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	38 (17%)	54(23%)	44 (21%)	42 (22%)
	hypertrophy	11 (5%)	13(6%)	15 (7%)	18 (9%)
	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

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[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 in to 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 served 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 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.

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 subject, 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 SVO_2.

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.

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