

Table 96. ECG data (P01:04-05)¹¹⁰

| | | Baseline | | Week 12 | |
|----------------------|-------------------------------------|-----------|-----------|-----------|-----------|
| | | Veh | UT-15 | Veh | UT-15 |
| ECG status | Unknown | 6 | 6 | 42 | 26 |
| | Normal | 8 | 2 | 5 | 6 |
| | Abnormal | 219 | 228 | 189 | 201 |
| Evaluable ECGs | N | 227 | 230 | 207 | 194 |
| | QTc >440 ms | 78 (34%) | 100 (43%) | 89 (43%) | 98 (51%) |
| | QRS >100 ms | 63 (28%) | 66 (29%) | 68 (33%) | 67 (35%) |
| | PR >200 ms | 19 (8%) | 18 (8%) | 22 (11%) | 33 (17%) |
| | Right axis deviation ¹¹¹ | 126 (56%) | 154 (67%) | 149 (72%) | 156 (80%) |
| | Right atrial enlarge | 37 (16%) | 39 (17%) | 35 (17%) | 35 (18%) |
| | Right ventricular hypertrophy | 38 (17%) | 54(23%) | 44 (21%) | 42 (22%) |
| | ST/T-wave abnormal | ----- | ----- | 6 (3%) | 6(3%) |
| | Nonspecific ST-T wave | | | 1 (<1%) | 1 (<1%) |
| | Specific ST depression | | | 3 (1%) | 0 (0%) |
| | Normal to abnormal | | | 1 (<1%) | 4 (2%) |
| | Abnormal to normal | | | | |
| Intervals Mean±SD | Heart rate | 80±14 | 81±14 | 80±14 | 82±13 |
| | Change | | | 0±11 | 1±12 |
| | PR interval | 175±32 | 171±29 | 171±32 | 169±30 |
| | Change | | | -2±21 | -3±27 |
| | QRS | 98±30 | 98±32 | 101±45 | 98±23 |
| | Change | | | 3±34 | 0±29 |
| | QT interval | 382±48 | 376±50 | 383±46 | 372±49 |
| | Change | | | 1±43 | -5±49 |
| QTc | 438±43 | 433±50 | 438±47 | 433±49 | |
| Change | | | 2±47 | 0±54 | |

Comparing UT-15 to vehicle there did not appear to any differences in the effect in ECG abnormalities or intervals.

A.4.4.9 Summary

This review consists of a description of the protocol and the results of studies P01:04 and P01:05. The procedures and measurements for both studies were identical. These two studies are the pivotal studies that are to support the approval of UT-15 for the treatment of pulmonary hypertension, whose etiology is either due to primary disease, collagen vascular disease or congenital left to right shunts. Although the individual and pooled studies are suggestive of an effect of UT-15, this reviewer does not feel that the results of the studies are sufficient by themselves to support approval.

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.

The primary end point of both studies was the change in walking distance from baseline at the end of week 12 in comparing UT-15 to vehicle infusion. For the pivotal analyses missing values for those who discontinued were imputed. Those who discontinued either because of death, deterioration or adverse events had the worse rank or value

¹¹⁰ Data derived from sponsor's tables 14.3.8.1A and 14.3.8.2A.

¹¹¹ QRS axis +90 to ±180°

imputed. Those who discontinued due to adverse events had their last rank or their last walk-distance carried forward.

The primary method of analysis was a non-parametric analysis of the pooled studies. The composite of walking distance both studies was pre-specified as pivotal in the analysis. The composite of both studies was to be considered demonstrating a benefit for UT-15 if either both individual 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 study by itself would not be considered successful. Neither of the studies demonstrated a p-value of < 0.049 , although their analysis demonstrated a p-value of < 0.01 for the pooled studies. The magnitude of the change in median walking distance ranged from 2 meters in study P01:04 to 19 meters in study P01:05, or between $< 1\%$ to a 6% increase in baseline walking distance and a mean increase of approximately 3% for the pooled studies.

Dr Lawrence, the FDA statistician, makes a cogent set of arguments, that when a study pre-specifies as a success the composite of several outcomes, the concept of "being close" is open to an enormous amount of ambiguity. In the absence of fulfilling the prespecified criteria for success all that can be said is that the study did not succeed.

Not only did the sponsor's analysis not meet the pre-specified criteria for considering the studies a success, 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, with nearly all such subjects arising from those treated with UT-15. Nearly all such subjects who discontinued due to adverse events had infusion site pain/infusion site reaction as the reason for discontinuation.

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 subsequently die, deteriorate or receive transplant. This fraction of subjects, therefore, was shielded from the worst imputed outcome values possible in this study.

Second, since nearly all subjects who discontinued in the UT-15 group did so because of infusion site pain/ reaction. Since infusion site pain was ubiquitous in the UT-15 infused subjects, the possibility exists that the discontinuation subjects were suffering from infusion site pain in conjunction with a worsening of their disease status.

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 clearly does not reflect their status at the time of discontinuation. Subjects who discontinue for pain, whose discontinuation fell within the time-window of an exercise test and who did not undergo further walk testing, the imputed values could be disparate with their clinical status at the time of discontinuation.

In order to deal with the inherent biases due to the unequal rates of discontinuation adverse events, this reviewer requested three additional analyses. The first analysis added the outcomes of three UT-15 and two vehicle subjects who died or were transplanted during the 100-day window defined for the 12-weeks of the study. Since these outcomes are really not subjective, the inclusion of these subjects at least partly corrects for the imbalance among those who discontinue for adverse events. Including the worst outcome for these subjects alters the p-value of the pooled database to 0.02 and that for the individual studies to > 0.1 .

The second analysis includes those, as having a worse outcome, 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. The immediate use of Flolan upon discontinuation of UT-15 suggests that the subject's status had deteriorated to the point that an optional treatment at baseline became a treatment of choice. The p-values for the pooled and individual studies when treating those subjects started on Flolan within 1 month of discontinuing UT-15 also as worse outcomes shifts the p-value for the pooled studies to 0.082. For each of 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 worse outcomes. In addition, there was one subject whose status at the time of continuation appeared to be inconsistent with the imputed measurement from week 1. The value for this subject was exclude. 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 three analyses presume that all subjects who discontinued UT-15 therapy and received Flolan did so because of the deterioration in their status. 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 worse 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 or P01:05 was by itself statistically significant by a method of analysis that biases results towards UT-15 treatment. Other treatments, particularly of those who discontinued for adverse events further diminish the positive nature of any results.

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 of 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 some 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 average net change for those who completed the study favored UT-15 by + 1 units. 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 improved 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 into 4 domains. This QOL questionnaire was validated among subjects with CHF and not pulmonary hypertension, though the questions and limitation are somewhat similar among groups. The questionnaire is often analyzed as a global and three subcategories, physical, economical and emotional dimension. This questionnaire was not apparently administered to all subjects. Overall there was no global signal for this questionnaire. The global QOL did not differ between the two treatments. The physical dimension, 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 adverse events that would indicate the specific treatment. 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.

