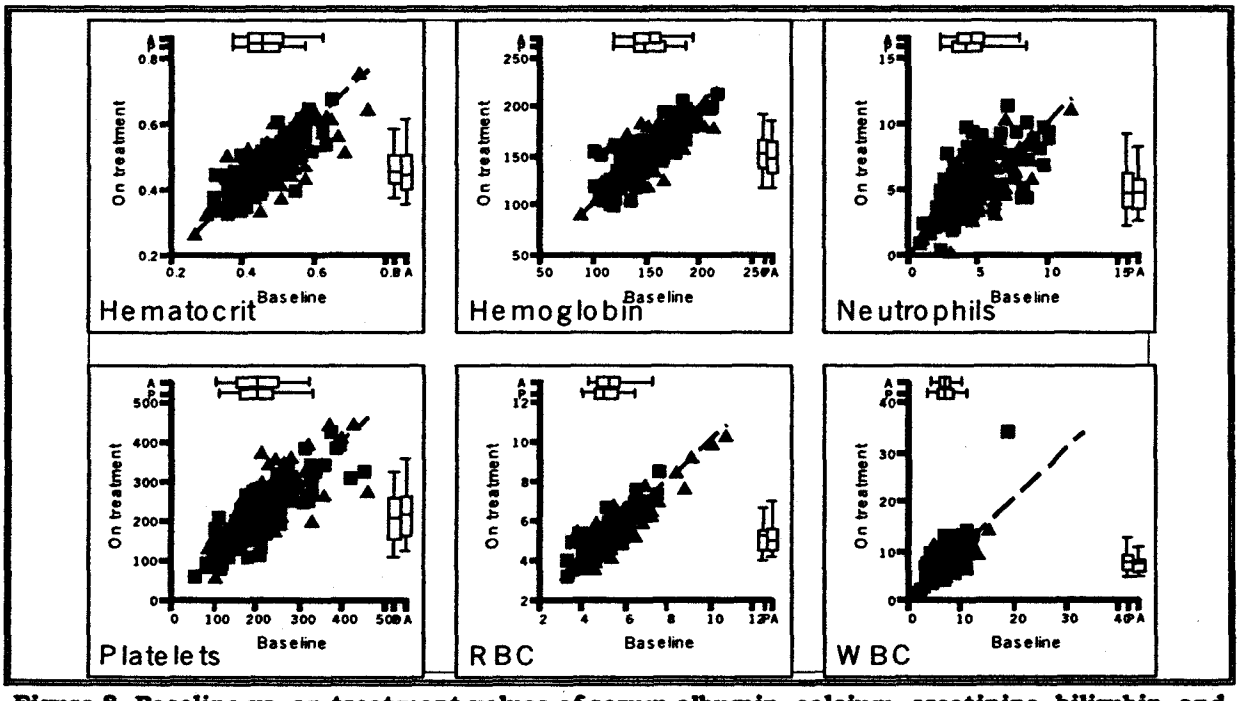

Figure 8. Baseline vs. on-treatment values of serum albumin, calcium, creatinine, bilirubin, and BUN (studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

Of these laboratory assessments, there is an apparent trend to a reduction in potassium on treatment, but the shift does not appear to be related to treatment group.

6.2.8 Vital signs

Vital signs were assessed at intervals follow the first dose of randomized study drug. Changes in vital signs from baseline to 8 hours are shown in Table 11.

Table 11. Changes from baseline to 8 hours in vital signs (Studies P01:04, P01:05).

	Placebo	Active	Difference
SBP (mmHg)	-3.7	-1.9	1.8
DBP (mmHg)	-2.9	-2.8	0.1
HR (bpm)	-2.2	-3.5	-1.3

Despite the monitoring being generally in the afternoon to evening, these data show remarkably little placebo effect or nighttime decline. There is no significant effect of treatment on vital signs.

