

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203496Orig1s000

MEDICAL REVIEW(S)

NDA#203496 SD#32

Oral treprostinil

Medical Review: Maryann Gordon, MD

Date submitted: 6-17-2013

Conclusions

I agree that the combination studies with current drugs used for pulmonary hypertension show inconsistent results. Although the NDA reviewers found that the studies with oral treprostinil on top of background therapy (#301 and #308) did not demonstrate efficacy, there are numerous reasons for study failure including small sample size and/or poor administration of background therapy.

In conclusion, the sponsor of a new PAH drug is not required to show that their drug has additional efficacy when used in combination with other agents approved for the same indication.

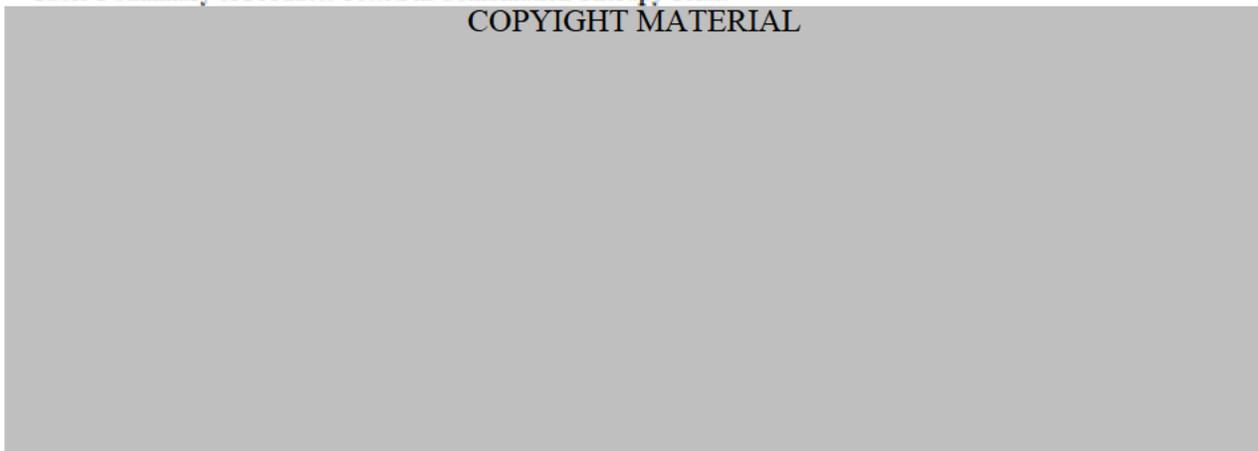
Background

Summary of Published Combination Therapy Trials with Vasodilator Therapies in PAH

Eight randomized, double-blind, placebo-controlled combination therapy studies were conducted in WHO Group 1 PAH patients with 4 studies evaluating the addition of a prostacyclin to existing background therapy, two studies evaluating addition of a PDE-5 inhibitor, and two studies evaluating addition of an ERA. The studies were 12 to 26 weeks in duration with enrollment of NYHA Functional Class II through IV patients (Table 1).

Table 1 Summary of Products Tested in Combination Therapy Trials

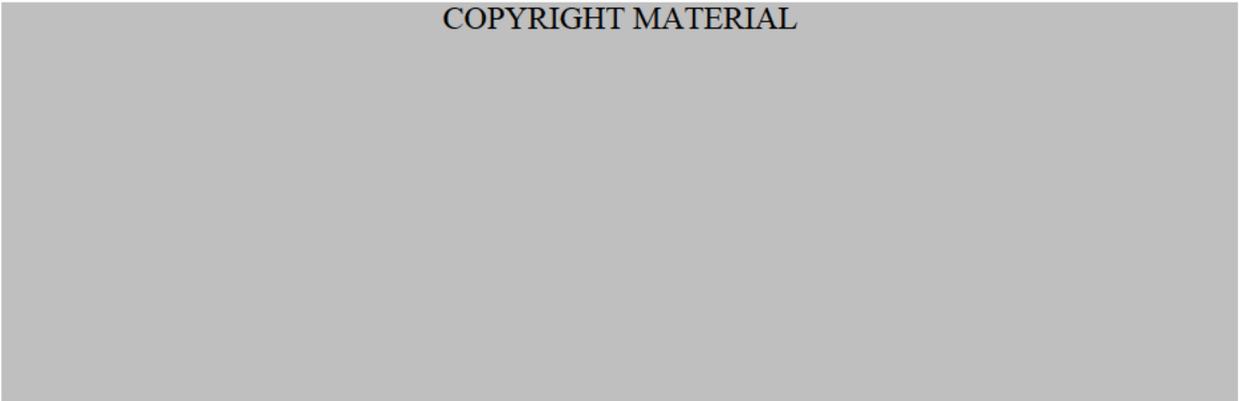
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A summary of the 6-minute walk distance (6MWD) results from these combination therapy trials is provided in [Figure 1](#).

Figure 1 Summary of Placebo-Corrected Results from Combination Therapy Trials

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Study design:

Study #301 and #308 randomized subjects in a 1:1 ratio to UT-15C: placebo.

Study #302 randomized subjects in a 2:1 ratio to UT-15C: placebo. Study #302 was a 12-week study. Studies #301 and #308 were 16-week study. Patients eligible for enrollment in the three studies is similar to previous study for PAH drugs. Patients must have evidence for PAH and no evidence of left sided disease. They must be able to perform a walk test with 6MWD to be between 100 and 450 meters

Dose:

All three studies were titration to either tolerance or to adequate effect. Major differences in the three studies were doses and titration algorithms and the available dose formulation for the study. In general, subjects were started on a low dose of UT-15C with upward titration at 3 day intervals based on symptoms of PAH as well as tolerability. All doses were taken with food.

The overall conclusions by the FDA reviewers regarding the efficacy of the studies #301 and #308 are summarized by Dr. Norman Stockbridge in his review dated 10-23-2012.

Neither study 301 nor 308 (with background) was statistically significant at the 16-week assessment. An unplanned analysis of their combined results showed differences of 4 m at 4 weeks, 5 m at 8 weeks (neither $p < 0.05$), 10 m at 12 weeks, and 10 m at 16 weeks (the latter two time points were nominally statistically significant at $p < 0.01$).

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/s/

MARYANN GORDON
09/11/2013

SHARI L TARGUM
09/16/2013



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 203496 Treprostinil extended-release tablets for pulmonary arterial hypertension.

Sponsor: United Therapeutics

Review date: 22 March 2013

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 203496

This memo conveys the Division's recommendation to issue a second Complete Response letter for treprostinil extended-release tablets.

This application has been the subject of review by Dr. Karkowsky (5 March 2013), CDTL for the original submission. There is a subsequent review (21 March 2013) by Dr. Papoian that concludes that further consideration of the carcinogenic potential of treprostinil diolamine/diethanolamine can be deferred until the ongoing carcinogenicity study is complete.

The Division previously issued a Complete Response letter for this application (23 October 2012). Below, I give the issues in that letter, the sponsor's response, and my current thinking. There are no new studies of oral treprostinil.

You were able to demonstrate an effect on 6-minute walk only in study 302. The effect in that study was quite small and of dubious clinical importance. The estimated mean effect probably exaggerates the true effect, as much of the effect seems to be attributable to how values are imputed to subjects missing week 12 data. (This appears to have been less of an issue with inhaled treprostinil. In addition, we note our disagreement about how some subjects in study 302 were categorized for the purposes of imputation.)

The sponsor does not dispute the overall treatment effect size, but points out that it is the same as with other formulations of treprostinil, faint praise indeed. This effect is achieved at peak (where plasma levels are 7 to 10 times levels at trough with twice daily dosing. At trough, a statistically significant effect was not demonstrated, but the nominal effect was 13 m, about half the effect at peak.

In defense of the clinical significance of this effect, the sponsor says that it is similar to the effect of subcutaneous treprostinil on 6-minute walk, and subcutaneous treprostinil was able to avert clinical worsening in patients discontinuing Flolan. However, I am skeptical that oral treprostinil would recapitulate this benefit, as subcutaneous administration does not result in peak-trough excursions of 7- to 10-fold.

The sponsor also points out that survival in open label use of oral treprostinil is similar to that of subcutaneous treprostinil and that of bosentan and better than that seen in historical data. While this is somewhat reassuring from a safety perspective, neither subcutaneous treprostinil nor bosentan have mortality claims based on these open-label, historically controlled data, and there is no basis for attributing such good outcomes to oral treprostinil either.

The sponsor notes that in the long-term open-label study, only 19% of subjects add another vasodilator in the first year. I do not know how to interpret that observation, but I am skeptical that it reflects normalization of subjects' symptoms on oral treprostiniil.

In the primary analysis of study 302, 21% of subjects on oral treprostiniil and 14% of subjects on placebo had imputed values, with the differences being among subjects assigned average placebo rank (4% vs. 0%) and those assigned last rank carried forward (8% vs. 1%). The differences that resulted in net better rank on oral treprostiniil probably reflect its poorer tolerability; clinical deterioration and death were similar on study drug and placebo.

In addition, pre-specified sensitivity analyses that (a) carry forward last rank for all missing data, (b) analyze completers only, or (c) use data obtained post-withdrawal, all show similar effect sizes and nominal p-values. In addition, analyses based on the FDA reviewer's opinion of cause for withdrawal or on Dr. Wittes's "worst reasonable case" all retain a similar effect size and at least nominal statistical significance.

Thus the sponsor shows that the results are not highly sensitive to the imputation process. Nevertheless, it is difficult to describe the 'advantage' in rank obtained because of poorer tolerability of oral treprostiniil.

You were unable to demonstrate an effect on time to clinical worsening in three phase 3 studies.

While this comment in the first Complete Response letter was intended to note merely that no benefit existed of greater clinical importance than the effect on 6-minute walk, the sponsor again reminds us that subcutaneous treprostiniil has the claim I noted previously. I again note skepticism that this can be expected to apply to oral treprostiniil, and that skepticism can be expected to make its way into labeling were oral treprostiniil to be approved.

You were unable to show an effect on 6-minute walk in two well-powered studies (301 and 308) in which subjects were on background therapy with other, possibly more effective but certainly better tolerated vasodilators. Given the meager effect of treprostiniil and its poor tolerability, it is difficult to name a clinical scenario in which use of oral treprostiniil is appropriate.

The sponsor does not refute the findings of studies 301 and 308, but they note that that 40 and 45% of subjects in these studies were on both a PDE5 inhibitor and an endothelin receptor antagonist. They do not follow up with an analysis by background treatment.

In response to characterization of oral treprostiniil as poorly tolerated, the sponsor notes that 824 subjects have participated in open-label studies, of whom 641 remained on treatment at 1 year. Whether that constitutes good tolerability is a matter of perspective, but I concede that some people tolerate long-term use. I also agree that no novel toxicity was associated with the oral formulation, and that the oral formulation avoids formulation-specific problems with inhaled, intravenous, and subcutaneous administration.

The sponsor responds to the challenge of naming a clinical scenario for use of oral treprostiniil by again noting open-label, long-term use and the low uptake of additional

therapy. I again note my skepticism that this is a reflection of benefit of oral treprostinil rather than a benefit of remaining in a study.

The sponsor goes on to argue that oral treprostinil has been adequately shown to work in some definable setting, asserting that it should be approved for use in that setting (monotherapy). I disagree. When there were only a few such drugs, then it made sense to approve them without concern about their interactions (or the small effect). Now there are multiple drugs in multiple classes. The symptomatic effects of any of them are so small as to be indiscernible by individual patients against the background of the day-to-day variability in symptoms¹; this is why it takes hundreds of subjects to detect a treatment effect. The magnitude of the effect matters here, and if a new product or new formulation cannot be shown to achieve a clinically important effect alone, it ought to be demonstrated to contribute to a meaningful effect; oral treprostinil has done neither.

The sponsor might reasonably attempt another study with a regimen giving less fluctuation in exposure across the inter-dosing interval, but showing an effect only absent other background therapy is of dubious value.

¹ Had this formulation demonstrated effects on more important end points, like mortality or progression, one might feel differently about the clinical importance of a small effect.

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/s/

NORMAN L STOCKBRIDGE
03/22/2013



MEMORANDUM
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 26, 2013

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of
Cardiovascular and Renal Products, HFD-110.

TO: Dr. Norman Stockbridge, M.D., Ph.D., Director, Division of
Cardiovascular and Renal Products, HFD-110.

SUBJECT Complete response recommendation for NDA 203496, Treprostinil
diolamine (no TRADENAME approved).

This memo is the Divisions response to United Therapeutics resubmission dated January 31, 2013 for oral Treprostinil (UT-15C). The Division's recommendation, that the oral formulation of Treprostinil diolamine not be approved for the indication [REDACTED] (b) (4) [REDACTED] as a BID dosing regimen, has not changed based on the above submitted rebuttal.

Only one study (#302) in the oral treprostinil application appears to demonstrate a placebo-subtracted median effect on six-minute walk distance (6MWD) that differed from zero in a pulmonary artery hypertension (PAH) population. There were two failed studies in this population when oral treprostinil was used on-top of approved therapies for PAH. There was also a failed set of studies that demonstrated no benefit in walk distance when treprostinil, as monotherapy, was subcutaneously administered. In the positive oral study the effect on walk-distance is substantially dependent on how missing values were imputed. Including the results of the initial application where treprostinil was administered subcutaneously the one nominally positive study was clearly an outlier. The single nominally positive study # 302 is insufficient, given the other negative study to allow for approval of the oral formulation of treprostinil diolamine.

In addition, the sponsor's proposed dosing instructions is based on an ever-shifting change in study protocol dosing strategy with lower doses and smaller dose increments recommended by the sponsor as the population demonstrated intolerance to the ongoing dosing regimens. UT-15C appears to be poorly tolerated and it is unlikely to be used as initial therapy. The two on-top of studies were unsuccessful and it would be difficult to recommend that UT-15C be used as adjunctive therapy to other PAH drugs. The pooled studies P01:04 and P01:05 utilizing subcutaneous infused treprostinil were as monotherapy. It is, therefore, not convincing to ascribe the failed oral studies were as a consequence of the use on top of concomitant therapies.

The current dosing regimen utilized in the clinical studies was a BID regimen. That decision seems to not be based on the performance characteristics of the oral formulation. Based on the degree of excursion from peak concentrations from C_{max} to C_{12} hours, a BID regimen does not afford adequate concentrations during the entire dosing interval. The FDA, based on pharmacokinetic considerations, would recommend a TID dosing regimen for the UT-15C. However, no available information on 6MWD is available utilizing a TID regimen. Any new study should, in addition, better define a dose-response effect as well as the starting dose and appropriate dose increments.

The two aspects, the large number of discontinuations requiring imputation of 6MWD values and the lack of an appropriate dosing set of instructions are likely to be intimately related. Should an appropriate dose regimen been used in the clinical trials, the number of discontinuations and particularly the number of early discontinuations would have been reduced and the impact of imputation of missing data would have been minimized.

Brief development summary of oral treprostinil:

There were three placebo-controlled studies submitted to support a benefit of treprostinil diolamine (UT-15C) oral formulation. Two of these studies (#301 and # 308) were on top of accepted therapies for PAH, either phosphodiesterase 5 (PDE-5) inhibitors, endothelin receptor antagonists (ERA) or both. These two studies were on face value unsuccessful in demonstrating a benefit in 6MWD. Pooling of the two unsuccessful oral formulation studies was never pre-planned and moreover, because of the disproportionate numbers of dropouts in the treated group, the p-values for each of these studies are likely to be inaccurate and favor treatment group.

The one nominally successful study (study #302) was a placebo-controlled study of UT-15C versus placebo in a pulmonary arterial hypertension (PAH) in the absence of approved background therapies. So, it becomes difficult to recommend the use of this drug with concurrent approved therapies.

There were a large number of discontinuations during the one successful study, with many discontinuations occurring early in therapy and prior to any assessment of the effect of drug on 6MWD. The outcome is, therefore, largely dependent on the imputed values for these subjects. It does not appear that the subjects were followed for events of interest after the subject discontinued.

Based on the discussion contained in the joint clinical/statistical review and the amendment dated 10-10-12, any benefit the use of UT-15C to increase walk distance in patients with pulmonary arterial hypertension (PAH) population is small, and toxicities are not trivial. There were a disproportionate number of dropouts in the UT-15C group early on in treatment in the one study which suggested a benefit (study #302). The assessment of the drug-effect markedly depends on the handling of these dropouts. The imputation rules are shown in Table 1. Several sensitivity analyses were contained in the

joint clinical/statistical review and amendment suggest that the walk distance is very sensitive to the nature of the imputation of the missing values.

Table 1: Missing data imputation algorithm study # 302

Lowest rank	For deaths, discontinuations due to clinical deterioration, transplantation or atrial septostomy or subject to ill to perform walk test
Mean rank	For subjects who withdrew prior to any 6MWD
LOCF	For subjects who prematurely withdrew.

With respect to the oral formulation of treprostinil (treprostinil diolamine), there were three studies #301, study # 302 and study # 308. The results of the sponsor's primary analysis are shown below. Also included are the results of the pooled subcutaneous therapy.

Study design:

Study #301 and #308 randomized subjects in a 1:1 ratio to UT-15C: placebo. Study #302 randomized subjects in a 2:1 ratio to UT-15C: placebo. Study #302 was a 12-week study. Studies #301 and #308 were 16-week study. Patients eligible for enrollment in the three studies is similar to previous study for PAH drugs. Patients must have evidence for PAH and no evidence of left sided disease. They must be able to perform a walk test with 6MWD to be between 100 and 450 meters

Dose:

All three studies were titration to either tolerance or to adequate effect. Major differences in the three studies were doses and titration algorithms and the available dose formulation for the study. In general, subjects were started on a low dose of UT-15C with upward titration at 3 day intervals based on symptoms of PAH as well as tolerability. All doses were taken with food. The table below defines the evolution of the dosing regimens used in each of the studies.

Table 2: Dosing changes during placebo-controlled oral studies.