It does not appear that UT-15 altered the natural course of pulmonary hypertension. Deaths, hospitalizations, hospitalizations for cardiovascular reasons or need for new or increases in medications or need for inotropic or Flolan during the 12-week study did not apparently differ between the two treatments. These metrics, however, were not prespecified as end-points, but are often collected and may serve as convincing endpoints of benefit.

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 crossed-over and while treated with 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 required hospitalization as a consequence of cardiovascular or pulmonary hypertension related.

Subjects whose 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.

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 either Flolan or inotropes. There were an additional 3 subjects, all in the vehicle group that received flolan early in the course of the study, that suggested the infusion was a provocative test for vascular responsiveness and not a treatment for disease decompensation. These three subjects were excluded from the above count.

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 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. Changes in CI, PAPm or PVR did not convincingly correlate with any benefit. The only consistent hemodynamic parameter with a positive correlation was SVO₂.

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.

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 hand-full of subjects who discontinued UT-15 acutely, no evidence of rebound was described.

With respect to safety, the duration of exposure was 81 days for those in the UT-15 group and 83 days for those treated with vehicle. The number of deaths and hospitalizations were equivalent between the two treatments. More UT-15 treated subjects than vehicle subjects had adverse events listed as severe in intensity (62% versus 20%). The vast majority of the difference reflects the irritating effect of active drug infusion.

Two subjects in the UT-15 group had episodes of hemolytic anemia. One subject discontinued treatment and the other subject continued on a lower dose of therapy. One additional subject had pancytopenia that the sponsor attributed to previous cyclophosphamide treatment. She continued on therapy. It does not appear that UT-15 is causative of these events since two of the three subjects continued on therapy.

The most frequent adverse events among those treated with UT-15 were also related to the "skin and appendage" system (94% versus 67%). The most frequently reported events were "infusion site pain" or "infusion site reaction", 85% and 83% of those enrolled, respectively, the corresponding numbers among those treated with vehicle were 27% and 27%, respectively. "Gastrointestinal" symptoms were more frequent in the UT-15 than vehicle group (45% versus 32%), predominantly "diarrhea" (25% versus 15%) and "nausea" (22% versus 18%). Adverse events associated with the "nervous" system were more frequent in the UT-15 group than vehicle (30% versus 22%), with the most common adverse event described as vasodilation (11% versus 5%). Adverse events associated with "Metabolic and Nutritional" system had more events in the UT-15 group than vehicle (20 versus 13 %). The most frequent increase was in edema (9% versus 3%).

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

With respect to laboratory and hematology, group mean difference existed for: total bilirubin, LDH, BUN, hemoglobin, hematocrit and white blood cell count were all decreased relative to vehicle group. Platelet counts were increased in UT-15 relative to vehicle. Hypokalemia was noted in five patients treated with UT-15 and none with vehicle.

ECG intervals did not apparently differ among groups.

Vital signs were poorly followed. Blood pressure was only recorded for the initial infusion day. The dose of UT-15, however, was very low and consequently allows no assurance that hemodynamics was not effected by credible infusion rates of UT-15. There were, however, 29 subjects treated with UT-15 who had their dose decreased for excessive pharmacologic effect, with no further description as to the specifics of the event.

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A.5 Study P01:07: A bioavailability study of UT-15 administered subcutaneously versus intravenously in healthy volunteers.

A.5.1 Sites and investigators

P01:07 was conducted at a single site in the United States.

Table 97. Investigators (P01:07).

| Site | Investigator |
|------|------------------------------------|
| 01 | PPD Development, West Austin Texas |

A.5.2 Background

Initial protocol submitted: N/A

Protocol amendments: None.

Subject enrollment: 6.4.99 to 6.24.99

A.5.3 Study design

This single-center, open-label, non-randomized Phase I trial examined the pharmacokinetics and safety of single IV doses of UT-15 administered either by IV or subcutaneous routes. Healthy volunteers were given the drug at a rate of 15 ng/kg/min IV or SQ for 150 minutes, during which time samples for pharmacokinetic assessment were obtained. The patients were also monitored for safety using serum chemistries, CBC, ECG monitoring and vital signs. The IV and SQ periods were separated by a 5 to 7-day washout period.

A.5.3.1 Objectives

To assess the safety pharmacokinetics of a single IV and SQ dose of UT-15 in healthy volunteers.

A.5.3.2 Number of subjects/ randomization

Fifteen patients were to be enrolled in the study.

A.5.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.5.3.4 Dosage/ administration

Healthy volunteers were given the drug at a rate of 15 ng/kg/min IV or SQ for 150 minutes.

A.5.3.5 Duration/ adjustment of therapy

Therapy was not adjusted for any individuals enrolled in the trial.

A.5.3.6 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. 2.22.

A.5.3.7 Statistical considerations

The statistics in the trial were observational in nature.

A.5.4 Results

Fifteen patients (7 female, 8 male) were enrolled in the trial and completed the infusion of both IV and SQ UT-15.

A.5.4.1 Efficacy

No efficacy data of clear relevance to the approvability of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyen and Gobburu.

A.5.4.2 Safety

There were no deaths reported in the study, and no SAEs during the IV or SQ infusions. The most common AEs reported were dizziness and headache, which were more common in the IV formulation than following the SQ formulation. Injection site pain was more common in the SQ dosing.

A.5.5 Summary

A.5.5.1 Efficacy summary

Study P01:07 studied the acute effects of IV and SQ UT-15 in normal volunteers. No acute hemodynamic changes were detected for either formulation.

A.5.5.2 Safety summary

The adverse events identified in this open-label study are similar to those reported in other small trials of IV and SQ UT-15.

A.5.5.3 Reviewer's conclusions

No new safety concerns were identified in this study.

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A.6 Study P01:08: A study to evaluate the effects of acetaminophen on the pharmacokinetics of UT-15 in healthy volunteers.

A.6.1 Sites and investigators

P01:08 was conducted at a single site in the United States.

Table 98. Investigators (P01:08).

| Site | Investigator |
|-------------|--|
| 01 | T. Hunt, M.D., PPD Development, West Austin Texas |

A.6.2 Background

Initial protocol submitted: N/A

Protocol amendments: None.

Subject enrollment: 8.3.99 to 9.20.99

A.6.3 Study design

This single-center, open-label, non-randomized Phase I trial examined the effect of acetaminophen on the pharmacokinetics and safety of SQ UT-15. Healthy volunteers were administered UT-15, 15 ng/kg/min SQ for 6 hours in two dosing intervals separated by a 7 day washout period. In the first period, patients were given acetaminophen starting 25 hours before start of UT-15 and continuing through period of infusion.

A.6.3.1 Objectives

1. To assess the effect of oral acetaminophen on the pharmacokinetics of SQ UT-15 in healthy volunteers.

A.6.3.2 Number of subjects/ randomization

Twenty-nine (29) patients were to be enrolled in the study and 26 completed.

A.6.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.6.3.4 Dosage/ administration

See trial design for details.

A.6.3.5 Duration/ adjustment of therapy

Therapy was not adjusted for any individuals enrolled in the trial. Two individuals were discontinued for drug-related reasons: one for pump failure (for SQ administration) and the other following vomiting of a dose of acetaminophen.