6.2.9 ECGs

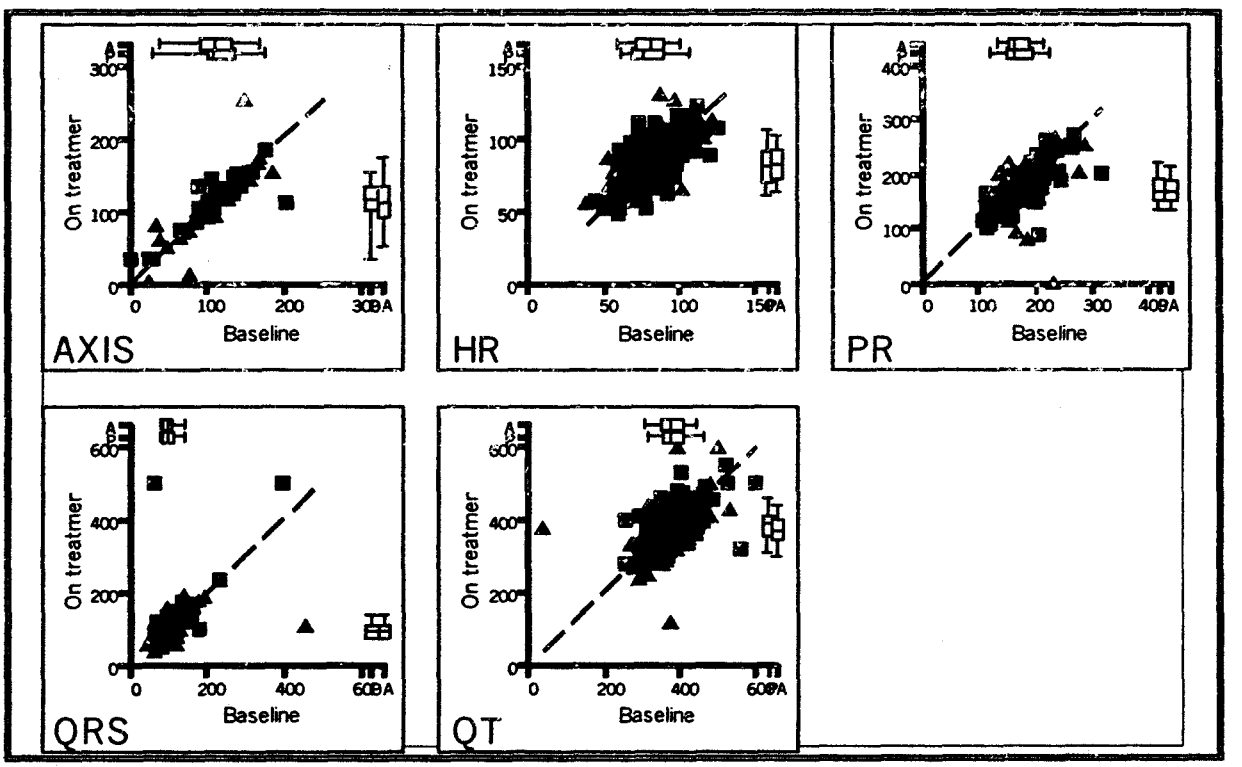

Figure 9. Baseline vs. on-treatment values for ECG parameters (Studies P01:04 and P01:05).

Analysis by reviewer. Data from studies P01:04 and P01:05 combined. Points represent all subjects with baseline and on-treatment values. Groups are P = placebo (squares) and A = active treatment (triangles).

Because of safety implications of outliers in QT or QTc, the numbers of subjects on placebo or active treatment were counted according to whether baseline and on-treatment QT or QTc were <450 ms. This analysis is shown in Table 12.

Table 12. Counts of subjects according to shifts in QT or QTc (Studies P01:04, P01:05)[17].

		QT				QTc			
		Placebo N=209		UT-15 N=194		Placebo N=209		UT-15 N=194	
		On-treatment value							
		<450	≥450	<450	≥450	<450	≥450	<450	≥450
Base-line	<450	184	9	186	3	109	35	104	27
	≥450	7	9	3	2	26	39	28	35

The analysis does not suggest that subjects on active treatment were more likely than subjects on placebo to have significant increases in QT or QTc.

6.3 Summary

Exposure was about 250 subjects or 50 subject-years in controlled studies and 631 subjects or 476 subject-years in long-term open-label use. This level of exposure would makes it moderately unlikely that the true rate of unwitnessed events is >1% or about 5% per year.