Study #	Initial formulations available	Amendments altering dosing (all doses were administered BID)	Dosing increments initial	Dosing increments at final
#301	1, 5 mg	0.5 mg and 0.25 mg amendments 3 and 4, respectively	Initial dose was 1 mg. Amendment 4 lowered starting dose to 0.5 mg	Dose was escalated every 3 days.
#302	1, 5 mg	0.5 mg and 0.25 mg amendments 3 and 4, respectively. Amendment 6 introduced 0.125 mg dose	Initial dose was 1 mg. Amendment 4 lowered starting dose to 0.5 mg. further lowered to 0.25 mg	Dose escalation was 1 mg every 5 days but changed to 0.5 mg every 3 days. Amended to 0.25 mg every 3 days
#308	0.25, 0.5 and 1 mg. Aside from sites in China a 0.125 mg dose became available.	Initial dose was 0.25 mg. Initial increments was 0.25 mg prior to week 4. After week 4 the dose increments could be either 0.25 or 0.5 mg increments. A 0.125 mg dose was allowed if the 0.25 mg dose increase was not tolerated	Initial dose was 0.25 mg. Initial increments was 0.25 mg prior to week 4. After week 4 the dose increments could be either 0.25 or 0.5 mg increments. A 0.125 mg dose was allowed if the 0.25 mg dose increase was not tolerated	

The demographics of those enrolled are shown in Table 12.

Table 3: Demographics of study #301, #302 and #308

Parameter	Study #301		Study # 302		Study # 308	
	UT-15C	placebo	UT-15C	placebo	UT-15C	placebo
N	174	176	233	116	157	153
Age	51.1	49.5	41	43	52	50
Gender (% female)	85%	80%	74%	78%	76%	80%
Race: %						
Caucasian	65%	68%	41%	41%	67%	63%
African/American	28%	24%	4%	<1%	7%	65
Asian	3%	6%	47%	48%	26%	29%
Native American	2%	2%	0	0	2%	3%
Other					<1%	0
Etiology						
Idiopathic/familial	113 (65%)	119 (68%)	171 (72%)	88 (76%)	104 (66%)	99 (65%)
CVD	49 (28%)	43 (24%)	48 (19%)	22 (19%)	48 (31%)	49 (32%)
Repaired CHD	11 (6%)	11 (6%)	12 (6%)	5 (4%)	3 (2%)	1 (<1%)
HIV	1 (<1%)	3 (2%)	2 (1%)	1 (<1%)	2 (1%)	4 (3%)
Other			< 1%	0		
Background therapy						
ERA	55 (32%)	51 (29%)			25 (16%)	28 (18%)
PDE5-I	45 (26%)	43 (24%)	None	None	67 (43%)	65 (42%)
Both	74 (43%)	82 (47%)			65 (41%)	60 (39%)
Functional class II/III	41 (24%)/127 (76%)	31/139				
Functional class I-II			90 (39%)	43 (37%)	43 (27%)	37 (24%)
III-IV			143 (61%)	73 (63%)	113 (72%)	115 (75%)

The most notable differences between the three studies were the large fraction of Asians enrolled into study # 302. There was a 2:1 randomization in study #302. Studies #301 and #308 include usage of concomitant therapies. More than half the patients had functional class III or worse.

Disposition of subjects:

The disposition of patients in each of the studies is shown in the table below. A greater fraction among those entering study # 302 discontinued prematurely had no measurements on therapy and a substantial fraction of the patients had values imputed.

Table 4 Completion status studies # 301, # 302 and # 308

	Study #301		Study #302		Study # 308	
	UT-15C	Placebo	UT-15C	Placebo	UT-15C	Placebo
N=	174	176	233	116	157	153
Completed study	153 (88%)	167 (95%)	182 (78%)	98 (84%)	132 (84%)	138 (90%)
D/C prematurely	21 (12%)	9 (5%)	51 (22%)	18 (16%)	25 (16%)	15 (10%)
Consent Withdrawn	13 (7%)	3 (2%)	3 (1%)		1 (<1%)	2 (1%)
Death	3 (2%)	2 (1%)	10 (4%)	6 (5%)	2 (1%)	3 (2%)
Lost to follow up	2 (1%)	1 (<1%)	4 (2%)		0	1 (<1%)
Other	2 (1%)	3 (2%)	4 (2%)	2 (2%)		
Protocol Violation	1 (<1%)	0				
Adverse event			23 (10%)	3 (3%)	18 (11%)	5 (3%)
Clinical deterioration			7 (3%)	7 (6%)	4 (3%)	4 (3%)

The completer status and nominal reason for discontinuation for the three controlled studies is shown in Table 4.

In each of the studies there was a greater fraction of patients who were allocated to UT-15C who discontinued for various reasons. Between 6-7% more patients treated with UT-15C discontinued than those who were treated with placebo.

Statistical plan:

The oral treprostinil studies were analyzed by an analysis of covariance, adjusted for baseline walk distance and when appropriate PAH background therapy. The magnitude of the treatment effects was defined by the Hodges-Lehmann method to estimate the median difference between treatment groups for the change from baseline in 6MWD. Missing values were imputed by the algorithm in Table 1.

The results of the three placebo-controlled studies for the pivotal walk distance metric are shown below. Study # 301 and # 308 were not statistically significant. The number of discontinuations (see Table 6) for the UT-15C subjects the numbers with imputed values was much greater than those in the placebo group.

Results:

The results of the 6 MWD data from the three UT-15C oral studies and from the pooled subcutaneous studies are shown below. Study # 302 appears as the clear outlier,

Table 5: 6MWD placebo-controlled studies (meters)

	Study 301	Study # 302	Study # 308	P-01:04-P01:05
Other therapy?	PDE-5, ERA	No	PDE-5, ERA	No
Week 4	4 (-2, 12)	14 (4, 25)	3(-4, 10)	
Week 8	9 (0, 18)	20 (7, 34)	1 (-9, 11)	
Week 11 trough		17 (3, 33)		
Week 12	13 (3,23)	25.5 (10, 41) p< 0.001	6 (-5, 19)	10 NS (from label)
Week 16	11 (0,22) NS		10 (-2 22) NS	

Consequence of Imputation:

Please refer to the addendum Joint Clinical/Statistical review dated October 13, 2012. There were two aspects that were addressed by this amendment. The first is the large difference in the number of subjects who required imputed values as a consequence of dropouts during the study. The second difference is the difference in rank between the UT-15C group and placebo among those where a value was imputed.

Each subject who enrolled in the study is assigned a rank at the end of the study based on the walk-distance or the imputed values. The ranks ranged from best (1.0 to worst 0.0). There were 59 subjects who had no 12-week walk test in the UT-15C group versus 18 in the placebo group (note there was a 2:1 randomization scheme UT-15C: placebo). Imputing worst outcome values either for the UT-15C population alone or all patients regardless of therapy totally p=0.92 to p=0.21, respectively).

In considering the 12-week data, the imputed rank for the 59 subjects who were in the UT-15C group and had no 12-week data was 0.36. The corresponding imputed rank score for the 19 placebo subjects was 0.11. So there appears to be a benefit simply because the imputed values in the UT-15C group were better than those of the placebo group.

The statistician attempted another approach. He utilized a multiple imputation method to assign the missing data. For each subject who died the worst rank was imputed in this analysis (as for other analyses). The statistician assumed that those who did not walk would generally fall in the lower quartile if forced to exercise. For subjects with missing 6MWD test, a random value between 0 to 0.25 was assigned as well as some variance. The mean imputed value that was assigned was 0.125. The uncertainty in the assessment of rank is captured by the imputed variance. The imputed values with the sponsor’s analysis had a value of 0.45 for the UT-15C group and 0.16 for the placebo group. The result of the multiple imputation analysis yields p-value slightly > 0.05.

As concluded by the Joint Medical/statistical review:

“In summary, the robustness of the efficacy results depends heavily on how the missing data are treated in the statistical analysis; the p-value range from 0.0001 (from the sponsor’s analysis) to 0.92 (from analysis giving all treatment subjects with missing data the worst score). So, in my opinion the efficacy of treprostinil tablets has not been convincingly demonstrated, based on this study.”

Safety:

Some selective adverse events from the three studies are shown below. The three general classes of adverse events that appear to be more frequent in the UT-15C group than the placebo group reflect drug action and are vasodilatation, gastrointestinal symptoms and bone-muscle-joint pain. Some of these events are so much more common in the UT-15C group that blinding of the treatment may not be protected.

Table 6: Adverse events in the categories of vasodilatation, gastrointestinal and prostacyclin-related.

	Study # 301		Study # 302		Study # 308	
	UT-15C	Placebo	UT-15C	Placebo	UT-15C	Placebo
Vasodilatation:						
Headache	150 (86%)	65 (37%)	160 (69%)	36 (31%)	112 (71%)	61 (40%)
Flushing	85 (49%)	27 (15%)	50 (21%)	9 (8%)	55 (35%)	16 (10%)
Dizziness	30 (17%)	28 (16%)			30 (19%)	15 (10%)
Gastrointestinal						
Nausea	112 (64%)	60 (34%)	91 (39%)	25 (22%)	73 (46%)	34 (22%)
Diarrhea	106 (61%)	48 (27%)	86 (37%)	21 (18%)	87 (55%)	38 (25%)
Vomiting	76 (43%)	14 (8%)	57 (24%)	19 (16%)	33 (21%)	16 (10%)
Abdominal distention	11 (6%)	11 (6%)	11 (5%)	4 (3%)		
Decreased appetite			19 (8%)	5 (4%)		
Abdominal pain			31 (13%)	9 (8%)		
Prostacyclin-related						
Pain in jaw	74 (43%)	21 (12%)	59 (25%)	8 (7%)	39 (25%)	10 (7%)
Pain in extremity	54 (31%)	17 (10%)	44 (19%)	9 (8%)	27 (17%)	11 (7%)
Myalgia	24 (14%)	6 (3%)	24 (10%)	5 (4%)	18 (11%)	10 (7%)
Arthralgia	18 (10%)	4 (2%)	15 (6%)	4 (3%)	12 (8%)	9 (6%)
Back pain	13 (7%)	10 (6%)	14 (6%)	4 (3%)	12 (8%)	6 (4%)

Other treprostinil therapies:

There are currently two approved dosing forms of treprostinil. Treprostinil (Remodulin®) is available for parenteral use administered either as a subcutaneous or intravenous infusion. The intravenous route was recommended for those who do not tolerate the drug by the subcutaneous route usually because of subcutaneous pain. The intravenous route was approved based on its kinetic equivalence to the use of Remodulin® by the subcutaneous route. Treprostinil (Tyvaso®) is also approved as an inhaled formulation. The steady state dose for the inhaled formulation was 9 breaths administered QID.

Treprostinil when administered as a parenteral formulation did not meaningfully alter walk distance in the pivotal studies that were performed for the initial NDA submission (2001). Moreover the point estimate for walk distance was small and again largely dependent on the handling of early dropouts and discontinuations.

The sponsor specified an algorithm for imputing values in P01:04-P01:05 pooled studies. This algorithm is shown below (Table 2). This algorithm allowed imputation of values which were dependent on the investigator's assessment of the reason for discontinuation. There are several hazards for accepting this imputation strategy. Since there were many more subjects in the treatment group than in the placebo group, the imputation algorithm alters the assessment of that population more than the placebo population.

A higher dropout rate that required imputation of values, biases the result in favor of that group with a higher discontinuation /dropout rate. A person who discontinues early for adverse event or withdraws consent can never have a worst outcome attributed to the patient. Second, the process of discontinuing from a study is an integrative assessment of how the subject feels. If the subject is doing poorly on drug even a modest adverse event would be sufficient to discontinue study. So, hidden under the rationale for the reason for stopping treatment is a component of worsening of status.

Table 7

Table 54. Imputation rules for subjects without a week 12 walk (P01:04-05)

	Alternative 1		Alternative 2	
	Non-parametric	Parametric	Non-parametric	Parametric
Death within 12-weeks; excluding accidents or death unrelated to disease or study	Lowest standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Clinical decompensation within 12 weeks; excluding accidents or death unrelated to disease or study	Lowest standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Transplantation	Last standardized rank of zero	0 Meters	Lowest standardized rank of zero	Baseline plus worst observed change
Accidents or death unrelated to disease or study	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
AE (survivor, week 12)	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
Lost to Follow-up (survivor, Week 12)	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*
Consent withdrawn (survivor, week 12)	Last standardized rank carried forward	LOCF	Regression Approach*	Regression Approach*

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The point estimate of median walk distance change comparing the Remodulin® group from the original application and pivotal studies (pooled P01:04 and P01:05) is shown below.

Table 8: Effect size for 6MWD in the Remodulin® (subcutaneous infusion) studies.

	P01:04		P01:05		Pooled P01:04/P01:05	
	Vehicle	UT-15	Vehicle	UT-15	Vehicle	UT-15
Median	1	3	-2	16	0	10
25 th , 75 th percentile	-53, 31	-27, 37	-37, 35	-20, 50	-43, 32	-24, 47
p-value	0.06		0.06		0.009	

The estimate of the walk-distance in the pooled P01:04 and P01:05 studies, is at best 10 meters.

The reviewers performed several additional analyses based on the information supplied regarding the outcome of patients who discontinued and had information as to outcome for the duration of the clinical trial (100 days window from the randomization). This exercise was intended to assess the consequence of early discontinuation and imputation of values on the assessment of walk-distance. There were a total of 33 subjects who discontinued in the pooled treprostinil group and 15 in the pooled placebo group.

Three analyses were performed. Analysis #1 includes patients who died or were transplanted during the 100 day window of the study as worst outcomes this analysis adds 3 UT-15 and 1 vehicle patient who were classified as an adverse event and were re-characterized as worst outcome

Analysis # 1: This analysis includes 3 UT-15 patients and 1 vehicle patient who died or was transplanted during the 100 day treatment window.

Table 9: Deaths and transplantations during the 100 day observation period were included.

	P01:04	P01:05	Pooled
p-value	0.10	0.10	0.02

Analysis #2: This analysis also includes patients with death, transplantation or required the initiation of epoprostenol therapy during the 100 day treatment window as worst outcomes. This analysis attributes a worst outcome to 10 patients treated with UT-15 and 1 to vehicle.

Table 10: Deaths, transplantations and institution of epoprostenol during the 100 day observation period were included as worse outcomes.

	P01:04	P01:05	Pooled
p-value	0.23	0.22	0.08

Analysis # 3: This analysis includes those who died, received transplantation, were started on epoprostenol or had a down-hill course. These subjects were treated as worst outcomes. This analysis now captures an additional 4 UT-15 patients (total 14 UT-15 patients and 1 vehicle patient).

Table 11: Deaths, transplantations, institution of epoprostenol as well as those who had a down-hill course during the 100 day observation period were included as worse outcomes

	P01:04	P01:05	Pooled
p-value	0.27	0.22	0.11

The above analyses show that the use of subcutaneous UT-15 only affords a minimal effect on 6-MWD and that this walk distance is extremely biased by the attribution of cause for dropout.

The original application for use of Remodulin® as a subcutaneous infusion was not approved. The UT-15 regimen, however, did show a benefit when the ranks for walk-distance and Borg dyspnea scale were combined and re-normalized. Since this was not the primary endpoint or even an easily interpreted metric, the subcutaneous treprostinil was approved under a Subpart H approval. Final approval resulted from the ability of treprostinil to prevent deterioration in a group of patients transitioning off of epoprostenol.

Since there were no convincing efficacy effects of UT-15 in enhancing walk distance in PAH patients when it is administered as a subcutaneous infusion, no serum correlation correlates between efficacy and exposure.

In addition to the parenteral route, treprostinil was also approved as an inhalation (Tyavso®). The dose by inhalation was initiated at 3 breaths (18 µg). The number of inhalations was increased by 3 breaths every 2-3 weeks. Maximal dose was 9 breaths four times daily. Walk distance at peak and trough was increased after 12-weeks of therapy.

The difference in walk distance using the Hodges-Lehmann estimate of approximately 20 meters at peak.

The number of discontinuation comparing treated to placebo patients was modest. There were 13/115 (11%) of those who were treated with inhaled treprostinil who discontinued due to any reason compared to 10/110 (9%) in the placebo-treated patients. The 6MWD, for this route of administration was not substantially dependent on the imputation rules and therefore appears credible.

One can conclude that treprostinil, at some concentration at the active site (as judged by the inhaled effect), can improve 6MWD. Unfortunately, the specific concentrations via the inhaled route at the active site are not known. Conversely, the parenteral formulations of treprostinil were not probative in defining a useful concentration range to define efficacy.

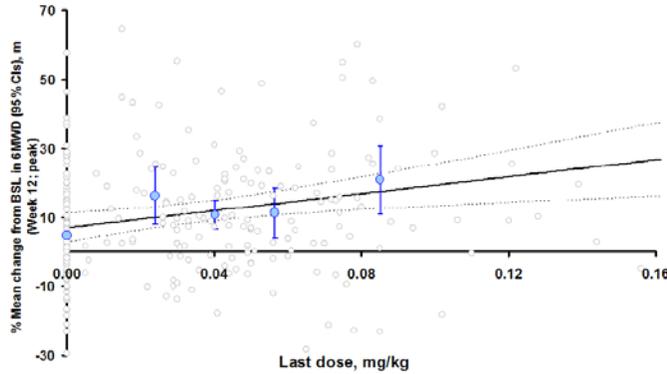
There are several additional conclusions which one may draw from the sum of the treprostinil experience.

- 1- Attribution of adverse events as a reason for discontinuation and, therefore, earning the rank of LOCF should be accepted only with caution. The true effect of drug is usually substantially less than those calculated by the imputed algorithm. The way to minimize bias is to follow these patients for meaningful deterioration for the length of the study.
- 2- If the correct dose is chosen, as with the inhaled treprostinil, the number of discontinuations can be minimized.

Model dependent data:

Is there a relationship between dose and effect for this drug? There were no dose-ranging studies for UT-15C. Dose-ranging modeling is derived from internal relationships between dose and in the clinical studies. The instructions for titration during the study, however, were to be guided by clinical response and tolerability. So, a subject who remained on a low dose could either remain on that dose because they demonstrated adequate benefit to that dose or because they demonstrated intolerance to any greater doses.

The relationship between last dose and 6- minute walk distance in study #302 is shown below. When the curve is anchored by the placebo effect there is a small shallow slope. Within the treatment quartiles, it is unclear if there is a consistent effect. The lowest quartile appears to have the same effect at the highest quartile. It is not obvious that the placebo group should be pooled with the UT-15C group since by the end of the study the discontinuation rate for the placebo group differed substantially from the UT-15C population. In summary, it is unclear how strong a dose response relationship can be gleaned from the internal data of study # 302. If one exists it is quite shallow with no evidence of saturation of effect. Higher doses (if recommended TID) might allow for a broader range of doses and if the modeled data is representative a greater effect.

Figure 1: Modeled data for study #302; 6MWD versus last dose.