A.6.3.6 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. 2.22.

A.6.3.7 Statistical considerations

The statistics in the trial were observational in nature.

A.6.4 Results

Twenty-nine (29) patients, 17 females and 12 males, were to be enrolled in the study and 26 completed. One person withdrew consent, one discontinued for pump failure (for SQ administration) and the other following vomiting of a dose of acetaminophen.

A.6.4.1 Efficacy

No efficacy data of clear relevance to the efficacy of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyen and Gobburu.

A.6.4.2 Safety

There were no deaths reported in the study, and no SAEs during the UT-15 infusions. The most common AEs reported were headache (59%) and nausea (38%).

A.6.5 Summary

A.6.5.1 Efficacy summary

Study P01:08 studied the acute effects of acetaminophen on the pharmacokinetics of UT-15. No acute hemodynamic changes were reported. The pharmacokinetics will be discussed in other reviews, but the sponsor reported no effect of acetaminophen on UT-15 pharmacokinetics.

A.6.5.2 Safety summary

The adverse events identified in this open-label study are similar to those reported in other small trials of SQ UT-15. The three discontinuations were unrelated to UT-15 adverse effects.

A.6.5.3 Reviewer's conclusions

No new safety concerns were identified in this study.

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A.7 Study P01:09: A chronic, dose-escalation study of the pharmacokinetics of UT-15 administered by continuous subcutaneous infusion in healthy volunteers.

A.7.1 Sites and investigators

P01:09 was conducted at a single site in the United States.

Table 99. Investigators (P01:09).

| Site | Investigator |
|------|--|
| 01 | T. Hunt, M.D., Ph.D. PPD Development, West Austin Texas |

A.7.2 Background

Initial protocol submitted: N/A

Protocol amendments: None

Subject enrollment: 7.15.99 to 8.28.99

A.7.3 Study design

This single-center, open-label, non-randomized, dose-escalation Phase I trial examined the pharmacokinetics of UT-15 administered via SQ infusion for 28 days. Healthy volunteers received UT-15, starting at a dose of 2.5 ng/kg/min for 7 days. Doses were increased at 7 day intervals to 5, 10 and 15 ng/kg/min respectively for periods 2, 3 and 4. Serial plasma samples were collected for PK as well as clinical chemistries, CBC and coagulation parameters. Additional samples for PK were collected after discontinuation of UT-15.

A.7.3.1 Objectives

1. To assess the chronic pharmacokinetics of UT-15 administered by continuous 28-day SQ infusion.
2. To assess the safety and tolerability of chronic SQ UT-15 infusion in healthy volunteers.

A.7.3.2 Number of subjects/ randomization

Fourteen (14) patients were to be enrolled in the study. Six subjects completed the trial; 8 others discontinued due to infusion site pain.

A.7.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.7.3.4 Dosage/ administration

See trial design for details.

A.7.3.5 Duration/ adjustment of therapy

Dose of UT-15 was adjusted as detailed in the study design section above. Study lasted for 28 days.

A.7.3.6 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. 2.22.

A.7.3.7 Statistical considerations

The statistics in the trial were observational in nature.

A.7.4 Results

Fourteen (14) patients were to be enrolled in the study. Six subjects completed the trial; 8 others discontinued due to infusion site pain.

A.7.4.1 Efficacy

No efficacy data of clear relevance to the approvability of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyen and Gobburu. The sponsor concluded that the trial demonstrated linear pharmacokinetics over the range of doses studied in the trial, with an apparent elimination half-life for the 15 ng/kg/min dose of 2.93 hours.

A.7.4.2 Safety

There were no deaths reported in the study, and no SAEs during the UT-15 infusions. The most common AEs reported were injection site pain (13/14 subjects), headache (11/14), nausea (7/14) and dizziness (7/14). Blood pressure and other vital signs did not change significantly from baseline in the patients. ECG evaluation did not find any significant changes from baseline.

A.7.5 Summary

A.7.5.1 Efficacy summary

Study P01:09 studied the pharmacokinetics of UT-15 during chronic SQ infusion. No hemodynamic changes during the 28 day study were seen. The pharmacokinetics will be discussed in other reviews.

A.7.5.2 Safety summary

The adverse events identified in this open-label study are similar to those reported in other long-term trials of UT-15, especially the prominent occurrence of site pain, which lead to the discontinuation of 8 of the 14 enrolled subjects.

A.7.5.3 Reviewer's conclusions

No new safety concerns were identified in this study.

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A.8 Study P01:10: A single-center, open-label, mass balance, urinary metabolite profiling, and safety study of 14C-UT-15 following an 8-hour subcutaneous infusion in six normal healthy male subjects.

A.8.1 Sites and investigators

P01:10 was conducted at a single site in the United States.

Table 100. Investigators (P01:10).

| Site | Investigator |
|------|---|
| 01 | Russell M. Dixon, M.D. Covance CRU, Madison WI |

A.8.2 Background

Initial protocol submitted: N/A

Protocol amendments: None

Subject enrollment: 1.6.00 to 1.16.00

A.8.3 Study design

This single-center, open-label, non-randomized, Phase I trial examined the metabolic fate of 14C-labeled UT-15 in healthy male volunteers. Each subject received a single 8-hour infusion (SQ) of 14C-UT-15 at a rate of 15 ng/kg/min. Vital signs, clinical labs, ECGs and adverse events were monitored throughout the trial and at its conclusion.

A.8.3.1 Objectives

1. To characterize whole blood and plasma radioactivity of 14C-UT-15 following an 8-hour subcutaneous infusion in normal healthy male volunteers.
2. To characterize the urinary and fecal excretion of radioactivity following an 8-hour SQ infusion of UT-15.
3. To evaluate the safety of UT-15 under the same conditions.
4. To examine the pattern of urinary metabolites following the 8-hour SQ administration of UT-15.

A.8.3.2 Number of subjects/ randomization

Six patients were to be enrolled in the study. Six subjects completed the study.

A.8.3.3 Inclusion/ exclusion criteria

Healthy volunteers were enrolled in the trial. Women were to be of non-child-bearing potential; subjects of child-bearing potential had to have a negative serum pregnancy test prior to study entry.

A.8.3.4 Dosage/ administration

See trial design for details.

A.8.3.5 Duration/ adjustment of therapy

No adjustment of UT-15 dose was allowed.

A.8.3.6 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. 2.23.

A.8.3.7 Statistical considerations

The statistics in the trial were observational in nature.

A.8.4 Results

All six enrolled subjects completed the trial.

A.8.4.1 Efficacy

No hemodynamic or symptom data related to the clinical effects of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. During the period of infusion there was no significant changes in any hemodynamic parameters per the sponsor. The pharmacokinetic analyses from the study will be discussed elsewhere by Drs. Nguyen and Gobburu. The majority of the radioactive label appeared in the urine (75.6% of dose). This radioactivity, analyzed by corresponded to metabolic products of UT-15, including an oxidation product and a product formed through glucuronidation.

A.8.4.2 Safety

There were no deaths reported in the study, and no SAEs during the UT-15 infusions.

