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

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

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

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

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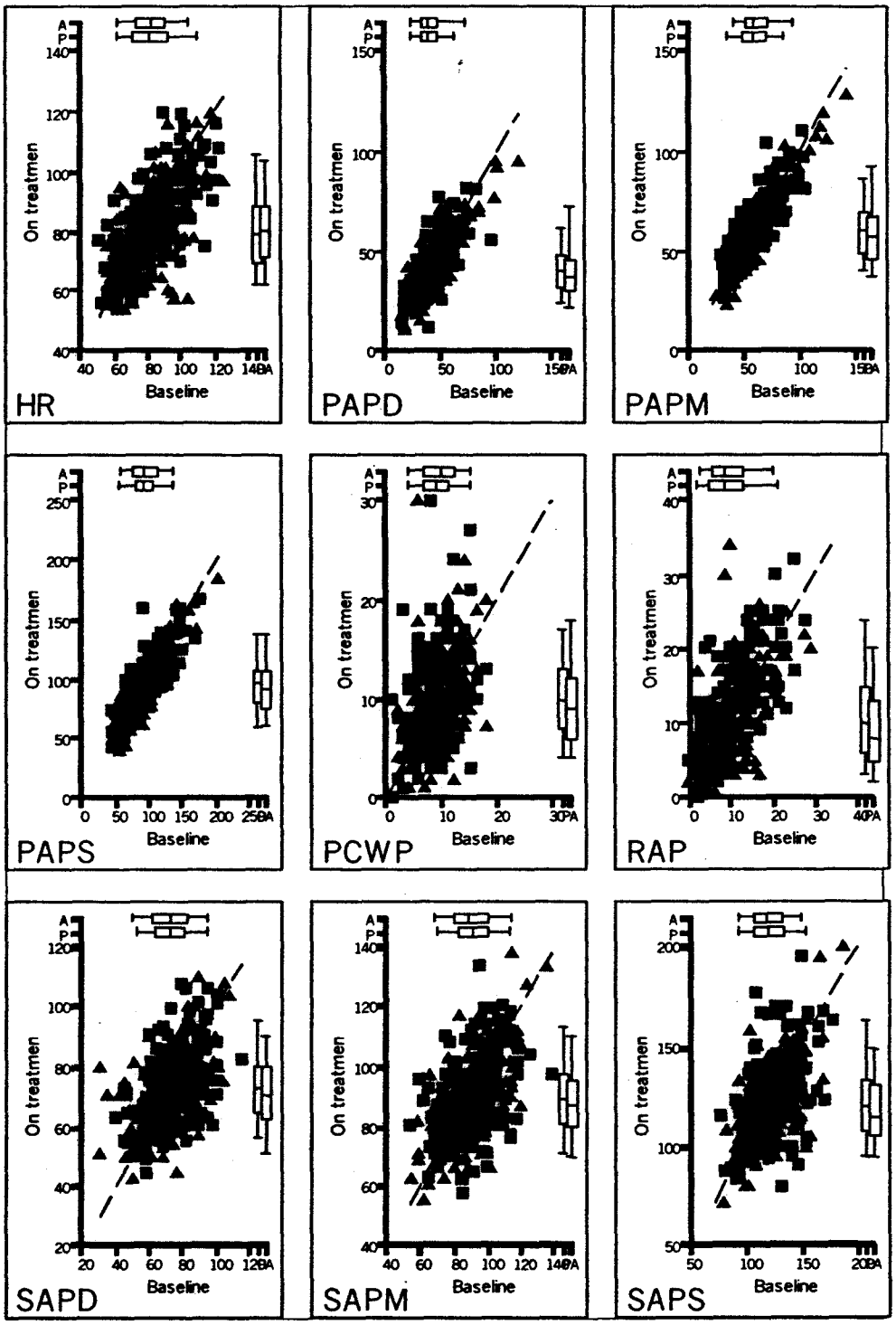

Figure 15. Hemodynamics scatter plots (P01:04-05)

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

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

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

Oxygen saturation

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

Other end points

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

Mortality

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

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

Hospitalizations

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

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

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Need for medication changes

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

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

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

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

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

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Table 77. Medication changes (P01:04-05)

		P01:04		P01:05		Pooled	
		Veh N=111	UT-15 N=113	Veh N=125	UT-15 N=120	Veh N=236	UT-15 N=233
Anticoagulants	Baseline	58 (52)	61 (54)	88 (82)	88 (73)	160 (68)	149 (64)
	Treatment	94 (85)	95 (84)	116 (92)	104 (87)	210 (89)	199 (85)
Calcium channel blockers	Baseline	50 (45)	49 (43)	48 (38)	48 (40)	98 (42)	97 (42)
	Treatment	52 (49)	50 (44)	49 (39)	51 (43)	101 (43)	101 (43)
Other vasodilators	Baseline	19 (17)	18 (16)	16 (13)	15 913)	35 (15	33 (14)
	Treatment	24 (22)	18 (16)	17 (14)	15 (13)	41 (17)	33 (14
Digoxin	Baseline	30 (27)	34 (30)	29 (23)	22 (18)	59 (25)	56 (24)
	Treatment	35 (32)	41 (36)	33 (26)	26 (22)	68 (29)	67 (29)
Diuretics	Baseline	54 (49)	69 (61)	75 (60)	57 (56)	129 (55)	136 (58)
	Treatment	71 (64)	82 (73)	86 (68)	74 (62)	157 (66)	156 (67)

Change in NYHA classification

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

Dose response

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

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

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