During 12-week, placebo-controlled studies P01:04 and P01:05, deaths on placebo and active treatment were evenly matched in number (approximately 3 per 1000 subject-weeks) and character. All were plausibly related to progression of underlying disease. The death rate during open-label follow-on study P01:06 was a little higher (approximately 5 per 1000 subject-weeks), but the events were similar to those in both treatment groups of studies P01:04 and P01:05.

The most common adverse events that were clearly treatment-related were injection site pain and injection site reaction. This has implications for the quality of life of patients receiving UT-15, and also implications for the quality of blinding in controlled studies. Diarrhea, nausea, vomiting, and jaw pain, all less common than inject site problems, are all highly likely to be related to treatment.

Serious adverse events were common in this population. There was little reason to believe any were related to study drug and not to underlying disease.

There were no apparent effects on laboratory assessments, vital signs, or ECG parameters.

The dose of study drug rose progressively throughout open-label study P01:06, a trend that is not attributable to up-titration of subjects newly receiving UT-15.

[17] *The query for QTc was "SELECT qryQT.TEXT_TRT, [qryqt].[QTc]<450 AS BL, [qryqt_1].[QTc]<450 AS OT, Sum([qryqt_1].[QTc]<450) AS T, Sum([qryqt_1].[QTc]>=450) AS F FROM qryQT INNER JOIN qryQT AS qryQT_1 ON qryQT.PATNUM = qryQT_1.PATNUM GROUP BY qryQT.TEXT_TRT, [qryqt].[QTc]<450, [qryqt_1].[QTc]<450, qryQT.MONVIS, qryQT_1.MONVIS HAVING (((qryQT.MONVIS) Like "S*") AND ((qryQT_1.MONVIS) Like "W*"));". Data were from the ECG datasets for both studies, with QTc computed according to Bazett.*

7 Labeling review

The sponsor's proposed label appears in the following pages. The reviewers' proposed changes appear as a red-lined mark-up. Annotations concerning these changes appear in the wide right margin.

19 page(s) of revised draft labeling has been redacted from this portion of the review.

8 Summary and recommendations

8.1 Chemistry, microbiology, scientific investigations

The are no issues that should impact on the approvability of UT-15.

8.2 Pharmacology and toxicology

The are no issues that should impact on the approvability of UT-15.

8.3 Biopharmaceutics

The are no issues that should impact on the approvability of UT-15.

There were no data appropriate to address the observed dose escalation.

8.4 Effectiveness

The sponsor's development program was intended to demonstrate a beneficial effect of UT-15 on 6-minute walk in a population with primary or secondary pulmonary hypertension. Three trials contribute to this evaluation.

Study P01:03, only 43 subjects, did not demonstrate a nominally statistically significant effect on walking distance, but there is a trend in favor of UT-15.

Studies P01:04 and P01:05 had the same protocol and they were intended to be analyzed together. The prospective plan for deciding these studies comprised compelling evidence of effectiveness was a $p<0.049$ for each study or $p<0.049$ for one study and $p<0.01$ for the combined analysis. By none of the sponsor's 4 proposed analyses and none of the 4 FDA medical and statistical reviewers' analyses do these trials meet the prospective criteria for effectiveness.

The trend in studies P01:04 and P01:05 is in favor of a benefit for UT-15; the apparent failure to meet the statistical test appears to be attributable to a smaller than expected treatment effect, rather than a wider than expected variance.

Supporting data from the P01:04-05 studies include nominally to highly statistically significant effects of treatment on secondary end points of signs and symptoms (largely chest pain, dizziness, and palpitations), dyspnea-fatigue index (each of the domains of magnitude of task, magnitude of pace, and functional impairment), Borg dyspnea scale, but not on quality of life assessment.

Supportive short-term hemodynamic findings included favorable effects on right atrial pressure, pulmonary arterial pressure, and pulmonary arterial resistance, but unfavorable effects on cardiac output and stroke volume.

During long-term open-label administration, the dose of UT-15 rose progressively, at a rate exceeding that seen in the Flolan development program. Possible explanations for the rising dose include (1) development of tolerance to the effectiveness of UT-15, (2) accommodation to pain associated with UT-15, and (3) disease progression. Existing data do not allow distinguishable among these.

8.5 Safety

Mortality was about 3 per 1000 subject-weeks in both treatment arms of controlled studies and about 5 per 1000 subject-weeks during open label exposure. In none of these events was study drug thought by sponsor or reviewers to be plausibly related to study drug.