Relationship between last stabilized dose (body weight normalized) and corresponding percent change from baseline in **peak 6-minute walk distance** at week 12 from Study TDE-PH-302 in completers [N = 246; active=160 (40 per bin), placebo=86]. A positive slope for the relationship was observed [Mean and 95% CIs: 1.23 (0.418 – 2.04) as percent change from baseline-per-0.01 mg/kg of treprostinil].

In summary: Only one study appears to show a benefit of treprostinil oral formulation in increasing 6MWD. The results of that study, however, are very much dependent on the imputation algorithm utilized. Two other studies utilizing the oral formulation were unsuccessful in demonstrating a benefit of the use of oral treprostinil. Subcutaneously administered treprostinil was also unsuccessful in demonstrating a benefit in walk distance.

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/s/

ABRAHAM M KARKOWSKY

03/05/2013

none



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 203496 Treprostinil extended-release tablets for pulmonary arterial hypertension.

Sponsor: United Therapeutics

Review date: 23 October 2012

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 203496

This memo conveys the Division's recommendation to issue a Complete Response letter for treprostinil extended-release tablets. (No brand name has been deemed acceptable.)

This application has been the subject of reviews of CMC (Bhamidipati, 28 August and 19 October 2012), biopharmaceutics (Khairuzzman, 30 August 2012), pharmacology/toxicology (Joseph, 3 October 2012), clinical pharmacology (Hariharan, 2 October 2012), and medical and statistical (Gordon and Lawrence, 3 and 10 October 2012). There is a comprehensive CDTL memo (Karkowsky, 19 October 2012) with which I am largely in agreement.

A fairly complete pharmacology/toxicology package was submitted, out of concern that the different kinetics and possibly different metabolism by the oral route might matter. Dose-dependent GI toxicity (nausea, vomiting, diarrhea, ulcers) was seen in dogs, not actually different from other routes. Carcinogenicity was addressed through a 26-week transgenic mouse study, results benign. Fetal skeletal malformations occur in rabbits at a low multiple of the human dose.

The new formulation is an osmotically-driven extended-release tablet, with which there are no CMC issues.

This formulation demonstrated only 17% bioavailability, but intra-subject variability was less than inter-subject variability under controlled conditions. However, food increased exposure 50%, mild hepatic impairment by 100% (8-fold at severe hepatic impairment), and CYP 2C8 inhibition by 100%. Twice-daily dosing results in a peak-trough ratio of 7 to 10; the clinical pharmacology team recommended approval with thrice daily dosing, a regimen never studied. They describe a shallow exposure-response relationship for 6MW, but I find that difficult to interpret given the titration design of the underlying studies.

Those studies were 302 (n=399) a 12-week study with 2:1 randomization on no PAH background therapy, and studies 301 (n=354) and 308 (n=313), both 16-week studies with 1:1 randomization, and on a background of endothelin receptor antagonist or PDE5 inhibitor. All 3 studies were double-blind, and all had 6-minute walk (6MW) as a primary end point and clinical worsening as a secondary end point. All compared one titration scheme to placebo; the starting dose had to be lowered to keep subjects from early withdrawal.

Analysis of 6MW (near peak) was by non-parametric ANCOVA, adjusted for baseline and background therapy. Median responses were compared by Lehman-Hodges. Subjects who died or discontinued for clinical worsening were assigned a worst rank. Those discontinuing with no post-baseline assessment were assigned the mean placebo

response. Those leaving for any other reason were assigned last rank carried forward (LRCF).

Imputation mattered greatly in the results. In study 301, 25% of subjects on study drug and 11% on placebo required imputation at 12 weeks. In studies 301 and 308 (combined), the numbers were 19% and 12%.

In study 302 (no background), treatment differences were nominally 14 m at 4 weeks, 20 m at 8 weeks, 17 m at trough on week 11, and 25 m on week 12, $p < 0.01$ at all time points. In this study, subjects with “other” reasons for missing 12-week data (requiring LRCF) were 11 on study drug vs. 2 on placebo, and the clinical-statistical review reasonably questions whether many of these were clinical worsening. They employ several alternative, post-hoc imputation schemes to illustrate how sensitive the findings are to how imputation is done.

Neither study 301 nor 308 (with background) was statistically significant at the 16-week assessment. An unplanned analysis of their combined results showed differences of 4 m at 4 weeks, 5 m at 8 weeks (neither $p < 0.05$), 10 m at 12 weeks, and 10 m at 16 weeks (the latter two time points were nominally statistically significant at $p < 0.01$).

Clinical worsening demonstrated no significant difference in any study.

Deaths were 4% on study drug and 4% on placebo in the controlled studies. Deaths were 7% per year in open-label and uncontrolled follow-up. While the results show no apparent signal, the uncertainties are large, considering the scarcely sustainable treatment effect.

Treprostinil was originally approved for subcutaneous administration, on the basis of a post-hoc effect on the combination of 6MW and dyspnea. Approval for intravenous administration followed, supported by pharmacokinetic data. Approval by the inhaled route was based on 6MW; in that setting, the modest effect (20 m) was accomplished with similar rates of withdrawal on study drug and placebo.

Thus, the actual treatment effect on 6MW is small or non-existent—by any of the routes. By the oral route, the effect is not discernible when treprostinil is used with other approved therapy, even taking the imputation-driven results at face value. The effect seen with no background was of similar size regardless of baseline walk, and so small as not to be sensible standalone treatment for anyone with PAH severe enough to impede walking. These results are regrettable in as much as the subcutaneous route is quite painful, the intravenous route conveys risk of sepsis, and the inhaled route is inconvenient.

The sponsor might reasonably attempt another study with a regimen giving less fluctuation in exposure across the inter-dosing interval, but showing an effect only absent other background therapy is of dubious value.

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/s/

NORMAN L STOCKBRIDGE
10/23/2012



MEMORANDUM
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 18, 2012

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of
Cardiovascular and Renal Products, HFD-110.

TO: Dr. Norman Stockbridge, M.D., Ph.D., Director, Division of
Cardiovascular and Renal Products, HFD-110.

SUBJECT Complete response recommendation for NDA 203496, Treprostinil
diolamine (no TRADENAME approved).

This memo recommends that a complete response be forwarded to the sponsor, that treprostinil diolamine (UT-15C) not be approved for the indication [REDACTED] (b) (4) as a BID dosing regimen. The sum of the results of the three pivotal studies is unconvincing. Only one study appears to demonstrate an effect on six-minute walk distance (6MWD) and the effect is substantially dependent on how missing values were imputed.

In addition, the sponsor's proposed dosing instructions is based on an ever-shifting change in study protocol dosing strategy with lower doses and smaller dose increments recommended by the sponsor as the population demonstrated intolerance to the ongoing dosing regimens. The drug appears to be poorly tolerated and it is unlikely to be used as initial therapy. The two on-top of studies were unsuccessful and it would be difficult to recommend that UT-15C be used as adjunctive therapy to other PAH drugs.

The FDA, based on pharmacokinetic considerations would recommend that a TID regimen be used and not the BID recommendation per sponsor. There is currently no experience with walk distance utilizing a TID regimen for UT-15C.

The two aspects, the large number of discontinuations requiring imputed 6MWD values and the lack of an appropriate dosing set of instructions are likely to be intimately related. Should an appropriate dose regimen been used in the clinical trials, the number of discontinuations and particularly the number of early discontinuations would have been reduced and the impact of imputation of missing data would have been minimized.

Brief development summary:

There were three placebo-controlled studies submitted to support a benefit of treprostinil diolamine (UT-15C). Two of these studies were on unsuccessful. These two studies (#301 and # 308) explored the benefit of UT-15C on top of approved therapies

either phosphodiesterase 5 (PDE-5) inhibitors, endothelin receptor antagonists (ERA) or both. The one nominally successful study (study #302) was a placebo-controlled study of UT-15C versus placebo in a pulmonary arterial hypertension (PAH) in the absence of approved background therapies. So, even if you decide to approve UT-15C, it becomes difficult to recommend the use of this drug with concurrent approved therapies. Pooling of the two unsuccessful studies was never pre-planned and moreover, because of the disproportionate numbers of dropouts in the treated group, the p-values are likely too optimistic.

There were a large number of discontinuations during the one successful study, with many discontinuations occurring early in therapy and prior to any assessment of the effect of drug on 6MWD. The outcome is, therefore, largely dependent on the imputed values for these subjects.

Based on the discussion contained in the joint clinical/statistical review and the amendment dated 10-10-12, any benefit the use of UT-15C to increase walk distance in patients with pulmonary arterial hypertension (PAH) population is small, and toxicities are not trivial. There were a disproportionate number of dropouts in the UT-15C group early on in treatment in the one study which suggested a benefit (study #302). The assessment of the drug-effect markedly depends on the handling of these dropouts. The imputation rules are shown in Table 1. Several sensitivity analyses were contained in the joint clinical/statistical review and amendment suggest that the walk distance is very sensitive to the nature of the imputation of the missing values.

Table 1: Missing data imputation algorithm study # 302

Lowest rank	For deaths, discontinuations due to clinical deterioration, transplantation or atrial septostomy or subject to ill to perform walk test
Mean rank	For subjects who withdrew prior to any 6MWT
LOCF	For subjects who prematurely withdrew.

The initial dose, dose increments and maximal tolerated doses changed frequently during the several studies and even within the pivotal efficacy study. The pharmacokinetics of UT-15C is better suited to a TID regimen as opposed to the BID regimen utilized in the clinical studies. An additional study in which the final dosing increments that was considered by the sponsor as tolerable but utilized these daily increments as a TID regimen (starting with 0.125 mg) would be important to establish the effect size of UT-15C while minimizing the impact of imputed values. The study should include a substantial population treated with approved therapies because the toxicities of UT-15C make it unlikely that UT-15C will be front-line therapy.

Other treprostinil therapies:

There are currently two approved dosing forms of treprostinil. Treprostinil (Remodulin®) is available for parenteral use administered either as a subcutaneous or intravenous infusion. The intravenous route was recommended for those who do not tolerate the drug by the subcutaneous route. Treprostinil (Tyvaso®) is also approved as an inhaled formulation. The steady state dose for the inhaled formulation was 9 breaths administered QID.

Treprostinil when administered as a parenteral formulation did not meaningfully alter walk distance in the pivotal studies that were performed for the initial NDA submission. The drug did show a benefit when the ranks for walk-distance and Borg dyspnea scale were combined and re-normalized. Since this was not the primary endpoint or even an easily interpreted metric the subcutaneous treprostinil was approved under a Subpart H approval. Final approval resulted from the ability of treprostinil to prevent deterioration in a group of patients transitioning off of epoprostenol. In essence, there was no evidence that treprostinil at the doses used in the subcutaneous development program had a positive effect on 6MWD.

When available data about the patients who discontinued was incorporated into the imputation assessment of the original NDA application, the p-value deteriorated from approximately 0.05 to approximately 0.15. This was not surprising since a subject who discontinues early adverse events could never sustain a worst rank for deterioration unless they were scrupulously followed for the planned duration of the study. Any analysis where there is a disproportionate dropout early in the study affords a bias to treprostinil treatment group.

In addition to the parenteral route, treprostinil was also approved as an inhalation (Tyavso®). The dose by inhalation was initiated at 3 breaths (18 µg). The number of inhalations was increased by 3 breaths every 2-3 weeks. Maximal dose was 9 breaths four times daily. Walk distance at peak and trough was increased after 12-weeks of therapy. The difference in walk distance using the Hodges-Lehmann estimate of approximately 20 meters at peak.

The number of discontinuation comparing treated to placebo patients was modest. There were 13/115 (11%) of those who were treated with inhaled treprostinil who discontinued due to any reason compared to 10/110 (9%) in the placebo-treated patients. The 6MWD, for this route of administration was not substantially dependent on the imputation rules and therefore appears credible.

One can conclude that treprostinil, at some concentration at the active site (as judged by the inhaled effect), can improve 6MWD. Unfortunately, the specific concentrations via the inhaled route at the active site are not known. Conversely, the parenteral formulations of treprostinil were not probative in defining a useful concentration range to define efficacy.

There are several conclusions which one may draw from the sum of the treprostinil experience.

- 1- Attribution of adverse events as a reason for discontinuation and, therefore, earning the rank of LOCF should be accepted only with caution. The true effect of drug is usually substantially less than those calculated by the imputed algorithm.
- 2- If the correct dose is chosen, as with the inhaled treprostinil, the number of discontinuations can be minimized.

The following reviews and memos were consulted in the construction of this document.

- ◆ Joint clinical/statistical review by John P. Lawrence Ph.D., and Maryann Gordon, M.D., dated 10/3/2012; addendum dated 10/10/2012.
- ◆ Pharmacology/toxicology NDA review and evaluation by Xavier Joseph D.V.M., dated 1/20/2012.
- ◆ Executive CAC meeting dated June 26, 2012.
- ◆ Clinical inspection summary by Sharon K. Gershon dated 10/3/2012.
- ◆ Clinical pharmacology review by Sudharshan Hariharan, Ph.D. dated 10/2/2012.
- ◆ Chemistry Review by Shastri Bhamidipati, Ph.D., dated 8/28/2012.
- ◆ Proprietary Name Review by Irene Z. Chan, PharmD., BCPS, Team Leader, Division of Medication Error Prevention and Analysis dated 9/4/2012, and Ray Ford RPH, safety Evaluator dated 5/17/2012.
- ◆ Biopharmaceutic review by AKM Khairuzzaman Ph.D., dated 8/28/2012.
- ◆ TQT review by Monica Fiszman, M.D. and Nitin Mehrota dated 6/11/2012.

Housekeeping issues:

As of now, there is no acceptable Tradename. Two Tradenames (b) (4) and (b) (4) were found unacceptable (b) (4)

The release characteristics of UT-15C indicate that the product should be labeled as an “Extended release” formulation.

Inspections:

Three clinical sites were recommended for inspection. Full inspection reports are not yet available. Based on the preliminary description of the results of the inspection, there did not appear to be concerns regarding the integrity of the data. The

Table 2: Specifics of study sites recommended for inspection

Name, Institution and Location	Site / # subjects	Final classification	Comments:
R. James E. White Mary Parkes Asthma Center Rochester, NY	Site #46 15 subjects	NAI	
Keyur Harshadray Parikh Care Institute of Medical Sciences Gujarat, India	Site #174 44 subjects	VAI	Not all female subjects received pregnancy tests. One subject was not on stable diuretics for the protocol stipulated 14 days. One subject had a discrepancy in the grading of dyspnea.
Zhicheng, Jing Shanghai Pulmonary Hospital Shanghai, China	Site #200 51 subjects.	Preliminary EIR	Dose escalation was not carried out per protocol. Instead dose escalation was carried out every 5-10 days on average.

Financial:

There are seven investigators with financial interests to declare. The sponsor asserts that these payments were for consulting and research.

Pediatric studies:

No pediatric protocols have yet been submitted. The sponsor requested a waiver from pediatric studies. Earlier formulations of treprostinil were granted orphan status and thus were waived from performing pediatric studies.

TQT and long-term controlled studies:

A TQT study was performed with the inhaled formulation of treprostinil. The results suggested a small increase in QT interval with dose. The increase in QT intervals in the inhaled study may be related partially to the rapid changes in heart rates. No TQT study was performed for the oral treprostinil formulation.

There were no long-term controlled outcome studies for UT-15C.

Pharmacology:

The studies submitted for this application bridge the current knowledge of the pharmacology of the sodium salt of treprostinil (used for parenteral therapy) to that of the oral formulation UT-15C. In addition to those bridging information studies, carcinogenicity and fertility/teratogenicity studies were also performed.

The effect of UT-15C and treprostinil sodium in a rat blood pressure model when administered intravenously was similar.

The bioavailability of treprostinil at a dose of 1 mg/kg oral versus a similar intravenous dose was approximately 10%. There were 5 new metabolites which were detected after oral administration of oral UT-15C that were not observed during subcutaneous infusion. In the rat blood pressure model, these metabolites had minimal biological effect. No full receptor screen for each of these metabolites was submitted.

Tissue distribution studies with ^{14}C labeled treprostinil and ^3H labeled diolamine at an oral dose of approximately 1.5 mg/kg showed a broad distribution of drug and counterion. Tissues with the highest [^{14}C]-radioactivity (treprostinil) concentrations, excluding gastrointestinal contents, were small intestine, liver, large intestine, cecum, and stomach. The highest [^3H]-radioactivity (diethanolamine) concentrations in tissues, excluding gastrointestinal contents, were in spleen, adrenal glands, thyroid, kidneys, and liver. [^3H]-Diethanolamine-derived radioactivity was quantifiable in all tissues analyzed at all time points.

With respect to 13-week toxicity studies, the gastrointestinal tract appears to be the most vulnerable target. Lesions included moderate to chronic inflammation with ulceration and lymphatic dilation. One female at the highest dose was euthanized on day 16 due to an intussusception.

There was no evidence of polychromasia rat micronucleus assay in male or female rats. In a 26-week carcinogenicity study with UT-15C administered to hemizygous Tg.rasH2 mouse there was no increase in tumorigenicity.

In a rabbit embryo-fetal development study, the incidence of skeletal malformation was increased in the group taking treprostinil. The NOAEL dose was 0.5 mg/kg/day approximately 5 times the exposure of a dose of 3.4 mg BID in humans.

Lastly, the potential gastric irritability of UT-15C as a GITS formulation was assessed in an *ex vivo* rat mucosa preparations. The amount of released LDH and histologic changes were the metrics defining tissue damage. The degree of both LDH release and histologic destruction with UT-15C was substantially less than for sustained release KCl, which was used as the positive control. Unfortunately, the dwell time of the UT-15C formulation was limited to 3 hours. Under optimal dissolution conditions the amount of discharged UT-15C during a three hour infusion is approximately 25% of the contained drug (based on the dissolution specifications). The gut mucosa irritability test, therefore an inadequate test to determine whether direct release of UT-15C is irritation to gut mucosa.

Chemistry:

From the perspective of CMC, the application is approvable. Still pending is the final recommendation for the inspection of the drug product site in North Carolina. The chemists recommend a 36-month shelf life for the 0.125, (b)(4) and 1 mg tablet strengths and a 24 month shelf life for the 0.25 and 2.5 mg strengths.

Biopharmaceutics:

Based on an *in-vitro* study the integrity of the permeable barrier is altered in the presence of alcohol. The potential for dose dumping with loss of tablet integrity needs to be assessed in an *in vivo* study, when the GITS formulation is administered with alcohol.