A.8.5 Summary

A.8.5.1 Efficacy summary

Study P01:10 studied the metabolism of UT-15 using radioactive labeling. These results will be discussed separately. No hemodynamic effects of UT-15 in the population were detected.

A.8.5.2 Safety summary

No deaths and no SAEs were reported. Adverse events related to drug administration were common but did not lead to drug discontinuation.

A.8.5.3 Reviewer's conclusions

No new safety concerns were identified in study P01:10. The pharmacokinetic results from this trial will be discussed separately by Drs. Nguyen and Gobburu.

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A.9 Study P01:11: A multicenter, uncontrolled, open study in patients with pulmonary hypertension, transitioning from chronic intravenous flolan therapy to chronic subcutaneous uniprost.

A.9.1 Sites and investigators

P01:01 was conducted at 2 sites in the United States. The investigators are shown in Table 101.

Table 101. Investigators (P01:11).

| Site | Investigator |
|------|-----------------|
| 01 | Robyn Barst, MD |
| 53 | R. Naeije, MD |

A.9.2 Background

Initial protocol submitted: 2.3.97

Protocol amendments: None.

Subject enrollment: 1.13.00 to ongoing (interim report as of 9.18.00).

A.9.3 Study design

This is an ongoing open-label protocol that allows for the transition of patients from Flolan to UT-15. The safety population at data cutoff for this submission consists of 3 patients and pharmacokinetic data on the use of subcutaneous UT-15 in pulmonary hypertension.

A.9.3.1 Objectives

1) To assess the safety of transitioning patients with pulmonary hypertension from Flolan to UT-15.

A.9.3.2 Number of subjects/ randomization

Three patients had been enrolled at the entry cut-off date for the interim report.

A.9.3.3 Inclusion/ exclusion criteria

Women and men receiving Flolan were eligible if they were able to give informed consent and could be trained in the use of the subcutaneous pump to administer the UT-15.

A.9.3.4 Dosage/ administration

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

A.9.3.5 Duration/ adjustment of therapy

Patients are eligible continue UT-15 for up to 36 months or until the drug approval.

A.9.3.6 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. 2.62.

A.9.3.7 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.9.4 Results

Three patients only were enrolled in the trial, eliminating the utility of discussions of demographics, trial discontinuation, concomitant therapies, and standard safety analysis.

A.9.4.1 Pharmacokinetics analyses

The pharmacokinetic results from the trial are reviewed elsewhere by Drs. Nyugen and Gobburu.

A.9.4.2 Efficacy

No relevant efficacy data were obtained in this small study.

A.9.4.3 Safety

The three patients were taken off of Flolan and started on UT-15 for adverse events related to the use of a central venous catheter used for Flolan administration (sepsis, paradoxical cerebral emboli). The transition to UT-15 took place over 22 to 36 hours. Of the three patients enrolled, none of them were discontinued from UT-15 use for an adverse event during the available period of follow-up. The observed AEs were those reported in other larger trials included in the NDA 21-272: restlessness, headache and flushing. There were no deaths and no Serious Adverse Events reported during UT-15 administration during the follow-up for the three patients (followed for approximately one week, 6 months and 8 months respectively).

A.9.5 Summary

A.9.5.1 Efficacy summary

Study P01:11 is intended as an open-label study of the consequences of a switch from Flolan to UT-15. The three patients reported give minimal information in this regards, although all three were successfully transitioned, and have remained on UT-15.

A.9.5.2 Safety summary

No new safety concerns were identified in these three patients plausibly related to the initiation of UT-15 closely following the discontinuation of Flolan.

A.9.5.3 Reviewer's conclusions

This trial provides little information not available from other trials. The three patients were successfully transitioned to UT-15 from Flolan over a period of 22 to 36 hours.

**APPEARS THIS WAY
ON ORIGINAL**

A.10 Study P02:01: A pharmacokinetic study of subcutaneous 15AU81 (UT-15) in patients with secondary pulmonary hypertension: a study in patients with portopulmonary hypertension.

A.10.1 Sites and investigators

P02:01 was conducted at 7 sites in the United States. The investigators are shown in Table 102.

Table 102. Investigators (P02:01).

| Site | Investigator |
|------|---|
| 01 | Sean Gaine, Univ. of Maryland, Baltimore |
| 02 | V. McLaughlin, Rush Presbyterian, Chicago |
| 03 | R. Oudiz, Harbor UCLA, Torrance |
| 04 | M. Krowka, Mayo Clinic, Rochester |
| 05 | D. Badesch, Univ. of Colorado |
| 06 | A. Frost, Baylor School of Medicine |
| 07 | R. Bourge, Univ. of Alabama Birmingham |

A.10.2 Background

Initial protocol submitted: 9.12.97

Protocol amendments: None.

Subject enrollment: 1.20.98 to 10.15.98

A.10.3 Study design

This is a multi-center, open-label, baseline-control, single-dose study in subjects with portopulmonary hypertension with mild to moderate hepatic dysfunction.

A.10.3.1 Objectives

- 1) To measure the effects of subcutaneous 15AU81 on pulmonary and systemic hemodynamics in subjects with portopulmonary hypertension with mild to moderate hepatic dysfunction.
- 2) To characterize the pharmacokinetic profile of 15AU81 administered as a subcutaneous infusion in this patient population.

A.10.3.2 Number of subjects/ randomization

Twelve (12) patients were enrolled in the study.

A.10.3.3 Inclusion/ exclusion criteria

Inclusion Criteria:

1. At least 18 years of age;
2. If female, either surgically sterile, post-menopausal, or have a negative pregnancy test;
3. Have a diagnosis of severe, symptomatic pulmonary hypertension, NYHA Class II or III despite the use of oral vasodilators for at least one month;
4. Have pulmonary function tests c/w pulmonary hypertension, with only mild reductions in total lung capacity and forced vital capacity or a high-resolution CT scan showing no interstitial disease;

5. Have an echocardiogram within the past year c/w pulmonary hypertension: evidence for right ventricular hypertrophy or dilation; evidence of normal left ventricular function; absence of mitral valve stenosis;
6. Have a cardiac catheterization c/w pulmonary hypertension: pulmonary artery pressure >25 mm Hg; PCWP or left end-diastolic pressure >15 mm Hg; absence of congenital heart disease, with the exception of patent foramen ovale;
7. Signed consent form.

Exclusion Criteria (Following must not be present):

1. New form of vasodilator, diuretic or digoxin within the past one month.
2. Any medication discontinued in the past two weeks;
3. Any disease known to cause secondary pulmonary hypertension other than portal hypertension (COPD, thromboembolic disease, collagen vascular disease, sickle cell anemia, mitral valve stenosis, HIV disease).
4. Currently using another investigational medication or have received one in the past 30 days.
5. Severe heart failure (NYHA class IV);
6. Severe hepatic dysfunction (Grade C on Pugh classification scale).
7. Taking medications known to affect hepatic enzymes (i.e., cimetidine, phenytoin, rifampin);
8. Be more than moderately obese or underweight (>30% above ideal body weight)

A.10.3.4 Dosage/ administration

UT-15 was administered subcutaneously at a dose of 10 ng/kg/min for 150 minutes, or until an adverse event occurred which, in the opinion of the investigator, warranted discontinuation of the infusion. Following this, patients were followed for 300 minutes off UT-15 for adverse events.

