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.

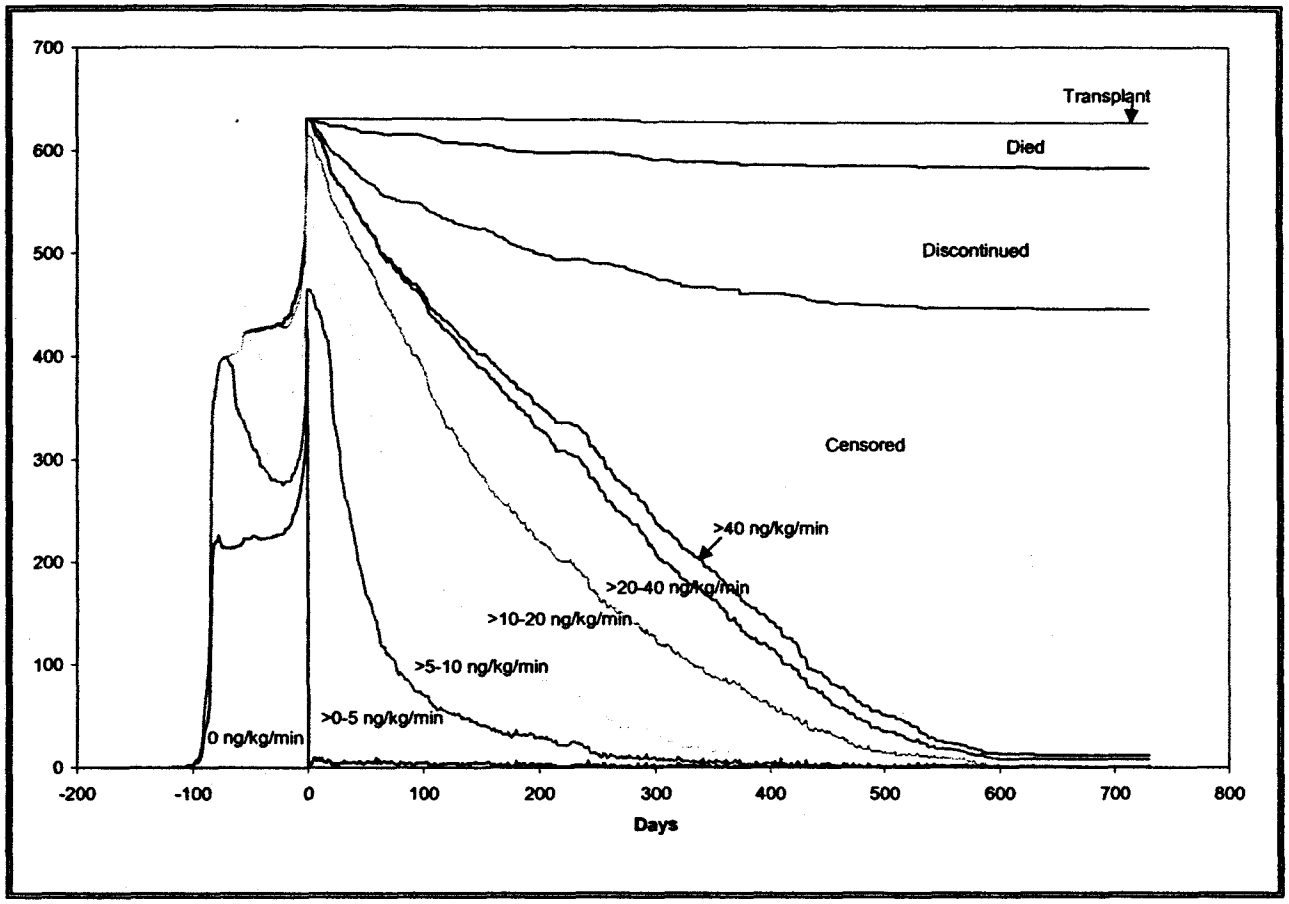


**Figure 1. Exposure to UT-15 (P01:06)**

**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.

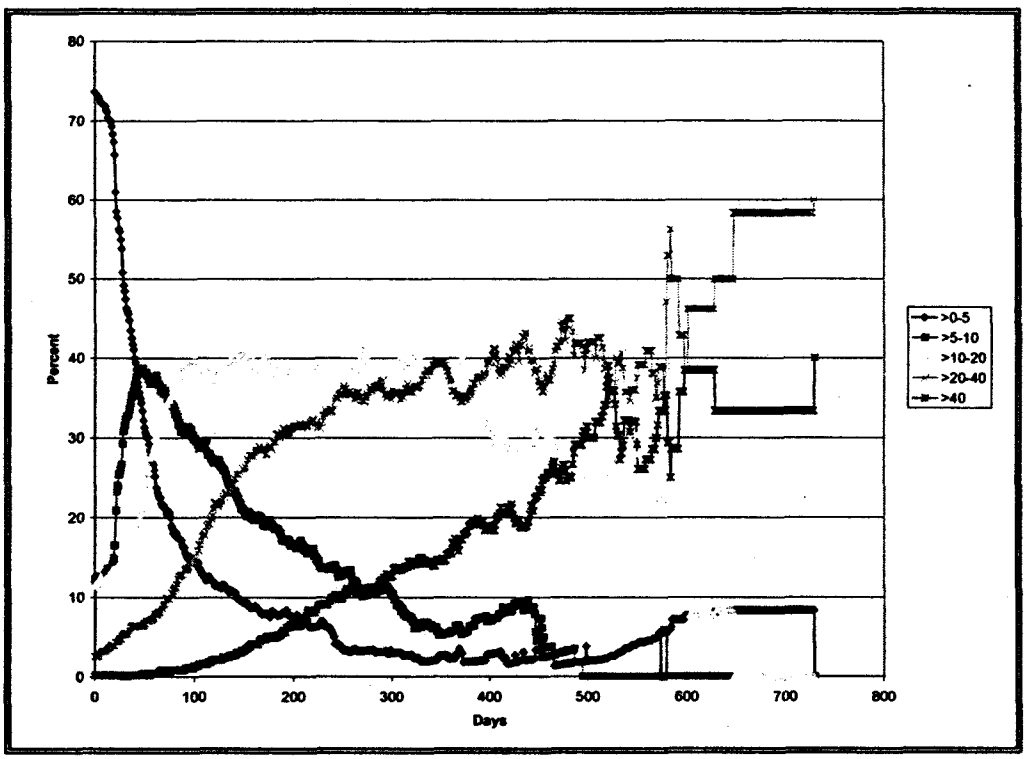


**Figure 3. Censored view of dosing (P01:06)**

**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.

# 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

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[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

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