Clinical/Statistical:

There were three placebo-controlled studies which were submitted to support this application. In addition, there was a long-term extension study which defines the long-term tolerability among those who successfully completed the placebo-controlled studies. Of the three placebo-controlled studies, only study #302 which was a monotherapy study was nominally significant. The other two studies # 301 and #308 which were for the use of UT-15C on top of either an ERA, PDE-5 inhibitor or both.

Patients eligible for enrollment in the three studies is similar to previous study for PAH drugs. Patients must have evidence for PAH and no evidence of left sided disease. They must be able to perform a walk test with 6MWD to be between 100 and 450 meters.

Study design:

Study #301 and #308 randomized subjects in a 1:1 ratio to UT-15C: placebo. Study #302 randomized subjects in a 2:1 ratio to UT-15C: placebo. Study #302 was a 12-week study. Studies #301 and #308 were 16-week study.

Dose:

All three studies were titration to either tolerance or to adequate effect. Major differences in the three studies were doses and titration algorithms and the available dose formulation for the study. In general, subjects were started on a low dose of UT-15C with upward titration at 3 day intervals based on symptoms of PAH as well as tolerability. All doses were taken with food. The table below defines the evolution of the dosing regimens used in each of the studies.

Table 3 Dosing changes during and between placebo-controlled studies.

Study #	Initial formulations available	Amendments altering dosing (all doses were administered BID)	Dosing increments initial	Dosing increments at final
#301	1, 5 mg	0.5 mg and 0.25 mg amendments 3 and 4, respectively	Initial dose was 1 mg. Amendment 4 lowered starting dose to 0.5 mg	Dose was escalated every 3 days.
#302	1, 5 mg	0.5 mg and 0.25 mg amendments 3 and 4, respectively. Amendment 6 introduced 0.125 mg dose,	Initial dose was 1 mg. Amendment 4 lowered starting dose to 0.5 mg ?? further lowered to 0.25 mg	Dose escalation was 1 mg every 5 days but changed to 0.5 mg every 3 days. Amended to 0.25 mg every 3 days
#308	0.25, 0.5 and 1 mg. Aside from sites in China a 0.125 mg dose became available.	Initial dose was 0.25 mg. Initial increments was 0.25 mg prior to week 4. After week 4 the dose increments could be either 0.25 or 0.5 mg increments. A 0.125 mg dose was allowed if the 0.25 mg dose increase was not tolerated	Initial dose was 0.25 mg. Initial increments was 0.25 mg prior to week 4. After week 4 the dose increments could be either 0.25 or 0.5 mg increments. A 0.125 mg dose was allowed if the 0.25 mg dose increase was not tolerated	

The demographics of those enrolled are shown in Table 4.

Table 4 Demographics of study #301, #302 and #308

Parameter	Study #301		Study # 302		Study # 308	
	UT-15C	placebo	UT-15C	placebo	UT-15C	placebo
N	174	176	233	116	157	153
Age	51.1	49.5	41	43	52	50
Gender (% female)	85%	80%	74%	78%	76%	80%
Race: %						
Caucasian	65%	68%	41%	41%	67%	63%
African/American	28%	24%	4%	<1%	7%	65
Asian	3%	6%	47%	48%	26%	29%
Native American	2%	2%	0	0	2%	3%
Other					<1%)	0
Etiology						
Idiopathic/familial	113 (65%)	119 (68%)	171 (72%)	88 (76%)	104 (66%)	99 (65%)
CVD	49 (28%)	43 (24%)	48 (19%)	22 (19%)	48 (31%)	49 (32%)
Repaired CHD	11 (6%)	11 (6%)	12 (6%)	5 (4%)	3 (2%)	1 (<1%)
HIV	1 (<1%)	3 (2%)	2 (1%)	1 (<1%)	2 (1%)	4 (3%)
Other			< 1%	0		
Background therapy						
ERA	55 (32%)	51 (29%)			25 (16%)	28 (18%)
PDE5-I	45 (26%)	43 (24%)	None	None	67 (43%)	65 (42%)
Both	74 (43%)	82 (47%)			65 (41%)	60 (39%)
Functional class II/III	41 (24%)/127 (76%)	31/139				
Functional class I-II			90 (39%)	43 (37%)	43 (27%)	37 (24%)
III-IV			143 (61%)	73 (63%)	113 (72%)	115 (75%)

The most notable differences between the three studies were the large fraction of Asians enrolled into study # 302. There was a 2:1 randomization in study #302. Studies #301 and #308 include usage of concomitant therapies. More than half the patients had functional class III or worse.

The completer status and nominal reason for discontinuation for the three controlled studies is shown in Table 5 .

Table 5 Completion status studies # 301, # 302 and # 308

	Study #301		Study #302		Study # 308	
	UT-15C	Placebo	UT-15C	Placebo	UT-15C	Placebo
N=	174	176	233	116	157	153
Completed study	153 (88%)	167 (95%)	182 (78%)	98 (84%)	132 (84%)	138 (90%)
D/C prematurely	21 (12%)	9 (5%)	51 (22%)	18 (16%)	25 (16%)	15 (10%)
Consent Withdrawn	13 (7%)	3 (2%)	3 (1%)		1 (<1%)	2 (1%)
Death	3 (2%)	2 (1%)	10 (4%)	6 (5%)	2 (1%)	3 (2%)
Lost to follow up	2 (1%)	1 (<1%)	4 (2%)		0	1 (<1%)
Other	2 (1%)	3 (2%)	4 (2%)	2 (2%)		
Protocol Violation	1 (<1%)	0				
Adverse event			23 (10%)	3 (3%)	18 (11%)	5 (3%)
Clinical deterioration			7 (3%)	7 (6%)	4 (3%)	4 (3%)

In each of the studies there was a greater fraction of patients who were allocated to UT-15C who discontinued for various reasons. Between 6-7% more patients treated with UT-15C discontinued than those who were treated with placebo.

Statistical plan:

The studies were analyzed by an analysis of covariance, adjusted for baseline walk distance and when appropriate PAH background therapy. The magnitude of the treatment effects was defined by the Hodges-Lehmann method to estimate the median difference between treatment groups for the change from baseline in 6MWD. Missing values were imputed by the algorithm in Table 1.

The results of the three placebo-controlled studies for the pivotal walk distance metric are shown below. Study # 301 and # 308 were not statistically significant. The number of discontinuations (see Table) for the UT-15C subjects the numbers with imputed values was much greater than those in the placebo group.

Table 6 6MWD placebo-controlled studies

	Study 301	Study # 302	Study # 308
Week 4	4 (-2, 12)	14 (4, 25)	3(-4, 10)
Week 8	9 (0, 18)	20 (7, 34)	1 (-9, 11)
Week 11 trough		17 (3, 33)	
Week 12	13 (3,23)	25.5 (10, 41) p< 0.001	6 (-5, 19)
Week 16	11 (0,22) NS		10 (-2 22) NS

Consequence of Imputation:

Please refer to the addendum Joint Clinical/Statistical review. There were two aspects that were addressed by this amendment. The first is the large difference in the number of subjects who required imputed values as a consequence of dropouts during the study. The second difference is the difference in rank between the UT-15C group and placebo among those where a value was imputed.

Each subject who enrolled in the study is assigned a rank at the end of the study based on the walk-distance or the imputed values. The ranks ranged from best (1.0 to worst 0.0). There were 59 subjects who had no 12-week walk test in the UT-15C group versus 18 in the placebo group (note there was a 2:1 randomization scheme UT-15C: placebo). Imputing worst outcome values either for the UT-15C population alone or all patients regardless of therapy totally p=0.92 to p=0.21, respectively).

In considering the 12 –week data, the imputed rank for the 59 subjects who were in the UT-15C group and had no 12-week data was 0.36. The corresponding imputed rank score for the 19 placebo subjects was 0.11. So there appears to be a benefit simply because the imputed values in the UT-15C group were better than those of the placebo group.

The statistician attempted another approach. He utilized a multiple imputation method to assign the missing data. For each subject who died the worst rank was imputed in this analysis (as for other analyses). The statistician assumed that those who did not walk would generally fall in the lower quartile if forced to exercise. For subjects with missing 6MWD test, a random value between 0 to 0.25 was assigned as well as some variance. The mean imputed value that was assigned was 0.125. The uncertainty in the assessment of rank is captured by the imputed variance. The imputed values with the sponsor's analysis had a value of 0.45 for the UT-15C group and 0.16 for the placebo group. The result of the multiple imputation analysis yields p-value slightly > 0.05.

As concluded by the Joint Medical/statistical review:

“In summary, the robustness of the efficacy results depends heavily on how the missing data are treated in the statistical analysis; the p-value range from 0.0001 (from the sponsor’s analysis) to 0.92 (from analysis giving all treatment subjects with missing data the worst score). So, in my opinion the efficacy of treprostinil tablets has not been convincingly demonstrated, based on this study.”

Safety:

Some selective adverse events from the three studies are shown below. The three general classes of adverse events that appear to be more frequent in the UT-15C group than the placebo group reflect drug action and are vasodilatation, gastrointestinal symptoms and bone-muscle-joint pain. Some of these events are so much more common in the UT-15C group that blinding of the treatment may not be protected.

Table 7 Adverse events in the categories of vasodilatation, gastrointestinal and prostacyclin-related.

	Study # 301		Study # 302		Study # 308	
	UT-15C	Placebo	UT-15C	Placebo	UT-15C	Placebo
Vasodilatation:						
Headache	150 (86%)	65 (37%)	160 (69%)	36 (31%)	112 (71%)	61 (40%)
Flushing	85 (49%)	27 (15%)	50 (21%)	9 (8%)	55 (35%)	16 (10%)
Dizziness	30 (17%)	28 (16%)			30 (19%)	15 (10%)
Gastrointestinal						
Nausea	112 (64%)	60 (34%)	91 (39%)	25 (22%)	73 (46%)	34 (22%)
Diarrhea	106 (61%)	48 (27%)	86 (37%)	21 (18%)	87 (55%)	38 (25%)
Vomiting	76 (43%)	14 (8%)	57 (24%)	19 (16%)	33 (21%)	16 (10%)
Abdominal distention	11 (6%)	11 (6%)	11 (5%)	4 (3%)		
Decreased appetite			19 (8%)	5 (4%)		
Abdominal pain			31 (13%)	9 (8%)		
Prostacyclin-related						
Pain in jaw	74 (43%)	21 (12%)	59 (25%)	8 (7%)	39 (25%)	10 (7%)
Pain in extremity	54 (31%)	17 (10%)	44 (19%)	9 (8%)	27 (17%)	11 (7%)
Myalgia	24 (14%)	6 (3%)	24 (10%)	5 (4%)	18 (11%)	10 (7%)
Arthralgia	18 (10%)	4 (2%)	15 (6%)	4 (3%)	12 (8%)	9 (6%)
Back pain	13 (7%)	10 (6%)	14 (6%)	4 (3%)	12 (8%)	6 (4%)

Long-term extension:

The study was a long-term extension study, enrolling mostly those treated with either UT-15C or placebo from studies #301, #302 and #308. Placebo patients from the above studies were also eligible for enrollment. Other patients from UT-15C development programs as well as de novo patients could enter this open label study. Entry in the study was directly from the double-blind assessments. After the pivotal 6WMD was completed, the blind was broken on the same visit and those treated with UT-15C were maintained on the same dose of UT-15C as was employed during the double-blind study. Placebo patients were titrated as per protocol to dose.

Those enrolled into this open-label extension were those who completed the double blind portion of the study and excluded those who permanently discontinued

Based on the pharmacokinetic profile, the most appropriate dosing interval should be TID not BID as utilized during the clinical trials.

Systemic exposure in hepatic impaired subjects increases from mild to moderate to severe in a ratio of 2:5:8 fold. No change in concentration as a function of renal impairment was noted. With respect to dosing recommendation in patients with hepatic impairment, the available dose increments (0.125, 0.25, ^{(b) (4)} 1.0 and 2.5) make it difficult to parallel the tested dosing regimens in normals for which dropouts were frequent.

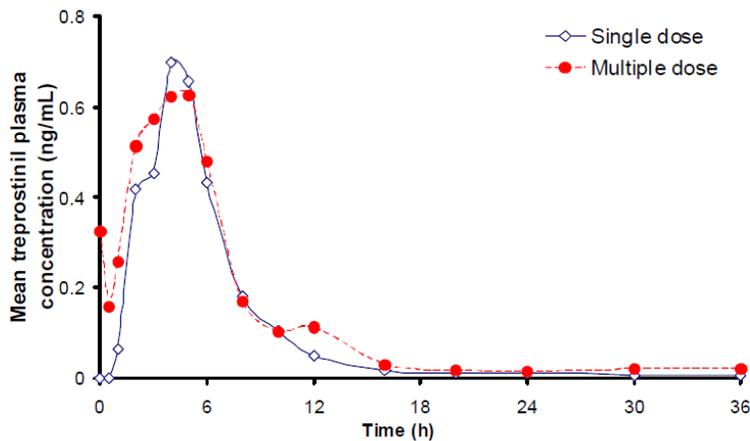
Important pharmacokinetic metrics following 1 mg oral administration of treprostinil on day 1 (single dose) and day 13 (twice-daily repeat dose)

Table 8 Pharmacokinetic parameters for single and multiple dosing of UT-15C

Parameter	Mean (%CV)	
	Single dose (N=9) 1 mg, Day 1	Multiple dose (N=9) 1 mg BID, Day 13
C_{max} (ng/mL)	0.99 (61)	0.87 (40)
T_{max} (h) [†]	4.01	3.20
AUC_{0-t} (ng.h/mL)	3.79 (64)	4.07 (38)

[†] Median

Figure 2: Mean concentration-time course of treprostinil following 1 mg oral administration on day 1 (single dose) and day 13 (twice-daily repeat dose).

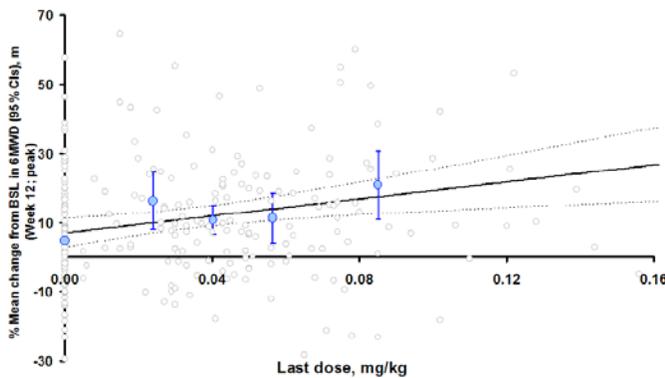


Model dependent data

Is there a relationship between dose and effect for this drug? There were no dose-ranging studies for UT-15C. Dose-ranging data are derived from internal relationships between dose and in the clinical studies. The instructions for titration during the study, however, were to be guided by clinical response and tolerability. So, a subject who remained on a low dose could either remain on that dose because they demonstrated adequate benefit to that dose or because they demonstrated intolerance to any greater doses.

The relationship between last dose and 6- minute walk distance in study #302 is shown below. When the curve is anchored by the placebo effect there is a small shallow slope. Within the treatment quartiles, it is unclear if there is a consistent effect. The lowest quartile appears to have the same effect at the highest quartile. It is not obvious that the placebo group should be pooled with the UT-15C group since by the end of the study the discontinuation rate for the placebo group differed substantially from the UT-15C population. In summary, it is unclear how strong a dose response relationship can be gleaned from the internal data of study # 302. if one exists it is quite shallow with no evidence of saturation of effect. Higher doses (if recommended TID) might allow for a broader range of doses and if the modeled data is representative a greater effect.

Figure 3: Modeled data for study #302; 6MWD versus last dose.



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Relationship between last stabilized dose (body weight normalized) and corresponding percent change from baseline in **peak 6-minute walk distance** at week 12 from Study TDE-PH-302 in completers [N = 246; active=160 (40 per bin), placebo=86]. A positive slope for the relationship was observed [Mean and 95% CIs: 1.23 (0.418 – 2.04) as percent change from baseline-per-0.01 mg/kg of treprostinil].

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/s/

ABRAHAM M KARKOWSKY
10/18/2012

Joint Clinical/Statistical Review

Application Type NDA
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Priority or Standard S

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Reviewer Name(s)
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Established Name Trepstinil
(Proposed) Trade Name 
Therapeutic Class analog of prostacyclin (PGI2)
Applicant United Therapeutics Corp.

Formulation(s) Sustained release tablets
Dosing Regimen Twice daily
Indication(s) The treatment of PAH
Intended Population(s) WHO Group 1

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Appendix 1 Forms 3455

Appendix 2 Study review TDE-PH-301

Appendix 3 Study review TDE-PH-302

Appendix 4 Study review TDE-PH-304

Appendix 5 Study review TDE-PH-308

Appendix 6 Study review TDE-DU-201

Appendix 7 List of phase I studies, PK studies, studies in indications other than PAH
(showing serious safety)

Appendix 8 List of ongoing studies not included in NDA

Appendix 9 Study review substudy 305

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommendation of the reviewers is that this NDA not be approved for marketing for the following reasons:

- 1) There was no convincing demonstration of drug effect. The results of the one study (TDE-PH-302) that showed a statistically significant treatment effect on exercise are not reliable.

The development program for treprostini tablets (UT-15C) includes one placebo controlled, monotherapy study that initially showed a significant improvement in exercise capacity in the one UT-15C dose group compared to placebo. There were mean treatment effects at weeks 4, 8, 11, and 12 that ranged from 14 m (week 4) to 25.5 m (week 12).

However, when I reviewed the CRFs for a large number of subjects who dropped from the trial, particularly in the UT-15C group, I disagreed with the sponsors' reasons for dropping out. When all drop outs were reassigned, the corrected the p-value became insignificant (please see complete review of the study in the appendix).

In addition, the secondary endpoints (BORG scale, clinical worsening, WHO functional class, symptoms of PAH) evaluated in this study showed no convincing effect of UT15-C.

- 2) The results of the two other efficacy studies (TDE-PH-301 and -308) comparing UT-15C to placebo on top of background PAH therapy did not show a significant treatment effect.

This is a troubling finding because, if approved, UT-15C will be used as add-on therapy rather than single therapy.

- 3) There is insufficient dosing information.

The sponsor made no attempt to determine if there is a dose response for UT-15C and there was difficulty in determining the initial dose of this drug (see review of TDE-PH-302).

- 4) The drug is difficult for patients to tolerate.

The initial starting dose of UT-15C was changed numerous times because of lack of tolerability (nausea, vomiting, headache). Other common adverse events include flushing, pain in extremity, jaw pain, myalgia.