Local injection site pain and injection site reactions were clearly more common on UT-15 than on vehicle, but there was no discernible dose-relatedness. On the other hand, it may be that tolerance related to local pain and reaction limits the dose. One manifestation of the injection site problems is the high use of anti-inflammatory agents, opioids, and other pain-relief medications.

8.6 Relationship with Flolan

Flolan is approved for the treatment of patients with primary pulmonary hypertension Class III and IV. However, its use is difficult and inconvenient. The infusion of Flolan requires the insertion of an indwelling central catheter with the attendant risks of the inserting the catheter and the subsequent risk of catheter infection. Flolan has a rapid half-life and rapid dissipation of its hemodynamic effects. Any inadvertent interruption of the infusion is potentially life threatening. Flolan is chemically labile at room temperatures and must be reconstituted every 8 hours or kept at cold temperatures during the infusion. UT-15 was developed to avoid these problems and thereby delay the time till Flolan treatment becomes infusion.

There is no scientific rationale to concurrently use UT-15 with Flolan. There is also no empirical safety or efficacy information on the concurrent use of these drugs. UT-15 is intended as treatment of pulmonary hypertension solely to postpone starting Flolan. There is no study that randomized patients to Flolan or UT-15 that demonstrates equivalent outcomes so that there may be unintended negative consequences in the delay of Flolan infusion. Comparing the labeling of Flolan to the likely labeling of UT-15 the mortality benefit for Flolan does not appear to be uniformly observed with UT-15. The current labeling of Flolan states:

> *"Survival was improved in NYHA functional Class III and IV PPH patients treated with FLOLAN for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period 8 of 40 patients receiving standard therapy alone died, whereas none of the 41 patients receiving FLOLAN died (P=0.003)."*

In the pivotal UT-15 studies (P01:04 and P01:05) the drug demonstrated no mortality benefit. The UT-15 study population consisted of predominantly (55%) primary pulmonary hypertension patients with the vast majority NYHA Class III and this portion of the population coincides with the population for which Flolan demonstrated a mortality benefit. There were 9 deaths among those randomized to UT-15 and 10 deaths among those randomized to vehicle during the 12-week study. Five of the 9 deaths on UT-15 were patients with primary pulmonary hypertension while 8 of the 10 deaths on vehicle were patients with primary pulmonary hypertension.

Performance benefit on the 6-minute walk for UT-15 patients was small, approximately 3% of the baseline walk distance. Performance among those with Flolan was approximately 35-50% of baseline walk distance. Admittedly, the basis of comparison is across studies with different designs. Nevertheless, the magnitude of effects a does give one pause before assuming equivalence.

8.7 Recommended regulatory action

An appropriate trend in the exercise data in favor of UT-15 and favorable effects on various measures of symptoms provide reasonable assurance that UT-15 is an effective treatment for pulmonary hypertension, although it falls short of the usual two-trials test and the less stringent prospective analysis plan. A reasonable interpretation of these data is that UT-15 is not very effective, possibly because of difficulties in achieving appropriate doses.

Had the population been a complete overlap with that for Flolan, it would be hard to argue that the small effect of treatment plus the less invasive subcutaneous administration make UT-15 a reasonable alternative to the probably more effective and life-saving Flolan. But the UT-15 study population is somewhat broader, and the comparison with Flolan needs be made cautiously.

The final major consideration is that UT-15 doses rise dramatically with the time of exposure. The explanation for this rise, considerably larger than that seen with Flolan, is not known.

The reviewers conclude that the small benefits of treatment, the lack of effect on mortality, the ominous dose escalation, and the problematic management of injection site pain do not sum to make UT-15 a useful treatment for pulmonary hypertension.

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Appendix A Reviews of individual studies.

This section contains reviews of the individual studies comprising the sponsor's development program for UT-15 in pulmonary hypertension. Of the studies submitted with NDA 21-272, only study P01:06, the long-term, open-label extension study, is not represented here. Safety findings from study P01:06 are described in section 6 on page 15.

A.1 Study P01:01: A dose-range-finding study of intravenous 15AU81 (UT-15) patients with primary pulmonary hypertension.