15AU81 is constituted in a liquid at a concentration of 0.5 mg/ml. For a 70 kg man, the average rate of infusion will be 0.0014 ml/minute.

A.10.3.5 Duration/ adjustment of therapy

Patients were administered UT-15 for up to 150 minutes, or as tolerated by adverse events.

A.10.3.6 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. 2.62.

A.10.3.7 Statistical considerations

The statistics in the trial were observational in nature given the small numbers with the exception of the pharmacokinetic assessments. The pharmacokinetic parameters of the patients were compared with the pharmacokinetics of healthy volunteers obtained in study P01:07. These pharmacokinetic analyses are discussed in a separate review by Nhi Nyugen, Ph.D. and Joga Gobburu, Ph.D.

A.10.4 Results

Only nine patients enrolled, of the 12 proposed. All nine completed the 150 minute infusion of UT-15 with no reported deaths or SAEs during the infusion.

A.10.4.1 Pharmacokinetics analyses

The pharmacokinetic results from the trial are reviewed elsewhere by Drs. Nguyen and Gobburu.

A.10.4.2 Efficacy

No relevant hemodynamic efficacy data were obtained in this small study. The estimated half-life of UT-15 in this population was 1.3 to 1.4 hours, a value not different from healthy volunteers studied in P01:07.

A.10.4.3 Safety

All nine of the patients tolerated the 150 minute UT-15 infusion and the 300 minute washout period without reported SAEs. No deaths were reported during the study. The most commonly reported AEs were headache (78%), flushing (44%) and vomiting (22%). No significant changes in blood chemistries, urinalyses, CBC, vital signs or ECG compared with baseline were seen at 24 or 48 hours post-treatment.

A.10.5 Summary**A.10.5.1 Efficacy summary**

Study P02:01 studied the effects of subcutaneous infusion of UT-15 in a population with porto-pulmonary hypertension. The study was too small for standard hemodynamic efficacy measures to be significant in the review of UT-15. The pharmacokinetic analyses will be examined elsewhere in the NDA review.

A.10.5.2 Safety summary

No new safety concerns were identified in this population. No evidence of rebound pulmonary hypertension was detected in the study, although the reported hemodynamic changes were minimal.

A.10.5.3 Reviewer's conclusions

This trial provides additional safety exposure in a population that differs from the population studied in the majority of the trials in the NDA. No new safety concerns were identified in the trial, although the small numbers of patients greatly limits the studies ability to detect such events.

APPEARS THIS WAY
ON ORIGINAL

A.1 Study P03:01: A dose range-finding pilot study of intravenous LRX-15 in patients with peripheral vascular disease: a study in patients with severe lower limb ischemia.

A.10.6 Sites and investigators

P03:01 was conducted at a single site in the United States.

Table 103. Investigators (P03:01).

| Site | Investigator |
|------|---|
| 01 | Emile Mohler, Univ. of Pennsylvania, Philadelphia |

A.10.7 Background

Initial protocol submitted: 12.23.97

Protocol amendments: None.

Subject enrollment: 3.30.98 to 10.01.98

A.10.8 Study design

This was a single-center, open-label, within-patient placebo-controlled sequential dose-escalation pilot study of LRX-15 (later renamed UT-15) administered as an intravenous infusion in subjects with severe lower limb ischemia. Subjects who meet the inclusion criteria, but none of the exclusion criteria, completed four phases: 1) a screening phase (days -7 to -1); 2) a baseline phase (study day 1); 3) a treatment phase (day 1); and 4) a post-treatment phase (days 1 to 3). During the treatment phase, subjects will receive: a) a dose-ranging segment, beginning with a 30-minute placebo infusion followed by escalating doses of UT-15 as tolerated; b) a maintenance segment, in which the subject will receive a 120-minute infusion of UT-15 at the maximum tolerated dose; and c) a washout period.

A.10.8.1 Objectives

1. To assess the safety, dose-tolerance and acute hemodynamic effects of subcutaneous 15AU81 in patients with portopulmonary hypertension with mild to moderate hepatic dysfunction.;
2. To characterize the pharmacokinetic profile of 15AU81 administered as a subcutaneous infusion in this patient population.

A.10.8.2 Number of subjects/ randomization

Eight patients were to be enrolled in the study.

A.10.8.3 Inclusion/ exclusion criteria

Inclusion Criteria (must be present):

1. Male or female, between the age of 40 and 75 years.
2. If female, either surgically sterile, post-menopausal, or have a negative pregnancy test;
3. Have a history of severe claudication confirmed by Doppler or other appropriate exam.
4. Have a diagnosis of Fontaine Stage III severe lower-limb ischemia; have an ankle:brachial index ≤ 0.5 (range 0.35 to 0.5); or toe pressure < 30 mmHg; and be ambulatory.

01 15 for pulmonary hypertension

5. Have an angiogram or MRI of the affected limb within 6 months of entering baseline consistent with 'severe ischemia.'

6. Able to sign an informed consent.

Exclusion Criteria (Following must not be present):

1. Prior history of:
 - a. bleeding disorder;
 - b. stroke or symptom of TIAs.
 - c. myocardial infarction, angina pectoris, or unstable angina or heart failure;
 - d. syncope.
2. An unstable concurrent medical condition.
3. Serum creatinine \leq 2.5 mg/dl.
4. New therapy for PVD added within past one month.
5. Impaired liver function, defined as AST or ALT \geq 2X upper limits of normal.
6. Have a toe ulcer on the ischemic leg.
7. Be hospitalized for limb-threatening ischemia.
8. Be receiving anticoagulants.
9. History of alcohol or drug dependence in past 3 months.
10. Be receiving an investigational agent, or having received one in the past 30 days.

A.10.8.4 Dosage/ administration

During the dose-ranging segment of the treatment phase, subjects will receive IV infusion of UT-15 for a minimum of 30 minutes for each dose in the following order: sterile citrate buffer (placebo), 10, 20, 40, 60, 80, 100, and 120 ng/kg/min UT-15. Dose escalation will continue until a clinically unacceptable change in hemodynamic parameters or vital signs is observed, or until other clinical signs or symptoms, including adverse experiences, are observed. The infusion rate immediately before the rate producing the unacceptable effect will be defined as the maximum tolerated dose for purposes of the maintenance phase.

Immediately following the dose-ranging phase, subjects will receive a 120-minute infusion of UT-15 at the maximum tolerated dose. If any adverse clinical effects of UT-15 are noted during this period, the infusion rate of UT-15 is to be decreased or discontinued at the discretion of the investigator.

A.10.8.5 Duration/ adjustment of therapy

If any adverse clinical effects of UT-15 are noted during the constant infusion period, the infusion rate of UT-15 was to be decreased or discontinued at the discretion of the investigator.

A.10.8.6 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. 2.63.

A.10.8.7 Statistical considerations

The statistics in the trial were observational in nature .