One subject (TDE-PH-301/131102) suffered a Mallory-Weiss tear following an episode of vomiting and hematemesis requiring hospitalization five hours after receiving UT-15C 1 mg.

Another subject (TDE-PH-302/025201) died after an episode of nausea, vomiting and hypotension forty minutes after dosing with UT-15C. Death report stated that submitted information indicating that death was due to a profound vasovagal syncope causing hypotension (acute circulatory failure), leading to loss of consciousness, aspiration of stomach content and cardiac arrest in a patient who had moderately severe pulmonary arterial hypertension.

5) There is no long term controlled safety data.

1.2 Risk Benefit Assessment

The benefit seen with this agent is small compared to the adverse events.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

Treprostinil, [[(1R,2R,3aS,9aS) 2,3,3a,4,9,9a hexahydro 2 hydroxy 1 [(3S) 3 hydroxyoctyl] 1H benz [f]inden 5 yl]oxy]acetic acid, is a chemically stable tricyclic analog of prostacyclin (PGI₂).

Associated INDs: #71537 (pulmonary arterial hypertension), (b) (4)

2.1 Product Information

The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, inhibition of platelet aggregation, and inhibition of vascular smooth muscle cell proliferation.

In vitro, treprostinil induced concentration-dependent relaxation of rabbit isolated precontracted mesenteric arteries, and inhibition of adenosine diphosphate (ADP) induced platelet aggregation in human and rat platelet rich plasma. In addition, treprostinil binds to prostacyclin receptors resulting in increased intracellular cAMP. In animals, the vasodilatory effects of treprostinil reduce right and left ventricular afterload, also increasing cardiac output and stroke volume.

2.2 Tables of Currently Available Treatments for Proposed Indications

Drugs approved for PAH:

bosentan (Tracleer)
ambrisentan (Letairis)

sildenafil (Revatio)
tadalafil (Adcirca)
trepstinil injection (Remodulin)
trepstinil inhalation (Tyvaso)
iloprost (Ventavis)
epoprostenol (Flolan)

2.3 Availability of Proposed Active Ingredient in the United States

Information pending

2.4 Important Safety Issues with Consideration to Related Drugs

REMODULIN (trepstinil) Injection

1) Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

TYVASO (trepstinil) inhalation solution

- 1) In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension.
- 2) Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants.
- 3) Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.
- 4) Hepatic or renal insufficiency may increase exposure and decrease tolerability.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

During the Pre-NDA meeting on 11-16-2011 the sponsor asked “Does the Agency agree that the results of the single pivotal clinical trial TDE-PH-302 (FREEDOM-M) support the filing and review of an NDA for trepstinil diethanolamine (UT-15C) sustained release tablets for the proposed indication/labeling included in this package?”

FDA Response:

While one study usually suffices to support a new route of administration, please consider the following issues:

ϕ **We note that the original application for subcutaneous trepstinil did not strongly demonstrate a benefit on walk distance compared to placebo. As such, other forms of this medication do not have a support study from other routes of administration of the drug. With respect to the inhaled form of trepstinil we do not have a way to assess the relationship between the concentrations at the active site compared with those as administered orally.**

ϕ **The application appears thin on information we usually require. We cannot ascertain whether the effects of the administration of drug persist during the entire dosing interval. In addition, we cannot ascertain whether you know the relationship between dose and effect. Further, we do not know what limits dose, nor can we provide adequate instructions for use with the oral formulation, in contrast to the parenterally administered formulation**

where doses may be increased by several log units, for a patient whose condition worsens. These pieces of information would usually be required in the labeling.

–An exposure-response relationship has not been validated for treprostini. We recommend that you collect exposure-response data for 6MWD, pulmonary hemodynamics (e.g., mPAP, PVRI) and other measures of efficacy. We recommend you perform similar analyses across the different treprostini formulations (i.e., Remodulin and Tyvaso).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Trepstinil diethanolamine (approved name to be determined) Sustained Release Tablets:

United Therapeutics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

3.2 Compliance with Good Clinical Practices

Data Monitoring Committee (DMC)

A DMC was established for the efficacy study TDE-PH-302 and was composed of three independent members: two physicians knowledgeable in the treatment of pulmonary arterial hypertension and one statistician. Throughout the course of the study the DMC was to meet on a regular basis to monitor the safety of the study. Frequency of meetings was to depend on the rate of enrollment and rate of occurrence of serious adverse events.

I did not review any meeting minutes from the DMC.

Regulatory Requirements for TDE-PH-302

The study was to be conducted in accordance with ICH and GCP guidelines and all applicable national regulations. The sponsor was to obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study an annual safety report was to be compiled by the sponsor for submission to those regulatory authorities and IRBs/ECs that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB/EC were to be fulfilled during the conduct of the study.

Informed Consent Requirements

Before a subject is enrolled in the study, the Investigator or his/her designees had to explain the purpose and nature of the study, including potential benefits and risks and all study procedures to the subject. The subject had to sign and date an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to the conduct of any study-related activities.

A copy of the signed consent form was to be given to the subject and the original was to be retained in the study site's records.

3.3 Financial Disclosures

FORM FDA 3455: See appendix 1 for the list of the seven investigators with financial interests to disclose for the major efficacy studies TDE-PH-301, TDE-PH-302, and TDE-PH-308. The remaining investigators are listed in FORM FDA 3454.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See individual review

4.2 Clinical Microbiology

NA

4.3 Preclinical Pharmacology/Toxicology

See individual review

4.4 Clinical Pharmacology

See individual review

5 Sources of Clinical Data

Materials used for the clinical review of this NDA include the original submission (12-24-2011) and the safety update (4-26-2012).

5.1 Tables of Studies/Clinical Trials

The table below shows the completed trials. Data from these trials are part of the NDA.

Table 1-1 Overview of Completed Studies with UT-15C

Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
TDE-PH-101	Open-label, dose escalation, pharmacokinetic and safety study with UT-15C oral solution	24	0.05, 0.125, 0.25, or 0.5 mg	Every 2 hours x 4 doses
TDE-PH-102	Open-label, two period cross-over, pharmacokinetic and safety study with single doses of UT-15C administered as SR tablets and capsules in the fasted and fed states (8-hour formulations)	28	1 mg	Two separate doses separated by a washout period
TDE-PH-103	Open-label, two period, cross-over, pharmacokinetic and safety study with single doses of UT-15C SR administered as three tablet prototypes (12-hour formulations) in the fasted and fed states	30	1 mg	Three separate doses separated by washout periods
TDE-PH-104	Open-label, randomized, double blind, placebo controlled, parallel group, pharmacokinetic and safety study with UT-15C SR administered over 13 days in escalating doses	36	1 mg BID – 3 mg BID	13 days
TDE-PH-105	Open-label, randomized, three period, three sequence, cross-over study to evaluate the effect of bosentan on steady state UT-15C SR pharmacokinetics	24	1 mg	4.5 days of dosing with and without bosentan
TDE-PH-106	Open-label, randomized, three period, three sequence, cross-over study to evaluate the effect of sildenafil on steady state UT-15C SR pharmacokinetics	18	1 mg	4.5 days of dosing with and without sildenafil
TDE-PH-107	Open-label, mass balance, metabolite profiling and safety study of [¹⁴ C],[³ H]UT-15C (treprostinil diethanolamine)	8	0.5 mg	One dose
TDE-PH-108	Open-label, cross-over study to evaluate the bioavailability of a 1 mg dose of UT-15C SR administered as a single 1 mg tablet or two 0.5 mg tablets	20	1 mg	Two separate doses as 2, 0.5 mg tablets or 1, 1 mg
TDE-PH-109	Open-label, randomized, single sequence, cross-over study to evaluate the effect of repeated rifampin dosing on a single dose of UT-15C SR	20	1 mg	Two separate doses separated by a washout

Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
TDE-PH-110	Open-label, randomized, two-period, two-sequence, cross-over study to evaluate the effect of repeated gemfibrozil or fluconazole dosing on the pharmacokinetics of a single dose of UT-15C SR.	40	1 mg	Two cohorts each receiving two separate doses separated by a washout
TDE-PH-111	Open-label, cross-over study to evaluate the bioavailability of a 1 mg dose of UT-15C SR administered as a single 1 mg tablet or four 0.25 mg tablets	24	1 mg	Two separate doses as four 0.25 mg tablets or one 1 mg, separated by a washout
TDE-PH-112	Open-label, single-dose, pharmacokinetic and safety study in three cohorts of subjects with various degrees of hepatic impairment and one cohort of healthy volunteers	30	1 mg	One dose in four cohorts
TDE-PH-113	Open-label, two-sequence, cross-over study to evaluate the bioavailability of a 1 mg dose of UT-15C as compared to a 2.5 mg dose of UT-15C SR	28	1 mg and 2.5 mg	Two separate doses separated by a washout
TDE-PH-114	Open-label, two-sequence, cross-over study to evaluate the absolute bioavailability of a 1 mg dose of UT-15C SR as compared to an IV infusion of treprostinal sodium	24	1 mg and 0.2 mg Remodulin	Two separate doses separated by a washout
TDE-PH-115	Open-label, randomized, single-dose, four-period, cross-over pharmacokinetic and safety study evaluating the effect of different meal compositions on treprostinal pharmacokinetics	32	1 mg	Four separate doses separated by washouts
TDE-PH-116	Open-label, single sequence, cross-over study to evaluate the effect of repeated esomeprazole dosing on the pharmacokinetics of a single dose of UT-15C SR	30	1 mg	Two separate doses separated by a washout
TDE-PH-120	Open label, single-dose, pharmacokinetic, safety and tolerability study in healthy volunteers and patients with ESRD (Two-period, two-way cross-over for those subjects with ESRD)	16	1 mg	ESRD – two separate doses separated by a washout; healthy volunteers – one dose

Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
TDE-PH-121	Open-label, two sequence, cross-over study to evaluate the comparative bioavailability of a 1 mg dose of UT-15C SR manufactured by two independent facilities	64	1 mg	Two separate doses separated by a washout
TDE-PH-122	Open-label study to evaluate the comparative pharmacokinetics of a 0.5, 1 and 2.5 mg dose of UT-15C SR	36	0.5, 1, and 2.5 mg	Three separate doses separated by washouts
TDE-PH-123	Open-label, two-sequence, cross-over study to evaluate the comparative bioavailability of a 1 mg dose of UT-15C administered as a single UT-15C SR tablet or as a UT-15C oral solution	24	1 mg and 0.25 mg q2 hrs x 4 doses	Two doses separated by a washout
TDE-DU-101 (b) (4)	Open-label, two-part, PK study in two cohorts of patients with systemic sclerosis.	28	1-4 mg BID	Up to 8 weeks
TDE-DU-201 (b) (4)	Randomized, multi-center, placebo-controlled study in subjects with digital ulcers	148	0.25 mg BID starting dose with dose increasing over time	20 weeks
TDE-PH-201	Open-label, multi-center, four-cohort study in subjects with PAH	8	1 or 2 mg single dose	1 day
TDE-PH-301	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	354	0.25-1 mg BID starting dose with dose increasing over time	16 weeks
TDE-PH-302	Randomized, multi-center, placebo-controlled study in subjects with PAH on NOT receiving approved background therapy	349	0.25-1 mg BID starting dose with dose increasing over time	12 weeks
TDE-PH-305	Hemodynamic substudy	60	0.25-1 mg BID starting dose with dose increasing over time	12 or 16 weeks (substudy of TDE-PH-301 or 302)
TDE-PH-306	Open-label pharmacokinetic, study	74	0.25-1 mg BID starting dose with dose increasing over time	1 day (substudy of TDE-PH-304)
TDE-PH-308	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	310	0.25 mg BID starting dose with dose increasing over time	16 weeks

There are twenty phase 1 studies (TDE-PH-101-116, 120-123), one phase 2 study (TDE-PH-201), and three controlled clinical studies in patients with PAH (TDE-PH-301, 302, 308). In addition, three substudies (TDE-PH-305, 306, 307) were conducted as a part of the Phase 3 program. Currently, one open label extension study (TDE-PH-304) and two additional Phase 2

studies (TDE-PH-202, TDE-PH-203) are ongoing. (b) (4)

Ongoing studies

The table below shows the studies that are ongoing and, with the exception of TDE-PH-304 (long term, open label safety study), are not included in the NDA. TDE-PH-304 data were submitted as an interim report with data available through August 31, 2011.

Table 1-2 Overview of Ongoing Studies with UT-15C

Protocol Number	Study Description	Sample Size / Number Enrolled	Dose of Treprostinil	Duration of Dosing
TDE-DU-202 (b) (4)	Open-label extension study (patients formerly in study TDE-DU-201)	115 / 115	0.25 mg BID starting dose with dose increasing over time	Long term; study discontinued (data analysis ongoing)
TDE-PH-202	Open-label, randomized, dose response study – exercise hemodynamics	50 / 27	Three dosing cohorts: 0.25 mg BID; Titrate to 1.25 mg BID; Individual maximum tolerated dose	12 weeks
TDE-PH-203	Open-label study of UT-15C added to patients stabilized on inhaled treprostinil	50 / 1	0.25 mg BID starting dose with dose increasing over time	24 weeks with continuing open-label access
TDE-PH-304	Open-label extension study (patients formerly in studies TDE-PH-301, 302, 308, and 202)	900 / 824	0.25 mg BID starting dose with dose increasing over time	Continuing open-label access
TDE-PH-307	Biomarker substudy	33 / 33	0.25-1 mg BID starting dose with dose increasing over time	12 weeks (substudy of TDE-PH-302)

5.2 Review Strategy

This is a joint review between medical and biostatistics.

5.3 Discussion of Individual Studies/Clinical Trials

Complete reviews for the studies are in the attached appendix.

6 Review of Efficacy

6.1 Indication

The targeted indication is for the treatment of pulmonary arterial hypertension WHO group I to improve exercise ability.

6.1.1 Methods

There were three controlled clinical efficacy studies that were conducted to demonstrate the clinical effectiveness of UT-15C in subjects with PAH. These three studies (TDE-PH-302, TDE-PH-301 and TDE-PH-308) are briefly described in the table below.

Table 2-1 Overview of Studies with UT-15C

Protocol Number	Study Description	Sample Size	Dose of UT-15C	Duration of Dosing
<i>Study of UT-15C as Monotherapy</i>				
TDE-PH-302	Randomized, multi-center, placebo-controlled study in subjects with PAH NOT receiving approved background therapy	349	0.25-1 mg BID starting dose with dose increasing over time	12 weeks
<i>Studies of UT-15C in Combination with Approved PAH Therapy</i>				
TDE-PH-301	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	354	0.5-1 mg BID starting dose with dose increasing over time	16 weeks
TDE-PH-308	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	313	0.25 mg BID starting dose with dose increasing over time	16 weeks

These studies were double-blind, multi-center, international, randomized, placebo-controlled, parallel group pivotal studies in PAH subjects. The study 302 required that subjects not be receiving any approved therapy for their PAH while the other two (301 and 308) required subjects to be stabilized on approved oral therapy for PAH (either an ERA, a PDE5-I, or both).

The table below shows the major inclusion and exclusion criteria for these three studies.

Table 2-4 Relevant Inclusion and Exclusion Criteria for Phase 3 Clinical Trials

Protocol Number	Inclusion Criteria	Exclusion Criteria
TDE-PH-302	12-75 years; at least 40 kg; 6MWD 100-450 m; Not receiving PAH background therapy; previous RHC to confirm PAH diagnosis; IPAH, FPAH, APAH – CTD, repaired shunts, HIV	Any other disease associated with PAH; uncontrolled sleep apnea, renal insufficiency; history of left sided heart disease, parenchymal lung disease, systemic hypertension, or psychiatric condition
TDE-PH-301	12-70 years; at least 45 kg; 6MWD 100-450 m; Stable ERA and/or PDE5-I; previous RHC to confirm PAH diagnosis; IPAH, FPAH, APAH – CTD, repaired shunts, HIV	Any other disease associated with PAH; uncontrolled sleep apnea, renal insufficiency; history of left sided heart disease, parenchymal lung disease, systemic hypertension, or psychiatric condition
TDE-PH-308	18-75 years; at least 40 kg; 6MWD 150-425 m; Stable ERA and/or PDE5-I; previous RHC to confirm PAH diagnosis; IPAH, FPAH, APAH – CTD, repaired shunts, HIV	Any other disease associated with PAH; uncontrolled sleep apnea, renal insufficiency; history of left sided heart disease, parenchymal lung disease, systemic hypertension, or psychiatric condition

APAH=associated PAH; CTD=connective tissue disease; ERA = endothelin receptor antagonist; FPAH = Familial PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; kg=kilograms; m = meters; PDE5-I = phosphodiesterase type 5 inhibitor; RHC=right heart catheterization

Eligible study subjects were randomly allocated in a double blind fashion to receive either UT-15C or placebo. Randomization (UT-15C: placebo) was 2:1 for study 302 and 1:1 for studies 301 and 308.

All subjects were randomized using a centrally administered stratified permuted block randomization. Block sizes were variable and not disclosed to investigators. An interactive voice response system (IVRS) was utilized for the central randomization procedure.

The following stratifications were used:

- study 302 subjects were stratified by baseline 6MWD;
- studies 301 and 308 subjects were stratified by type of background therapy and baseline 6MWD.

Both UT-15C and placebo formulations were understood to be identical in appearance. Eligible subjects completing all study related assessments were able to participate in the open label extension study TDE-PH-304.

Following the completion of all final assessments in the controlled studies, the site personnel became un-blinded to that subject’s treatment assignment via the IVRS in order to titrate the dose of UT-15C in study 304.

Regarding dosing, the studies 301 and 302 initially used a starting dose of 1 mg twice daily. This dose was found to be intolerable to many subjects so the starting dose was lowered to 0.5 mg bid and then lowered again to 0.25 mg bid via protocol amendments.

Dose escalations of 0.25 mg twice daily every three days during the first four weeks of treatment and either 0.25 or 0.5 mg twice daily dose escalations every three days after the first four weeks of treatment were allowed at the discretion of the investigator. The maximum allowable dose was 12 or 16 mg twice daily at the end of 12 or 16-weeks, respectively. The subjects were instructed to take study drug immediately following a meal containing at least 500 calories.

The 0.125 mg tablet strength was implemented in studies 302 and 308 in addition to the 0.25 mg dose if the higher dose was not tolerated.

Study efficacy endpoints are shown in the following table.