A.1.1 Sites and investigators

P01:01 was conducted at 5 sites in the United States. The investigators are shown in Table 13.

Table 13. Investigators (P01:01).

Site	Investigator
01	Lewis Rubin, MD
02	Robyn Barst, MD
03	Stuart Rich, MD
04	Bruce Brundage, MD
05	Michael McGoon, MD

A.1.2 Background

Initial protocol submitted: 2.3.97

Protocol amendments: 4.7.97, 6.10.97, 7.18.97

These amendments are detailed in the study report. The most relevant of the changes were to exclude the use of anorexiants in the previous 3 months and to retain the enrollment of women of child-bearing potential.

Subject enrollment: 4.16.97 to 1.17.98

A.1.3 Study design

In this multi-center, parallel, sequential, open-label dose-escalation trial, eligible patients underwent cardiac catheterization and then entered a treatment phase, which consisted of five segments: (a) a Flolan dose-ranging segment from 2 ng/kg/min up to maximum tolerated dose of Flolan, (b) an 90 minute Flolan Washout Segment, (c) an IV UT-15 Dosing Segment starting at 5 ng/kg/min and increasing every 30 minutes up to a maximal tolerated dose (MTD) or 120 ng/kg/min, (d) a 90-minute time period when the patients were observed on the maximally tolerated dose of UT-15, and (e) a 120-minute Washout Segment.

Hemodynamics were assessed at the end of each dose increase, then every 15 minutes during the maintenance segment (segment e).

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

A.1.3.1 Objectives

1) To assess the safety, dose-tolerance, and acute hemodynamic effects of UT-15 IV in patients with severe primary pulmonary hypertension.

2) To compare the hemodynamic profile of UT-15 to Flolan using physiologic responses.

3) To attempt to estimate the apparent half-life of UT-15.

A.1.3.2 Number of subjects/ randomization

Fifteen (15) patients with pulmonary hypertension were enrolled into the study: 14 completed both Flolan and UT-15 infusions.

A.1.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- ≥ 12 years of age;

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

  PAPm ≥ 25 mmHg, and PCWP or a left ventricular end diastolic pressure ≤ 15 mmHg, and PVR > 3 mmHg/L/min, and absence of congenital heart disease (including atrial septal defect, ventricular septal defect, partial anomalous pulmonary venous drainage, but presence of a patent foramen ovale would not exclude a patient);
- had indicated willingness to participate by signing an informed consent form.
- no drugs for PPH discontinued in previous week except anticoagulants.

Exclusion criteria (may not be present)

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

A.1.3.4 Dosage/ administration

UT-15 and Flolan were administered IV through a central venous catheter.

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

A.1.3.5 Duration/ adjustment of therapy

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

A.1.3.6 Safety and efficacy endpoints measured

A listing of the measurements made during the trial can be found in the trial study report: NDA 21-272, vol. 2.16. Invasive hemodynamic measurements were made during the period of the infusions and at the end of the washout period along with pharmacokinetic sampling and routine vital signs. After washout and through the first 24 hours vital signs and ECGs were collected every 8 hours.

A.1.3.7 Statistical considerations

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

A.1.4 Results

A.1.4.1 Subject demographics & baseline characteristics

The majority of the patients in the trial were white (73%) and female (87%), with a mean age of 35 and a mean duration since diagnosis of PPH of 0.9 years. The majority (14/15, 93%) were NYHA Class III and the remaining one subject was NYHA Class IV. The reader is referred to the study report for additional demographics.

A.1.4.2 Disposition of subjects

Of the 15 patients enrolled, one patient was discontinued for an adverse event (vasovagal reaction) during the baseline phase of the study and 4 were discontinued during the maintenance phase (phase e). These last 4 patients are discussed in Safety below.

Subject selection. No information is available about subject selection in protocol P01:01.

Protocol violations & deviations. No significant protocol violations occurred.

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

A.1.4.3 Pharmacokinetics analyses

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

A.1.4.4 Hemodynamic changes

Table 14 below summarizes the hemodynamic changes from baseline for Flolan and UT-15. A total of 14 patients completed the dose-ranging parts of the study are their data are used for these comparisons. A total of 10 patients completed the maintenance phase and their data are included in this par of the summary. Baseline is taken as the last value before starting the infusion of Flolan or UT-15.