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A.10.9 Results

Eight patients were enrolled in the trial and completed the dose-ranging portion of the study. Seven patients completed the 120-minute maintenance infusion at the maximum tolerated dose.

A.10.9.1 Efficacy

No efficacy data of clear relevance to the approvability of subcutaneous UT-15 for pulmonary hypertension were obtained in this small study. Per the sponsor, IV administration of UT-15 resulted in an increase in blood flow for the common femoral artery and anterior tibial artery.

A.10.9.2 Safety

The maximum tolerated dose of UT-15 was 10 ng/kg/min for 3 (38%), 15 ng/kg/min for one (13%), 20 ng/kg/min for three (38%) and 30 ng/kg/min for one (13%) patient.

There were no deaths reported in the study, and no SAEs during the initial infusion or the 120-minute maintenance infusion periods. The most common AEs reported were headache (88%) and vomiting (25%).

One patient discontinued during the maintenance phase due to headache and vomiting. There were no significant changes from baseline for clinical chemistry values, hematology, coagulation parameters, urinalyses, hemodynamic values or physical exam findings.

A.10.10 Summary

A.10.10.1 Efficacy summary

Study P03:01 studied the acute effects of IV UT-15 in patients with lower limb ischemia. None of the efficacy measures were relevant to the potential approvability of UT-15 for treatment of pulmonary hypertension.

A.10.10.2 Safety summary

No new safety concerns were identified in these patients plausibly related to the initiation of UT-15. The adverse events identified in this open-label study are similar to those reported in other small trials of IV UT-15.

A.10.10.3 Reviewer's conclusions

This trial provides little information not available from other trials. No new safety concerns were identified in this study

**APPEARS THIS WAY
ON ORIGINAL**

A.11 Study P76:01: A dose-range-finding study of intravenous 15AU81 in patients with congestive heart failure.

A.11.1 Sites and investigators

P01:01 was conducted at 3 sites in the United States. The investigators are shown in Table 104.

Table 104. Investigators (P76:01).

| Investigator | Location |
|----------------------|--------------------------------|
| Kirkwood Adams, MD | Univ. of North Carolina |
| Mihai Gheorgiade, MD | Henry Ford Hospital, Detroit |
| Robert Bourge, MD | Univ. of Alabama at Birmingham |

A.11.2 Background

Initial protocol submitted: N/A

Protocol amendments: None

Subject enrollment: 8.26.91 to 10.11.91

A.11.3 Study design

This multi-center, open-label study used a sequential dose-escalation design to assess the efficacy and safety of intravenous UT-15 in patients with symptomatic CHF (NYHA Class III or IV). Eligible patients underwent right-heart catheterization, followed by study drug administration:

- 1) Dose-ranging segment, when increasing doses of UT-15 were administered.
- 2) Dose-maintenance segment, when the maximum tolerated dose of UT-15 was administered for 90 minutes.
- 3) Wash-out phase lasting 90 minutes.
- 4) Post-treatment evaluation lasting approximately 24 hours.

Dose of UT-15 was adjusted/reduced per a protocol in the event of adverse effects.

A.11.3.1 Objectives

- 1) To assess the safety, dose-tolerance, and acute hemodynamic effects of UT-15 IV in patients with symptomatic heart failure.
- 2) To attempt to estimate the apparent half-life of UT-15 in the population.

A.11.3.2 Number of subjects/ randomization

Twelve (12) patients were enrolled in the trial, and 10 completed all of the study segments.

A.11.3.3 Inclusion/ exclusion criteria

Inclusion criteria (must be present)

- >28 years of age;
- Females must be post-menopausal or surgically sterile,
- had a diagnosis of severe, symptomatic heart failure (NYHA Class III or IV) at Screening/Baseline and for at least one month,
- LVEF \leq 35%.

Exclusion criteria (may not be present)

- had a change in CHF therapy in the past 48 hours, including IV inotropes,
- systolic BP <80 mmHg or heart rate outside of 50-125 BPM.
- history of MI or resuscitated sudden death in past 3 months.
- History of v fib, unstable angina, or secondary cause of CHF (amyloid, thyroid disease, myocarditis).

A.11.3.4 Dosage/ administration

UT-15 was administered intravenously, with dose increased every 15 minutes in segment 1) as tolerated by the patients. The doses of UT-15 ranged between 5 and 120 ng/kg/min.

A.11.3.5 Duration/ adjustment of therapy

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

A.11.3.6 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. 2.62. Invasive hemodynamic, vital sign, and ECG monitoring 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, vital signs and ECGs, labs and adverse events were also measured at the time of discontinuation from the study (approximately 24 hours).

A.11.3.7 Statistical considerations

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

A.11.4 Results

A.11.4.1 Subject demographics & baseline characteristics

The majority of the patients in the trial were men (11/12, 89%), with seven blacks and 5 whites. The mean age was 47 years old. The mean LVEF was $16 \pm 2\%$, and the right-ventricular EF was $35 \pm 1.8\%$. The reader is referred to the study report for additional demographics.

A.11.4.2 Disposition of subjects

Of the 12 patients enrolled, 2 patients were discontinued for severe hypotension. These are discussed in Safety below.

Subject selection. No information is available about subject selection in protocol P76:01.

Protocol violations & deviations. No significant protocol violations were reported.

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

A.11.4.3 Pharmacokinetics analyses

The serum levels were below the threshold for their assay to detect, so no useful PK results exist.

A.11.4.4 Hemodynamic changes

The maximum tolerated dose of UT-15 IV varied between 10 and 60 ng/kg/min in the 10 patients who completed the study. The table below summarizes the hemodynamic changes in the trial, comparing the observed effects at the maximum tolerated dose

with the effects of the vehicle-only infusion. Acute effects of UT-15 on the measured parameters, including changes in PCWP and CO, trended in favor of UT-15.

Table 105. Change from baseline in hemodynamic parameters (P76:01)¹¹²

| | Change from vehicle only to MTD¹¹³ |
|--------------------------------|--|
| HR (bpm) | +0.8±2.5 |
| Right Atrial Press (mmHg) | -4.6±1.4 |
| Cardiac Output | +1.7±0.4 |
| Pulmonary Artery Press (mm Hg) | -9.7±2.5 |
| PCWP | -3.5±1.6 |

A.11.4.5 Safety

None of the adverse events reported in the trial were 'serious' per the sponsor, although hypotension lead to the discontinuation of two patients. An additional patient had chest pain radiating to his left arm but continued in the trial.

The two patients discontinued for hypotension developed hypotension, headache, and restlessness that did not respond to reduction in the dose of UT-15.

Headache and restlessness were the two most commonly reported adverse events, occurring in 75% and 40% of the patients respectively.

A.11.4.5.1 Comparisons of defined safety endpoints

Due to the small sample size, no formal comparisons are performed.

A.11.4.5.2 Comments on specific safety parameters

Deaths. There were no deaths reported for subjects in the trial.

Serious adverse events. No SAEs occurred during the administration of study drug, but see note above regarding two patients with hypotension.