Table 2-5 Endpoints for Phase 3 Clinical Trials

Protocol Number	Primary Endpoint	Secondary Endpoints
TDE-PH-302	Change in 6MWD from Baseline to Week 12 (in subjects with access to 0.25 mg tablets at the time of randomization which is defined as the modified intention to treat (mITT) population)	6MWD at trough plasma concentration (Week 11); Time to clinical worsening; Combined ranking of 6MWD and Borg dyspnea score from the 6MWT at Week 12; 6MWD at Week 8 and Week 4; WHO functional classification for PAH at Week 12; Borg dyspnea score from the 6MWT at Week 12; dyspnea-fatigue index at Week 12; Symptoms of PAH at Week 12; Safety and tolerability
TDE-PH-301	Change in 6MWD from Baseline to Week 16	6MWD at Week 12, Week 8 and Week 4; Time to clinical worsening; Combined ranking of distance and Borg dyspnea score from the 6MWT at Week 16; WHO functional classification for PAH at Week 16; Borg dyspnea score from the 6MWT at Week 16; dyspnea-fatigue index at Week 16; Symptoms of PAH at Week 16; Safety and tolerability
TDE-PH-308	Change in 6MWD from Baseline to Week 16	Time to clinical worsening; plasma NT-pro-BNP at Week 16; Combined ranking of 6MWD and Borg dyspnea score from the 6MWT at Week 16; 6MWD at Week 12, Week 8 and Week 4; WHO functional classification for PAH at Week 16; Borg dyspnea score from the 6MWT at Week 16; dyspnea-fatigue index at Week 16; Symptoms of PAH at Week 16; Safety and tolerability

Mostly, the endpoints were similar for all three studies and included change in 6MWD (primary endpoint), time to clinical worsening, change in Borg dyspnea score, change in WHO functional class, symptoms of PAH (secondary endpoints). These are standard endpoints used to evaluate the effectiveness of drugs in the symptomatic treatment of PAH.

Pre-specified plans for efficacy analyses

The “Intent-to-Treat” (ITT) population was defined as all randomized subjects who received at least one dose of study drug (also referred to as the entire study population).

For the primary analyses, a non-parametric analysis of covariance (NP-ANCOVA) was performed, with adjustment for Baseline walk (studies 302, 301, and 308) and background

therapy (studies 301 and 308 only). The median difference between treatment groups was determined by the Hodges-Lehmann (H-L) estimate.

Imputation was used for missing primary efficacy data as follows:

- Lowest rank was assigned for death or discontinuation due to clinical worsening.
- Average placebo rank was assigned if the subject discontinued and had no post-baseline assessments.
- Last rank carried forward was assigned to subjects that discontinued due to adverse events, withdrawal of consent and other reasons.

Analogous imputation was used for the calculation of summary statistics (where worst overall observed relative change, average placebo observation, and last observation carried forward were imputed, respectively). Sensitivity analyses were then applied to assess the impact and rigor of the various imputation methods.

Study 302 results provide the primary evidence for evaluation of the efficacy of oral UT-15C in the treatment of subjects who are using no background therapy for PAH. The efficacy results are not combined with those from any other clinical study.

The results of the studies 301 and 308 are similar in design, subject population, and use of approved background therapies. These two studies were combined into an integrated efficacy analysis in this review.

6.1.2 Demographics

Study 302: A total of 349 subjects were enrolled (with 233 randomized to UT-15C and 116 randomized to placebo). Mean age was around 41 years (range 12-73 years); most subjects were female (75%) and either Asian (47%) or white (40%). There were 105 subjects from USA/Canada, 92 from India, 71 from China, and 81 from other countries. The mean period of time between diagnosis of PAH and starting study was about 1 year for both treatment groups.

The majority of subjects (around 75%) had a PAH etiology of idiopathic/familial. The second most frequent etiology was collagen vascular disease (19%), followed by congenital heart defect (5%), HIV infection (1%), and other (<1%). The mean 6MWD at baseline was somewhat longer for the UT-15C group (332.3 m) compared to placebo (325.2 m). The difference was not statistically significant. The majority of subjects were WHO functional class III or IV. The treatment groups were fairly well balanced.

Most subjects took additional medication. The most commonly used drugs were furosemide, digoxin, and spironolactone. Oxygen was also frequently used by study subjects. Approved drugs for PAH were not allowed.

There were two subjects (174211, 174221) who used disallowed PAH therapy (e.g. PDE5-I or ERA) during the study. The sponsor claims that these subjects received this medication “in absence of clinical worsening”. Subject 174211 (UT-15C) was hospitalized twice for PAH

during the trial. Subject 174221 (placebo) complained of breathlessness and generalized weakness during the trial and walk distance went from 233 m at baseline to 100 m week 11 to 200 m week 12.

There were two subjects (013201 (UT-15C), 171201 (UT-15C)) who were prematurely unblinded to study medication.

Studies 301 and 308 combined

A total of 660 subjects with a mean age of 50.6 years (range 15 to 76 years) were enrolled in these studies and received at least one dose of study drug. The majority of these subjects were white (78%) and female (80%). The majority of subjects (66%) were diagnosed with IPAH or HPAH, 29% were diagnosed with PAH related to collagen vascular disease, 4% had PAH related to a repaired congenital heart defect, and ten subjects (2%) had PAH related to HIV infection. The population was predominantly WHO functional class III (74%) with a mean baseline 6MWD of 340 meters.

Subjects in 301 and 308 studies were to be stabilized on an approved ERA and/or an approved PDE5-I for at least 90 days and receiving a stable dose for at least 30 days prior to randomization. The table shows the use of ERA and PDE5-I at baseline.

Table 4-3 Summary of Background Therapy (studies TDE-PH-301 and TDE-PH-308 combined)

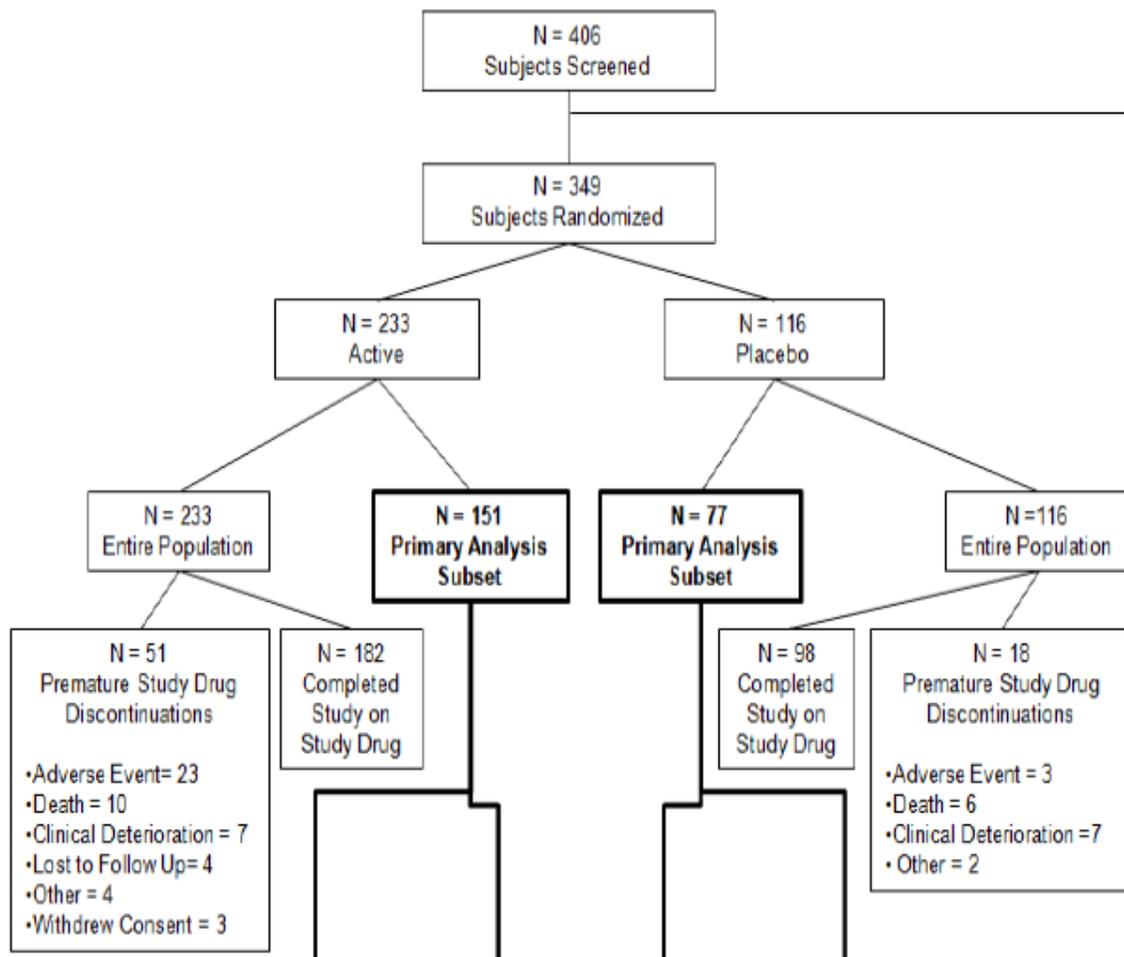
Characteristic	UT-15C (n =331)	Placebo (n =329)
ERA n (%)	80 (24%)	79 (24%)
Average time on ERA therapy; mean ± SD (weeks)	112.9 ± 88.6	137.6 ± 102.2
PDE5-I n (%)	112 (34%)	108 (33%)
Average time on PDE5-I therapy; mean ± SD (weeks)	86.5 ± 74.7	85.4 ± 65
ERA and PDE5-I n (%)	139 (42%)	142 (43%)
Average time on ERA and PDE5-I therapy; mean ± SD (weeks)	108.2 ± 86.6	121.4 ± 96.5

PAH background therapy use was found to be as follows: ERA only (24%), PDE5-I only (33%), and both (42%).

6.1.3 Subject Disposition

Study 302: the disposition of subjects is shown below.

Figure 10-1 Disposition of All Subjects



A greater percentage of subjects randomized to UT-15C stopped study drug (22%, 51/233) compared to subjects randomized to placebo (16%, 18/116). Overall, a higher percentage of placebo subjects (88%) agreed to rollover into the open label follow up study compared to UT-15C subjects (76%).

A detailed examination of the eleven UT-15C subjects and two placebo subjects who were reported to have discontinued for other/lost to follow up/consent withdrawn is in the complete study review appendix. Briefly, most of the subjects who were declared to have withdrawn for these reasons should be re-classified.

Studies 301 and 308 combined

The table below shows the reasons for premature study drug discontinuation.

Table 4-6 Disposition of Subjects (studies TDE-PH-301 and TDE-PH-308 combined)

Study Disposition	Treatment n (%)	
	UT-15C n = 331	Placebo n = 329
Completed Study on Study Drug	267 (81%)	290 (88%)
Discontinued Study Drug Prematurely	64 (19%)	39 (12%)
Adverse Event	43 (67%)	13 (33%)
Clinical Deterioration	11 (17%)	12 (31%)
Death*	2 (3%)	4 (10%)
Lost to Follow-up	2 (3%)	1 (3%)
Consent Withdrawn	2 (3%)	3 (8%)
Other	2 (3%)	4 (10%)
Transplant	1 (2%)	1 (3%)
Protocol Violation	1 (2%)	1 (3%)

*A total of nine deaths occurred in the UT-15C group and seven deaths in the placebo group during the 16-week treatment period regardless of whether the subject was still receiving study drug.

The discontinuation rate was greater for the UT-15C group (19%) compared to placebo (12%). More subjects in the UT-15C dropped out because of adverse events.

Following completion of the controlled trials, 76% who received UT-15C and 88% who received placebo enrolled in the open-label study TDE-PH-304.

Study drug exposure

Study 302: The table below shows the mean study dose at each visit.

Table 4-8 Mean Study Drug Dose at Each Scheduled Visit for the ITT Population (study TDE-PH-302)

Study Visit (n = UT-15C /Placebo)	Study Drug Dose Achieved Mean ± SD Dose (mg)	
	UT-15C	Placebo
Week 4 (n =223/113)	2.6 ± 1.6	3.3 ± 1.9
Week 8 (n = 204/104)	3.5 ± 2.2	4.8 ± 2.8
Week 12 (n =189/99)	3.6 ± 2.2	5.1 ± 3.1

At each visit, the dose of UT-15C was less than the dose of placebo.

Studies 301 and 308 combined

The table below shows the mean study dose at each visit.

Table 4-11 Mean Study Drug Dose at Each Scheduled Visit (studies TDE-PH-301 and TDE-PH-308 combined)

Study Visit (n = UT-15C /Placebo)	Study Drug Dose Achieved Mean ± SD Dose (mg)	
	UT-15C	Placebo
Week 4 (n =317/323)	2.2 ± 1.4	3.7 ± 2.4
Week 8 (n =300/315)	2.8 ± 2.0	6.0 ± 3.8
Week 12 (n =287/302)	3.2 ± 2.4	8.1 ± 4.9
Week 16 (n=273/295)	3.3 ± 2.5	8.7 ± 5.2

At each visit, the mean dose of study drug was less than the placebo dose. At weeks 8, 12, and 16 the mean dose of placebo was about three times as much as the mean dose of UT-15C.

6.1.4 Analysis of Primary Endpoint(s)

The 6 minute walk distance (6MWD) was the primary efficacy endpoint for the three trials.

Study 302: The primary efficacy analysis for this study compared change in 6MWD at Week 12 between treatment groups for all subjects in the ITT population.

Imputation was used for missing primary efficacy data as follows:

- Lowest rank (for NP-ANCOVA) or value corresponding to the worst overall relative change (for summary statistics) were assigned for death within 12 weeks (excluding accidents), discontinuation due to clinical deterioration, transplantation, or atrial septostomy and for subjects too ill to perform the 6MWT.
- Mean placebo rank (for NP-ANCOVA) or value corresponding to the geometric mean relative change for the placebo group was assigned to subjects who withdrew prior to any follow-up 6MWT.
- Last rank carried forward (for NP-ANCOVA) or last observation carried forward (for summary statistics) were assigned to subjects who withdrew prematurely or who did not perform the 6MWT due to any other reason not mentioned above.

Results

6MWD

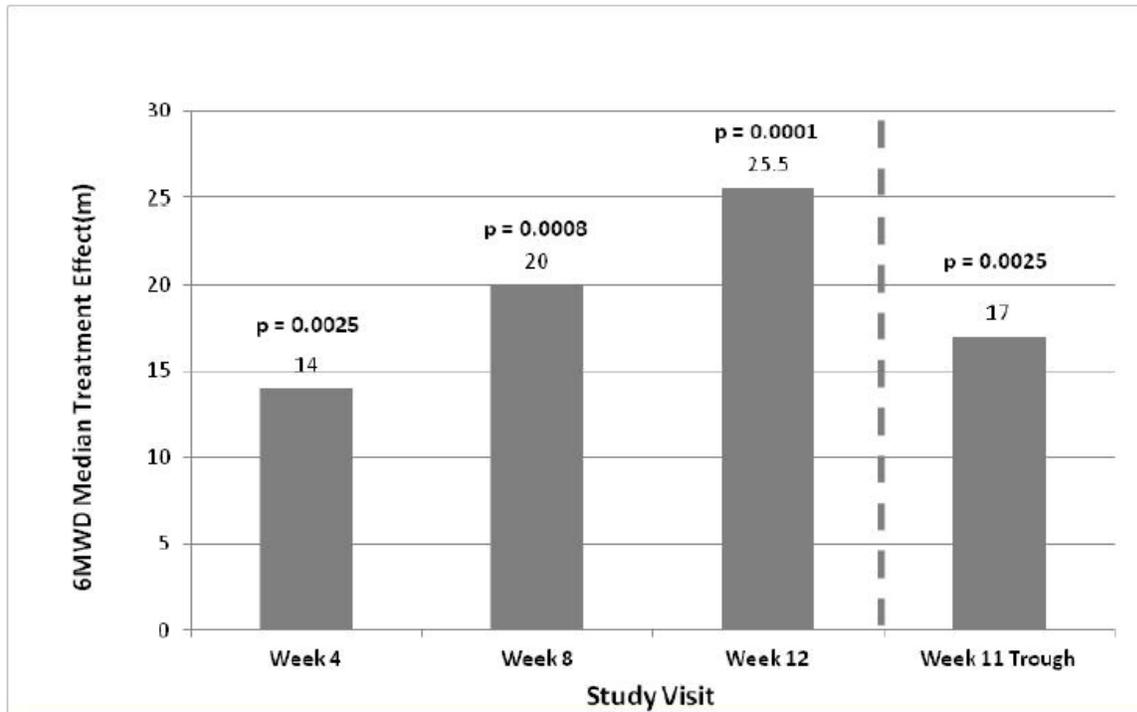
The primary efficacy objective was to assess the effect of UT-15C on exercise capacity as measured by the change in 6MWD from Baseline to Week 12 population. The results are shown in the table and figures below.

Table 11-3 Summary of Hodges-Lehmann Estimates of Treatment Effect for Entire Study Population

Time Period	Median 6MWD (meters)		Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
	Active n = 233	Placebo n = 116		
Baseline	347	339	—	—
Week 4	358	340	+14.0 (+4, +25)	0.0025
Week 8	360	340	+20.0 (+7, +34)	0.0008
Week 11*	351	327	+17.0 (+3, +33)	0.0025
Week 12	370	330	+25.5 (+10, +41)	0.0001

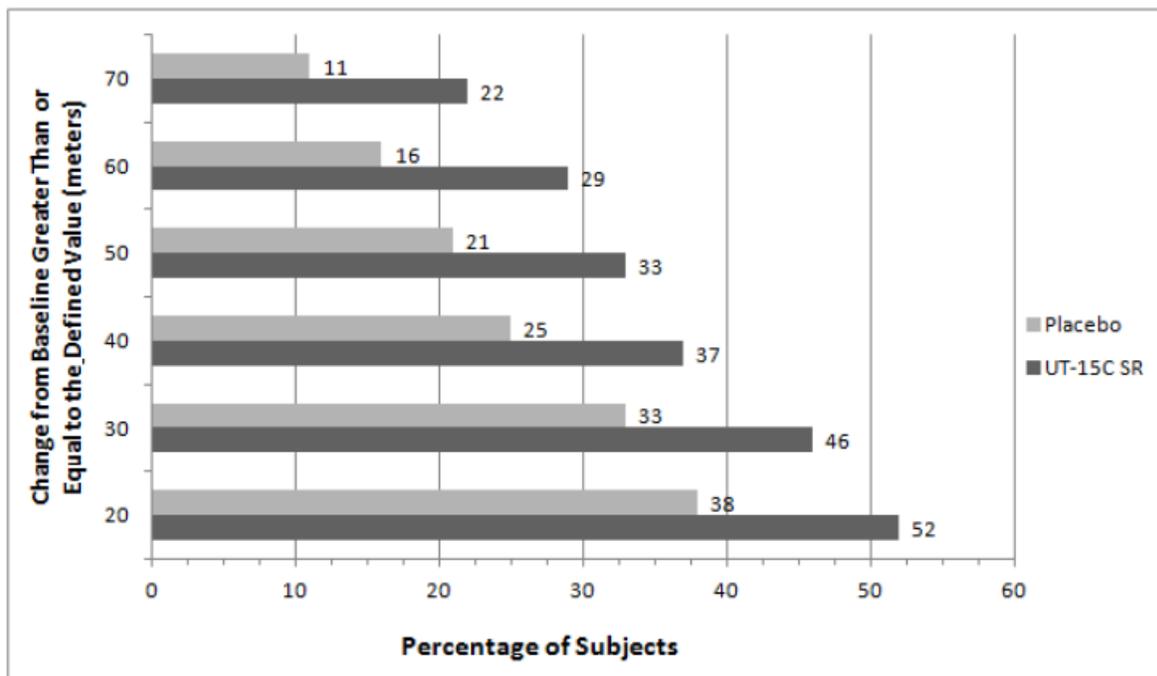
* 6MWT conducted at trough drug level (8 -13 hrs post dose of UT-15C)

Figure 4-6 Display of Hodges-Lehmann Estimates of Treatment Effect for the ITT Population (study TDE-PH-302)



*Trough 6MWT; conducted 8-13 hours after the last dose

Figure 4-7 Magnitude of Change in 6MWD at Week 12 for the ITT Population (study TDE-PH-302)



There were statistically significant mean treatment effects at weeks 4, 8, 11, and 12 that ranged from 14 m (week 4) to 25.5 m (week 12, $p=0.0001$). The walk distance at week 11 was to have been conducted at trough drug concentration. The mean treatment effect at week 11 was 17m ($p=0.0025$).

However, 59 subjects (25%) in the UT-15C group did not have the week 12 walk test compared to 18 subjects (11%) in the placebo group. When the 59 UT-15C subjects are given worst rank, the p value becomes 0.92. When the missing placebo subjects are assigned worst rank as well, the p value becomes 0.21 (see the addendum to this review for results of further sensitivity analyses).

Individual study 301: The primary efficacy endpoint of change in 6MWD from Baseline to Week 16 between treatment groups was 11 meters which failed to meet statistical significance (Hodges-Lehmann; $p = 0.072$).

Individual study 308: The treatment effect at each week was small and ranged from 1 m (week 8) to 10 m (week 16). The H-L estimates of treatment effect at all time points were not statistically significant using the pre-specified imputation methodology.

Studies 301 and 308 combined

The results of these studies are combined into an integrated analysis. The magnitude of the treatment effect was assessed using the H-L estimate of median between-treatment difference.

Imputation was used for missing primary efficacy data as follows:

- Lowest rank (for NP-ANCOVA) or value corresponding to the worst overall relative change (for summary statistics) was assigned for death within 16 weeks (excluding accidents), discontinuation due to clinical deterioration, transplantation, or atrial septostomy and for subjects too ill to perform the 6MWT.
- Mean placebo rank (for NP-ANCOVA) or value corresponding to the geometric mean relative change for the placebo group was assigned to subjects who withdrew prior to any follow-up 6MWT.
- Last rank carried forward (for NP-ANCOVA) or last observation carried forward (for summary statistics) was assigned to subjects who withdrew prematurely or who did not perform the 6MWT due to any other reason not mentioned above.

The primary efficacy endpoint of the TDE-PH-301 and TDE-PH-308 studies was change in 6MWD from Baseline to Week 16 as measured by the 6MWD recorded three to six hours following the last dose of study drug. Treatment effect was determined using the Hodges-Lehmann method to estimate the median difference between treatment groups for change from Baseline in 6MWD.

The results are shown in the table and figures below.

Table 4-17 Summary of Hodges-Lehmann Estimates of Treatment Effect (studies TDE-PH-301 and TDE-PH-308 combined)

Time Period	Median 6MWD (meters)		Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
	UT-15C n = 331	Placebo n = 329		
Baseline	360	360	--	--
Week 4	365	367	+4 (-1, +9)	0.125
Week 8	370	367	+5 (-1.9, +12)	0.1097
Week 12	372	363	+10.4 (+3, +18)	0.0059
Week 16	375	366	+10 (+3, +18.9)	0.00397

Figure 4-9 Display of Hodges-Lehmann Estimates of Treatment Effect (studies TDE-PH-301 and TDE-PH-308 combined)

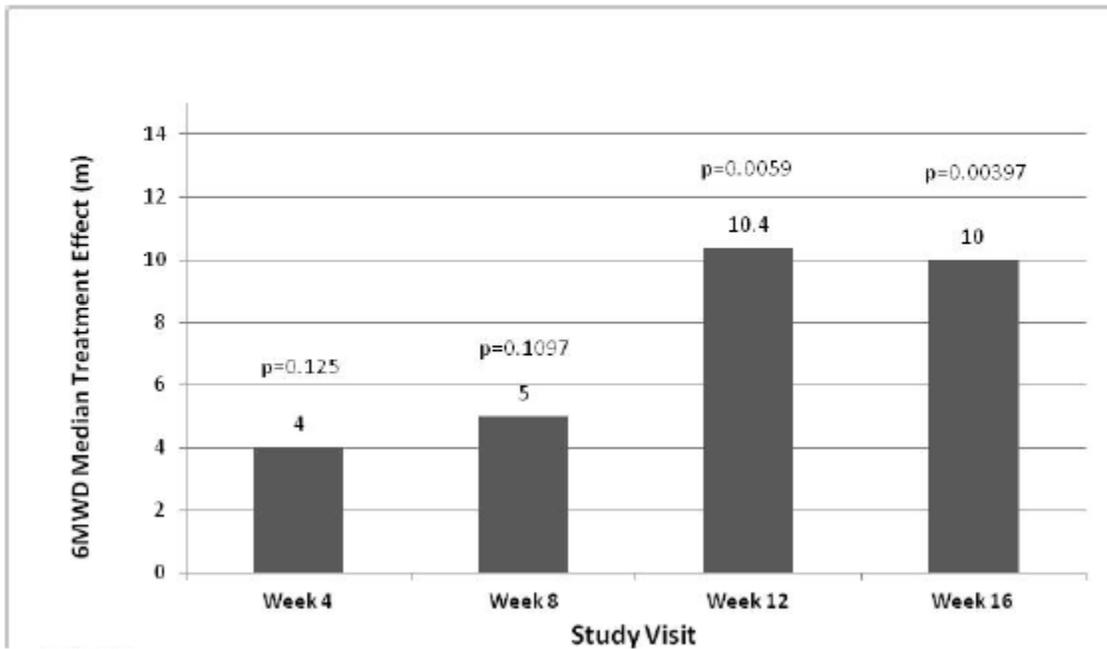
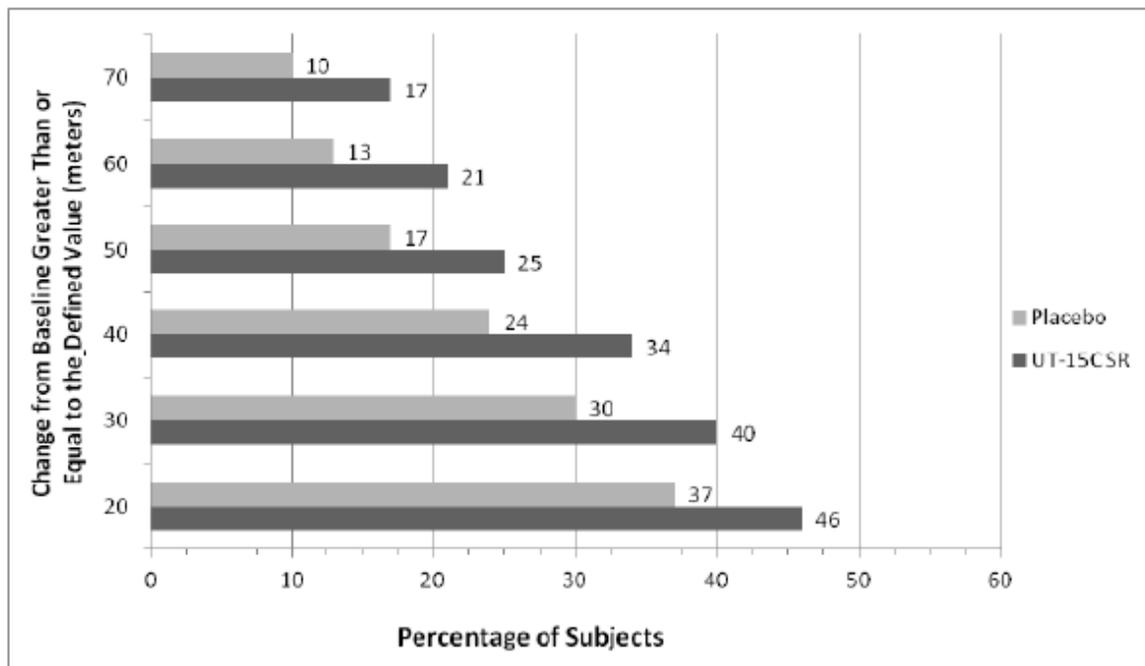


Figure 4-10 Magnitude of Change in 6MWD at Week 16 (studies TDE-PH-301 and TDE-PH-308 combined)



The 6MWD at Week 16 was statistically significantly better with a median difference of +10 meters (H-L; p = 0.00397). The 6MWD at Week 12 was also, statistically significantly improved with a median of +10.4 meters (H-L; p = 0.0059).

6.1.5 Analysis of Secondary Endpoints(s)

Study 302

Clinical worsening

Time to clinical worsening was defined as the time from randomization to the first of death (except due to accidental causes), transplantation, atrial septotomy, or hospitalization because of PAH. Subjects were also considered to have experienced clinical worsening if they had a 20% or greater decrease in 6MWD from baseline or were too ill to walk with a decrease in WHO functional class and had started a new PAH therapy including either an ERA, a PDE5-1 or a prostacyclin.

The table below shows the results by treatment group.

Table 14.2.2.2
 Summary of Clinical Worsening For the Entire Study Population

Variable	Category	Treatment		p-value
		Active	Placebo	
Clinical Worsening	n	233	116	0.3572
	No	211 (91%)	101 (87%)	
	Yes	22 (9%)	15 (13%)	
Clinical worsening event	n	233	116	
	No clinical worsening (censored)	211 (91%)	101 (87%)	
	Death	13 (6%)	8 (7%)	
	Clinical deterioration	9 (4%)	5 (4%)	
	>=20% decrease 6MWD, worsened WHO class & new PAH medication	0	2 (2%)	

There was a higher percentage of placebo subjects with clinical worsening (13%) compared to UT-15C group (9%). This difference was not statistically significant.

World Health Organization Functional Class

At baseline, the two treatment groups were similar regarding the percent of subjects by WHO functional class with around 60% of subjects being classified as WHO III.

At week 12, most subjects did not change from their baseline category. There were 36 (15%) UT-15C subjects who got worse compared to 21 (18%) placebo subjects. The overall changes were not significantly different.

Dyspnea-Fatigue Index

Each of the three components of the dyspnea-fatigue index were rated on a scale of 0 to 4 with 0 being the worst condition and 4 being the best condition for each component. The dyspnea-fatigue index was computed by summing the three component scores. The median index values remained unchanged at all post-baseline assessments compared to baseline values and changes did not differ between treatment groups at Week 12.

Symptoms of Pulmonary Arterial Hypertension

Symptoms of PAH including fatigue, dyspnea, edema, dizziness, syncope, chest pain, and orthopnea were assessed at Baseline and at Weeks 4, 8, and 12. Each symptom was given a severity grade value of 0 to 3. There was no observed treatment effect on symptoms of PAH for the entire population.

Studies 301 and 308 combined

The following additional secondary efficacy endpoints were assessed: combined ranking of change in 6MWD and Borg dyspnea score, clinical worsening, Borg dyspnea score, dyspnea fatigue index, WHO functional class, and symptoms of PAH. The results of these secondary endpoints are summarized below.

Clinical worsening

There is no difference between UT-15C and placebo regarding clinical worsening.

Table 4-23 Summary of Clinical Worsening (studies TDE-PH-301 and TDE-PH-308 combined)

Category	Clinical Worsening n (%)	
	UT-15C n = 331	Placebo n = 329
No Clinical Worsening	309 (93%)	305 (93%)
Clinical Worsening	22 (7%)	24 (7%)
Death	7 (2%)	7 (2%)
Transplantation or atrial septostomy	1 (<1%)	1 (<1%)
PAH Hospitalization	11 (3%)	10 (3%)
Twenty Percent Decrease in 6MWD and addition of new PAH therapy	3 (<1%)	5 (2%)
Added parenteral prostacyclin	0	1 (<1%)

6.1.6 Other Endpoints

Median Borg scores were similar for both treatment groups at baseline and remained so for most of the treatment period.

Table 4-24 Median Borg Dyspnea Scores (studies TDE-PH-301 and TDE-PH-308 combined)

Time Period	Median Score	
	UT-15C n = 331	Placebo n = 329
Baseline	4	4
Week 4	4	4
Week 8	4	4
Week 12	3	4
Week 16	4	4

World Health Organization Functional Class

The table below shows the WHO functional classifications by treatment group at baseline (most subjects were class III) and Week 16. The changes reported in classification at week 16 were similar across treatment groups.

Table 4-25 WHO Functional Class by Treatment Group (studies TDE-PH-301 and TDE-PH-308 combined)

WHO Functional Classification	Treatment (n Baseline/ n Week 16)	
	UT-15C n = 330	Placebo n = 328
I	2/3	1/4
II	84/122	68/98
III	237/181	254/199
IV	7/24	5/27

6.1.7

Symptoms of Pulmonary Arterial Hypertension

Symptoms of PAH including fatigue, dyspnea, edema, dizziness, syncope, chest pain, and orthopnea were assessed at Baseline and at Weeks 4, 8, 12, and 16. UT-15C had no observed treatment effect on symptoms of PAH.

6.1.8 Other Endpoints

Cardiopulmonary hemodynamics

Forty-five subjects (32 from TDE-PH-301 and 13 from TDE-PH-302) completed study and were included in the hemodynamic analysis. Thermodilution and the Fick method were used to determine CO at both RHC procedures in 80% and 16% of subjects, respectively. The table below shows the results of the hemodynamic analysis (by individual study).

Table 11-2 Summary of Hemodynamic Analysis: Pooled and by Individual Studies (TDE-PH-301 or TDE-PH-302)

Parameter	Hemodynamic Values (Mean ± SD)			
	Pooled			
	TDE-PH-301		TDE-PH-302	
	UT-15C SR n = 22*		Placebo n = 23**	
	Baseline	End of Study	Baseline	End of Study
HR (beats/min)	69.86 ± 10.83	73.91 ± 10.03	79.87 ± 11.41	81.04 ± 12.69
	66.77 ± 9.47	71.08 ± 10.58	80.11 ± 11.40	80.16 ± 10.96
	74.33 ± 11.64	78.00 ± 8.02	78.75 ± 13.15	85.25 ± 20.76
RAPm (mmHg)	9.23 ± 4.64	10.09 ± 4.77	8.77 ± 3.28	10.96 ± 4.37
	8.23 ± 4.38	10.23 ± 4.92	8.67 ± 3.57	10.72 ± 4.66
	10.67 ± 4.87	9.89 ± 4.83	9.25 ± 1.71	12.00 ± 2.94
CI [L/(min/m ²)]	2.48 ± 0.65	2.47 ± 0.68	2.37 ± 0.64	2.44 ± 0.66
	2.53 ± 0.64	2.39 ± 0.57	2.42 ± 0.65	2.52 ± 0.70
	2.40 ± 0.69	2.58 ± 0.84	2.06 ± 0.59	2.11 ± 0.29
PAPm (mmHg)	44.64 ± 10.89	44.27 ± 12.57	49.73 ± 11.81	53.27 ± 14.02
	42.39 ± 12.82	44.08 ± 15.05	48.17 ± 12.23	52.33 ± 15.38
	47.89 ± 6.70	44.56 ± 8.65	56.75 ± 6.85	57.50 ± 2.38
PVRI [mmHg/(L/min/m ²)]	14.64 ± 5.27	13.72 ± 6.16	18.81 ± 12.60	19.34 ± 9.05
	14.37 ± 5.83	14.26 ± 5.88	18.17 ± 12.69	18.74 ± 9.37
	15.02 ± 4.75	12.98 ± 6.87	29.60 ± N/A	24.70 ± 0.56
SAPm (mmHg)	87.64 ± 14.29	88.64 ± 15.60	84.32 ± 11.41	87.83 ± 15.53
	87.23 ± 16.62	89.39 ± 19.50	82.94 ± 11.89	88.32 ± 13.65
	88.22 ± 11.01	87.56 ± 8.10	90.50 ± 6.95	85.50 ± 25.33
SVRI [mmHg/(L/min/m ²)]	33.92 ± 11.86	34.81 ± 12.78	35.16 ± 14.89	34.36 ± 12.64
	33.69 ± 13.51	35.59 ± 12.80	33.77 ± 14.48	33.90 ± 11.98
	34.25 ± 9.75	33.69 ± 13.44	42.98 ± 17.93	36.30 ± 17.25
SaO ₂ (%)	93.14 ± 8.14	92.77 ± 8.30	93.78 ± 3.30	92.78 ± 6.66
	92.58 ± 10.56	91.46 ± 10.53	93.79 ± 3.34	92.42 ± 7.08
	93.89 ± 3.33	94.67 ± 2.74	93.75 ± 3.59	94.50 ± 4.44
SvO ₂ (%)	64.19 ± 10.64	63.67 ± 11.48	64.55 ± 10.52	66.40 ± 12.53
	65.33 ± 13.34	61.83 ± 13.55	64.00 ± 10.44	64.50 ± 10.87
	62.67 ± 5.79	66.11 ± 8.09	66.75 ± 12.18	74.00 ± 17.51
PCWPm (mmHg)	9.68 ± 3.54	11.16 ± 3.63	9.47 ± 4.16	9.70 ± 3.13
	8.36 ± 3.38	10.91 ± 3.56	9.35 ± 4.36	9.61 ± 3.18
	11.50 ± 3.07	11.50 ± 3.93	10.50 ± 2.12	10.50 ± 3.54

* Maximum sample size reported. Due to missing CRF data, sample size was variable across hemodynamic parameters. UT-15C SR at Baseline and End of Study: Pooled, n = 19 – 22; TDE-PH-301, n = 11 – 13; and TDE-PH-302, n = 8 – 9.