ECG changes. The sponsor reported that while baseline abnormalities existed in all ECGs at baseline, no changes in the ECGs between baseline and follow-up occurred.

A.11.5 Summary

A.11.5.1 Efficacy summary

Study P76:01 measured the acute hemodynamic effects of IV administration of UT-15 in patients with Class III/IV heart failure. The changes measured in this open-label trial were consistent with an acute effect of IV UT-15 on pulmonary vascular pressures, leading to an improvement in cardiac index. No pharmacokinetic analyses were performed due to technical failure of the assay used to measure the UT-15 concentrations.

A.11.5.2 Safety summary

There were no new safety concerns identified in this small study, but the route of administration differ from the proposed route (IV not subcutaneous), as does the study population. Significant hypotension was seen in two patients given UT-15 in the trial, along with the usual adverse events of headache and restlessness.

¹¹² Data from NDA vol. 2.62, table 9a.

¹¹³ Maximally tolerated dose.

A.11.5.3 Reviewer's conclusions

This small study of the acute effects of UT-15 on central hemodynamics found data consistent with an acute effect of IV UT-15 to cause pulmonary vascular dilatation. No information about the relationship between dose of UT-15 and hemodynamic effects can be obtained from a trial of this design (open-label, dose-ascending). No new safety concerns emerged from the trial that are of particular relevance to the proposed subcutaneous use of UT-15.

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Appendix B Response to Request for Information

On 20 November 2000, the FDA requested further information to support the classification of patients' discontinuation as due to an adverse event (infusion site pain) as opposed to clinical deterioration. Eighteen patients discontinued from Protocol P01:04/05 due to intolerable infusion site pain, as noted in NDA 21-272, Item 8, Study P01:04/05, Volume 2.34, Listing 16.2.1.6, page 6518. Narratives of these discontinuations were included in NDA 21-272, Item 8, Study P01:04/05, Volume 2.31, Table 14.3.4, page 5609.

The sponsor contacted each clinical center and discussed with study staff the clinical circumstances surrounding the patient discontinuation. Particular attention was given to why the patient was discontinued from the study and the patient's clinical status at the time of discontinuation. If Flolan was initiated, additional information was obtained describing the time course of, and reasons for its initiation. Patient status as of December 2000 was obtained. This information follows in brief narratives and is summarized in Table 1. In addition, individual patient data previously submitted in the NDA are listed in Table 2 including results of individual Six-Minute Walk tests and Dyspnea-Fatigue evaluations.

Patient 02001 was enrolled in the study for 43 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise decreased from baseline, though dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study; however increased dyspnea on exertion was noted post-UT-15. Flolan therapy was initiated six weeks post-UT-15 for worsening pulmonary hypertension. The patient was alive as of December 2000.

Patient 02006 was enrolled in the study for 71 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, but was initiated electively two weeks post-UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. The patient was alive as of December 2000.

Patient 02016 was enrolled in the study for 47 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient was improved during the study, but deteriorated with discontinuation of UT-15. The patient requested initiation of Flolan therapy four months post-UT-15 to replace the beneficial effect of UT-15. The patient was alive as of December 2000.

Patient 02020 was enrolled in the study for 38 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, but was initiated electively at one-month post-UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue ratings remained unchanged. In the investigator's opinion the clinical status of this patient was improved during the study, but deteriorated with discontinuation of UT-15. The patient was alive as of December 2000.

Patient 05009 was enrolled in the study for 42 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. In the investigator's opinion the clinical status of this patient did not deteriorate during the study, though exercise and dyspnea-fatigue rating worsened compared to baseline. The patient was alive as of December 2000.

Patient 07004 was enrolled in the study for 25 days¹¹⁴ when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. While receiving UT-15, exercise improved and dyspnea-fatigue rating remained essentially stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 10507 was enrolled in the study for 9 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 or until transplantation two months post-UT-15; the patient was listed for transplantation prior to study enrollment. While receiving UT-15, dyspnea-fatigue rating remained essentially stable compared to baseline; other than the baseline exercise, no other exercise test was conducted. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 11002 was enrolled in the study for 31 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise decreased from baseline though dyspnea-fatigue rating remained essentially stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. Pulmonary hypertension symptoms worsened post-UT-15 leading to Flolan treatment two months later. The patient was alive as of December 2000.

Patient 11003 was enrolled in the study for 56 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise improved and dyspnea-fatigue rating remained stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. Pulmonary hypertension symptoms worsened post-UT-15 leading to Flolan treatment three months later. The patient was alive as of December 2000.

Patient 14012 was enrolled in the study for 58 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. While receiving UT-15, exercise remained essentially stable with improvement in dyspnea-fatigue rating. In the investigator's opinion the clinical status of this patient was improved during the study; however increased dyspnea was noted after discontinuation of UT-15. The patient was alive as of December 2000.

Patient 19001 was enrolled in the study for 70 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan

¹¹⁴ NDA summary tables indicate patient 07004 was enrolled in the study for 87 days; however UT-15 was permanently discontinued on Day 25 as indicated above.

therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. In the investigator's opinion the clinical status of this patient was improved during the study though the dyspnea-fatigue rating worsened compared to baseline; a Week 6 exercise test was not performed. Flolan therapy was initiated two months post-UT-15 to replace the beneficial effect of UT-15. The patient was alive as of December 2000.

Patient 19005 was enrolled in the study for 69 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, nor for the first month post-UT-15. While receiving UT-15, exercise decreased from baseline though dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient did not deteriorate throughout the study. Flolan therapy was initiated five months post-UT-15 at a hospital outside of the clinical study. The patient was alive as of December 2000.

Patient 19008 was enrolled in the study for 45 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been required as of December 2000. While receiving UT-15, exercise was improved though dyspnea-fatigue rating was reduced modestly compared to baseline. In the investigator's opinion the patient's clinical status did not deteriorate during the study. The patient was alive as of December 2000.

Patient 19502 was enrolled in the study for 46 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15, but was initiated one-month post UT-15. While receiving UT-15, exercise was improved from baseline and dyspnea-fatigue rating remained stable. In the investigator's opinion the clinical status of this patient improved during the study. Pulmonary hypertension symptoms worsened post UT-15 leading to Flolan therapy one month later. The patient was alive as of December 2000.

Patient 52008 was enrolled in the study for 37 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was initiated electively immediately following discontinuation of UT-15. While receiving UT-15, exercise was modestly improved and dyspnea-fatigue rating remained stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate, but symptoms of pulmonary hypertension worsened post UT-15 while receiving Flolan. The patient underwent transplantation four months post-initiation of Flolan therapy. The patient was alive as of December 2000.

Patient 54011 was enrolled in the study for 31 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not required immediately following discontinuation of UT-15 and has not been initiated as of December 2000. While receiving UT-15, exercise was reduced though dyspnea-fatigue rating improved compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 54012 was enrolled in the study for 16 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. Flolan therapy was not initiated immediately following discontinuation of UT-15, but was initiated electively within the first week post-UT-15. While receiving UT-15, exercise was improved and dyspnea-fatigue rating remained stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

Patient 54018 enrolled in the study for 47 days when UT-15 therapy was discontinued due to intolerable infusion site pain as judged by the investigator. In anticipation of discontinuing UT-15, Flolan therapy was initiated electively one day prior to discontinuation of UT-15. While receiving UT-15, exercise and dyspnea-fatigue rating remained essentially stable compared to baseline. In the investigator's opinion the clinical status of this patient did not deteriorate during the study. The patient was alive as of December 2000.

In summary, following additional communication with the study centers, the sponsor maintains that all 18 patients are properly categorized by the investigators as discontinuations due to an adverse event (infusion site pain); none of the patients in question were withdrawn due to clinical deterioration.

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Table 2
 Listing of Information for Patients Who Discontinued Early
 Reason for Discontinuation: AE

| Trt | Pt | Etiology | NYHA | Disc. | Dose | Week | Date at | 12 | Death? | Flolan? | PVRI | CI | Six-Minute | | | |
|--------|-------|----------|------|-------|------|---------|---------|----|--------|---------|------|-----|------------|----------|-----|-------|
| | | | | | | | | | | | | | Walk | DF Score | | |
| | | | | | | | | | | | | | Day | Dist | Day | Score |
| Active | 02001 | Shunt | III | 43 | 5.00 | 09FEB99 | No | | | Yes:6w | 33.2 | 1.7 | 1 | 479 | 1 | 6 |
| | | | | | | | | | | | | | 9 | 446 | 8 | 6 |
| | | | | | | | | | | | | | 43 | 132 | 43 | 6 |
| | 02006 | CTD | III | 71 | 2.50 | 15APR99 | No | | | Yes:2w | 38.1 | 1.1 | 1 | 388 | 1 | 6 |
| | | | | | | | | | | | | | 9 | 470 | 6 | 6 |
| | | | | | | | | | | | | | 43 | 495 | 43 | 6 |
| | 02016 | Shunt | III | 47 | 3.75 | 22JUN99 | No | | | No | 14.8 | 2.2 | 1 | 198 | 2 | 6 |
| | | | | | | | | | | | | | 5 | 406 | 5 | 6 |
| | 02020 | PPH | III | 38 | 3.00 | 21OCT99 | No | | | Yes:4w | 24.1 | 2.3 | 1 | 264 | 1 | 8 |
| | | | | | | | | | | | | | 9 | 347 | 9 | 8 |
| | 05009 | Shunt | III | 42 | 1.25 | 30SEP99 | No | | | No | 24.1 | 2.4 | 0 | 337 | 0 | 7 |
| | | | | | | | | | | | | | 9 | 253 | 9 | 3 |
| | | | | | | | | | | | | | 42 | 276 | 42 | 3 |
| | 07004 | Shunt | II | 87 | 1.50 | 18AUG99 | No | | | No | 54.8 | 2.8 | 0 | 345 | 1 | 7 |
| | | | | | | | | | | | | | 10 | 393 | 10 | 6 |
| | | | | | | | | | | | | | 44 | Too Ill | 45 | 7 |
| | | | | | | | | | | | | | 87 | 398 | 87 | 6 |
| | 10507 | Shunt | IV | 9 | 1.25 | 25JAN00 | No | | | No | | | 2 | 183 | 2 | 1 |

| 11002 | PPH | II | 31 | 2.50 | 25MAY99 | No | No | 25.4 | 2.0 | 2 | 370 | 1 | 4 |
|-------|-------|-----|----|------|---------|----|--------|------|-----|-----|-----|-----|----|
| | | | | | | | | | | | 9 | 381 | 9 |
| | | | | | | | | | | | 30 | 229 | 30 |
| 11003 | Shunt | III | 56 | 2.50 | 29SEP99 | No | No | | | -11 | 287 | 1 | 2 |
| | | | | | | | | | | 7 | 323 | 7 | 2 |
| | | | | | | | | | | | | 36 | 2 |
| 14012 | CTD | III | 58 | 6.25 | 19NOV99 | No | No | 7.4 | 3.0 | 2 | 339 | 1 | 6 |
| | | | | | | | | | | | 9 | 345 | 9 |
| | | | | | | | | | | | 44 | 333 | 44 |
| | | | | | | | | | | | | 58 | 9 |
| 19001 | PPH | III | 70 | 3.75 | 04FEB99 | No | Yes:8w | 23.5 | 2.0 | 1 | 383 | 1 | 6 |
| | | | | | | | | | | | 8 | 383 | 8 |
| | | | | | | | | | | | 41 | ND | 41 |
| 19005 | PPH | III | 69 | 5.00 | 04MAY99 | No | No | 26.2 | 1.7 | 1 | 264 | 1 | 5 |
| | | | | | | | | | | | 10 | 276 | 10 |
| | | | | | | | | | | | 45 | 180 | 45 |

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Table 2
Listing of Information for Patients Who Discontinued Early
Reason for Discontinuation: AE

| Trt | Pt | Etiology | NYHA | Disc. | Dose | Week | Date at | 12 | Death? | Flolan? | PVRI | CI | Six-Minute | | | |
|--------|-------|----------|------|-------|------|---------|------------|----|---------|---------|------|----|------------|----------|-----|-------|
| | | | | | | | | | | | | | Walk | DF Score | | |
| | | | | | | | | | | | | | Day | Dist | Day | Score |
| Active | 19008 | PPH | III | 45 | 5.00 | 07SEP99 | No | | No | 27.6 | 2.2 | 1 | 315 | 1 | 7 | |
| | | | | | | | | | | | | | 12 | 343 | 10 | 5 |
| | | | | | | | | | | | | | 45 | 355 | 45 | 5 |
| | 19502 | CTD | IV | 46 | 1.30 | 18JAN00 | No | | Yes:4w | 22.6 | 2.0 | 1 | 186 | 1 | 2 | |
| | | | | | | | | | | | | | 8 | 207 | 8 | 4 |
| | | | | | | | | | | | | | 45 | 241 | 45 | 2 |
| | 52008 | PPH | III | 37 | 2.60 | 25JAN00 | No | | Yes:0d | 29.8 | 1.5 | 2 | 260 | 2 | 2 | |
| | | | | | | | | | | | | | 9 | 273 | 9 | 2 |
| | 54011 | Shunt | III | 31 | 2.50 | 11AUG99 | No | | No | | 2.5 | 2 | 288 | 0 | 3 | |
| | | | | | | | | | | | | | 9 | 235 | 8 | 6 |
| | 54012 | PPH | III | 16 | 2.50 | 19AUG99 | No | | Yes:5d | 41.3 | 1.2 | 1 | 233 | 1 | 3 | |
| | | | | | | | | | | | | | 9 | 275 | 10 | 3 |
| | 54018 | PPH | III | 47 | 4.37 | 14SEP99 | No | | Yes:-1d | 32.8 | 1.4 | 1 | 335 | 2 | 3 | |
| | | | | | | | | | | | | | 10 | 380 | 11 | 3 |
| | | | | | | | | | | | | | 46 | 325 | 47 | 3 |

Safety Update Review

Included in the March 9, 2001 Clinical Review (see pages 15-32, Integrated review of Safety).