** Placebo at Baseline: Pooled, n = 18 – 23; TDE-PH-301, n = 16 – 19; and TDE-PH-302, n = 1 – 4. Placebo at End of Study: Pooled, n = 20 – 23; TDE-PH-301, n = 16 – 19; and TDE-PH-302, n = 2 – 4.

Overall, there are no discernable effects of UT-15C on hemodynamic parameters.

6.1.9 Subpopulations

Study 302

By baseline 6MWD

The table below shows the study subjects grouped into quartiles according to their baseline 6MWD. It also shows the H-L estimates of median treatment effect categorized by Baseline 6MWD quartile for the mITT population. There is no obvious pattern seen in the results.

Table 4-28 Hodges-Lehmann Estimates of Median Placebo Corrected Change From Baseline in Peak 6MWD by Baseline 6MWD Quartiles for the mITT Population (study TDE-PH-302)

Baseline 6MWD Range (meters)	Number of Subjects UT-15C / placebo	Hodge's Lehmann Estimate of Treatment Effect (95% CI)
155 – 282	37 / 20	+13 (-27, +61)
283 – 347	37 / 20	+25 (-21, +69)
349 – 384	37 / 20	+39 (+4, +75)
385 – 450	40 / 17	+9 (-28, +42)

By disease etiology

The table below shows the H-L estimates of placebo-corrected median treatment effect at Week 12 by disease etiology for the mITT population. Overall, there is greater improvement in walk distance for the subjects with idiopathic/heritable PAH compared to subjects with PAH secondary to collagen vascular disease.

Table 4-29 Hodges-Lehmann Estimates of Median Placebo Corrected Change From Baseline in Peak 6MWD at Week 12 by Disease Etiology for the mITT Population (study TDE-PH-302)

Disease Etiology	Number of Subjects UT-15C / placebo	Hodges-Lehmann Estimate of Treatment Effect (95% CI) (Meters)
IPAH / HPAH	114 / 56	+32 (+10, +55)
CVD	26 / 17	-10 (-43.6, +15)
Other	11 / 4	+17 (-35, +65)

Other=HIV or repaired congenital cardiac shunts

By WHO functional class

The table below shows the H-L estimates of placebo-corrected median treatment effect for the mITT population by Baseline WHO functional class.

Table 4-30 Hodges-Lehmann Estimates of Median Placebo Corrected Change From Baseline in Peak 6MWD at Week 12 by Baseline WHO Functional Class for the mITT Population (study TDE-PH-302)

Baseline WHO Functional Class	Number of Subjects UT-15C / placebo	Hodges-Lehmann Estimate of Treatment Effect (95% CI)
I / II	53 / 25	+16 (-15, +47)
III / IV	98 / 52	+26 (1, +49)

Those subjects classified as WHO III/IV and randomized to UT-15C appear to walk a little longer compare to the subjects who were classified as WHO I/II.

6.1.10 Analysis of Clinical Information Relevant to Dosing Recommendations

No efficacy studies were conducted in order to determine if increasing doses of UT-15C produce increasing drug effect.

The placebo controlled study 302 had one UT-15C treatment arm. The study needed numerous dose modifications in order to find a “well” tolerated first dose. Starting with 1 mg QD and then BID, the study finally concluded that the starting dose of UT-15C should be 0.125 mg QD followed by BID. The dose of study drug was to be increased every 5 days, in the absence of dose-limiting drug-related adverse event. Weekly telephone calls between site personnel and the subject were to be conducted to monitor adverse events and make decisions about dose titration. The maximum allowable dose of study drug during the 12-week treatment phase was 12 mg BID.

The table below shows the mean dose achieved at Weeks 4, 8, and 12 for the entire study 302 population. The maximum dose of UT-15C achieved during this 12 week study was 10.0 mg BID.

Table 12-2 Mean Study Drug Dose at Each Scheduled Visit for the Entire Study Population

Study Visit (n = Active /Placebo)	Study Drug Dose Achieved Mean ± SD Dose (mg)	
	UT-15C	Placebo
Week 4 (n =223/113)	2.6 ± 1.6	3.3 ± 1.9
Week 8 (n = 204/104)	3.5 ± 2.2	4.8 ± 2.8
Week 12 (n =189/99)	3.6 ± 2.2	5.1 ± 3.1

The maximum doses achieved for this trial are shown in the table below.

Table 12-6 Maximum Dose Achieved Among Subjects in the Entire Study Population

Maximum Dose Achieved by Week 12 (mg)	Subjects Completing Study n (%)	
	UT-15C n=233	Placebo n = 116
> 0 – 1	31 (13)	8 (7)
>1 – 2	52 (22)	17 (15)
>2-4	83 (36)	30 (26)
>4-6	44 (19)	31 (27)
>6-8	13 (6)	15 (13)
>8-10	7 (3)	8 (7)
>10	3 (1)	7 (6)

Long term dosing was evaluated in open label, uncontrolled follow-up study 304. Subjects were instructed to take the appropriate amount of 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and/or 2.5 mg tablets based upon their prescribed dose in the base study. In general, the dose of UT-15C could be increased in 1 mg increments every five days prior to Amendment 2, 0.5 mg increments every three days after implementation of Amendment 2, and then 0.25 or 0.5 mg increments every three days after implementation of Amendment 4. Investigators are instructed to increase the dose of UT-15C in the absence of dose-limiting drug-related adverse events, to ensure each subject receives the optimal clinical dose throughout the study.

The table below shows the mean dose at each study visit (study 304).

Table 12-1 Mean Twice Daily Dose of UT-15C at Each Study Visit

Study Visit	Previous Study							
	TDE-PH-301 and TDE-PH-308		TDE-PH-302		De Novo		Overall	
	N	Mean ± SD (mg)	N	Mean ± SD (mg)	N	Mean ± SD (mg)	N	Mean ± SD (mg)
Month 6	360	3.5 ± 2.9	201	4.0 ± 2.6	2	2.7 ± 1.1	563	3.7 ± 2.8
Month 12	230	4.0 ± 3.3	130	4.6 ± 2.8	2	3.3 ± 0.4	362	4.2 ± 3.1
Month 24	145	4.8 ± 3.8	76	5.4 ± 3.4	1	2.5	222	5.0 ± 3.7
Month 36	99	5.5 ± 4.0	52	5.2 ± 3.8	1	2.5	152	5.3 ± 3.9

It appears that doses above 5.5 mg BID are difficult to tolerate by most subjects.

In conclusion, the minimum tolerated dose seems to be 0.125 mg. The maximum effective dose has yet to be determined.

6.2 Discussion of Persistence of Efficacy and/or Tolerance Effects

There are no controlled, long term efficacy data.

The interim analysis of the ongoing open-label extension study, TDE-PH-304, includes 824 subjects (279 subjects from the TDE-PH-302 study and 543 from either TDE-PH-301 or TDE-PH-308. Approximately 75%, 76%, and 78% of subjects that received UT-15C in TDE-PH-301, TDE-PH-302, and TDE-PH-308, respectively, opted to enroll in the TDE-PH-304 study. There were two subjects who directly entered into the study without previous completion of one of the blinded studies.

This interim data set reflects study subjects followed through 31 August 31, 2011.

The reported 6MWD changes from baseline at month 12 are shown below.

Table 6-4 Summary of Mean 6MWD change from Baseline at Month 12 (study TDE-PH-304)

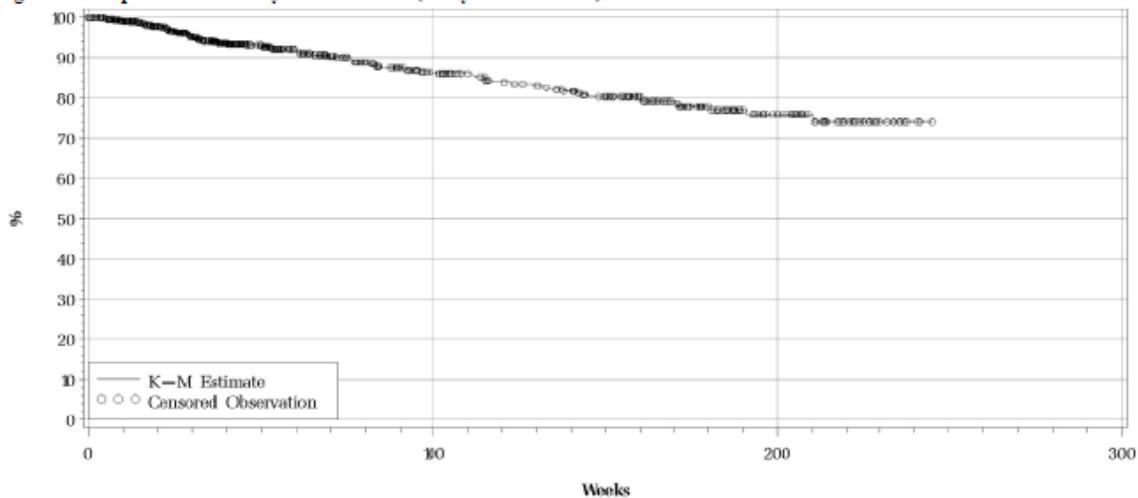
Previous Study Enrollment		Baseline	Month 12
TDE-PH-301 and TDE-PH-308	N	214	215
	Mean 6MWD (meters)	361	387
	Mean Change (meters)	---	+25.6
TDE-PH-302	N	122	122
	Mean 6MWD (meters)	336	362
	Mean Change (meters)	---	+25.9
De Novo	N	0	2
	Mean 6MWD (meters)	N/A	222
	Mean Change (meters)	---	N/A
Overall	N	336	339 ^a
	Mean 6MWD (meters)	352	377
	Mean Change (meters)	---	+25.7

^an=336; subjects 040806, 041401, and 041402 did not have a Baseline value recorded for 6MWD

Survival Analysis

The Kaplan-Meier analysis of survival for this open label study is shown in the figure below.

Figure 6-1 Kaplan-Meier Analysis of Survival (study TDE-PH-304)



Weeks	0	13	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	247	
# Events	0	8	27	42	46	53	59	63	67	71	74	79	80	82	85	86	86	87	87	87	87
# Censored	2	80	195	325	413	459	490	518	539	556	560	572	588	619	650	674	697	713	728	737	737
# Pts Remaining	822	736	602	457	365	311	275	243	218	197	190	173	156	123	89	64	41	24	8	0	0

The one, two, and three year survival estimates for the open-label study population were approximately 92.6 %, 86.0%, and 80.3%, respectively.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety was evaluated in four completed clinical studies conducted in subjects with PAH, 20 Phase I clinical studies conducted either in healthy subjects (18 studies) or volunteers with hepatic (1 study) or renal impairment (1 study). Additionally, interim safety data from an ongoing open-label extension study were reviewed.

Regarding safety information from other indications, there were two studies conducted in subjects with digital ulcers associated with scleroderma.

The ongoing studies that were not included in the NDA are shown in the table below.

Table 1-2 Overview of Ongoing Studies with UT-15C

Protocol Number	Study Description	Sample Size / Number Enrolled	Dose of Treprostinil	Duration of Dosing
TDE-DU-202 (b)(4)	Open-label extension study (patients formerly in study TDE-DU-201)	115 / 115	0.25 mg BID starting dose with dose increasing over time	Long term; study discontinued (data analysis ongoing)
TDE-PH-202	Open-label, randomized, dose response study – exercise hemodynamics	50 / 27	Three dosing cohorts: 0.25 mg BID; Titrate to 1.25 mg BID; Individual maximum tolerated dose	12 weeks
TDE-PH-203	Open-label study of UT-15C added to patients stabilized on inhaled treprostinil	50 / 1	0.25 mg BID starting dose with dose increasing over time	24 weeks with continuing open-label access
TDE-PH-304	Open-label extension study (patients formerly in studies TDE-PH-301, 302, 308, and 202)	900 / 824	0.25 mg BID starting dose with dose increasing over time	Continuing open-label access
TDE-PH-307	Biomarker substudy	33 / 33	0.25-1 mg BID starting dose with dose increasing over time	12 weeks (substudy of TDE-PH-302)

7.1.2 Categorization of Adverse Events

Clinical and safety data including adverse events were collected throughout the entire duration of each study. In the controlled clinical studies vital signs, including heart rate and blood pressure, were monitored at every study visit. Clinical laboratory tests for blood chemistry, hematology and urinalysis were obtained at baseline, at one time point during the study, and at the end of the study. Physical examinations and twelve-lead ECGs were performed in each of the clinical studies (assessments included: HR, PR interval, QRS duration, QT interval) at baseline and at the end of the study.

7.1.2.1 Analysis of Adverse Events

Verbatim adverse events recorded during the UT-15C clinical studies were coded by United Therapeutics to MedDRA Preferred terms (version 11.1 except where noted). Summaries included all treatment emergent events defined as those that were not present prior to receiving study drug or those that increased in seriousness or intensity after receiving study drug.

Adverse event data obtained from healthy volunteer studies, renal and hepatic insufficiency studies, controlled clinical studies in PAH, the on-going open-label PAH study and the digital ulcer studies in subjects with scleroderma were discussed separately.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Clinical studies were pooled into two groups:

- 1) clinical pharmacology healthy volunteer studies and
- 2) randomized, double-blind, placebo-controlled clinical trials in subjects with PAH.

Safety data from the following two additional sources are analyzed separately:

- 1) ongoing open-label PAH trial (TDE-PH-304) and
- 2) studies in populations for which an indication is not being sought by United Therapeutics in this NDA (TDE-DU-101 and TDE-DU-201).

7.2 Adequacy of Safety Assessments

Overall, the safety assessments appear to be adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

There were 20 Phase I trials that exposed 547 volunteers (18 Phase I studies in healthy adult volunteers and two studies in special populations) to at least one dose of UT-15C. The table below shows the number exposed to doses ranging from 0.5 to 2.5 mg with the majority (450) exposed to 1 mg.

Table 1.9.9
 Summary of Study Drug Dosing and Exposure for Volunteer Studies

	0.5 mg UT-15C SR fed (N=36)	1 mg UT-15C SR fed (N=450)	2.5 mg UT-15C SR fed (N=63)	1 mg UT-15C SR fasted (N=10)	Total (N=559)
Number of Subjects	36	450	63	10	559
Average Duration of Exposure (days)					
n	36	450	63	10	559
Mean	1.0	1.0	1.0	1.0	1.0
Std	0.00	0.00	0.00	0.00	0.00
Median	1.0	1.0	1.0	1.0	1.0
Min	1	1	1	1	1
Max	1	1	1	1	1
Average Exposure (mg)					
n	36	450	63	10	559
Mean	0.500	1.000	2.500	1.000	1.137
Std	0.0000	0.0000	0.0000	0.0000	0.5014
Median	0.500	1.000	2.500	1.000	1.000
Min	0.50	1.00	2.50	1.00	0.50
Max	0.50	1.00	2.50	1.00	2.50

The duration of exposure ranged from single dose to 13 days in the volunteer studies.

Of the 20 volunteer studies, 11 were not included in the integrated data sets. These 11 included 219 subjects and exposure ranged from four doses of 1 mg each to 13 days of 1-3 mg twice daily. The doses included in these studies were 0.05 mg, 0.125 mg, and 0.25 mg of oral solution, 0.5 mg to 1 mg with capsule or tablet, or 0.2 to 2 mg total dose of oral solution.

Regarding the controlled clinical studies in PAH populations, there were three placebo-controlled studies in subjects with PAH (studies TDE-PH-301, TDE-PH-302 and TDE-PH-308) with a total of 565 subjects who received at least one dose of UT-15C. The table below shows the exposure by duration for these subjects.

Table 1-4: Summary of Mean Dose for Controlled Clinical Studies in PAH

Mean duration of exposure (days)	92.6 (n=565)
Week 4 exposure (mg BID) (n)	2.36 (541)
Week 8 exposure (mg BID) (n)	3.08 (505)
Week 12 exposure (mg BID) (n)	3.35 (477)
Week 16 exposure (mg BID) (n)	3.28 (274)

The mean duration of exposure was 93 days and the mean dose at week 16 was 3.28 mg bid (with 274 subjects exposed to that dose). These studies involved a non-forced titration scheme.

The monotherapy study TDE-PH-302 study with 233 subjects had a mean dose of 3.6 mg bid after 12 weeks. In the two studies in which UT-15C was administered in combination with an ERA and/or a PDE5-I (Study TDE-PH-301 and Study TDE-PH-308), the 274 subjects that received UT-15C and completed the 16 week treatment period achieved a mean dose of 3.28 mg bid at Week 16.

Regarding the open label extension study TDE-PH-304 at the time of data cut-off, 824 subjects had received at least one dose of UT-15C. The mean duration of exposure was 73.5 weeks with a maximum duration of 245.3 weeks (nearly five years). The range of doses were between 0.25 and 21 mg bid, with a mean dose of 4.2, 5.0 and 5.3 mg bid achieved at one year (n = 362), two years (n = 222) and three years (n = 152), respectively.

7.2.2 Explorations for Dose Response

The sponsor proposed dosing recommendations are:

Initial starting dose: 0.25 mg twice daily (BID) with food approximately 12 hours apart. Dose should be increased over time based on clinical response. The recommended titration increment is 0.25 mg BID every 3 to 4 days as tolerated. If 0.25 mg dose increments are not tolerated, an increment of 0.125 mg is recommended. In clinical trials, the mean dose at 12 weeks was 3.4 mg BID. Abrupt discontinuation of dosing should be avoided.

There were no formal dose response studies. In the three placebo controlled trials with PAH subjects, investigators increased and decreased the dose of study drug as they deemed necessary based on efficacy and adverse events.

Study TDE-PH-302 required numerous amendments to the protocol in order to find an initial dose that could be tolerated. There are no controlled studies comparing dose and reported adverse event.

Signs and symptoms of intolerance reported by subjects include headache, nausea, vomiting, diarrhea, and hypotension. Most events resolved when the dose was decreased or UT-15C was discontinued.

7.3 Serious safety results

7.3.1 Deaths

There were no deaths reported during the healthy volunteer studies that included 547 volunteers.

In placebo controlled randomized trials there was a marginally higher incidence rate of reported deaths in subjects randomized to UT-15C (4.2%, 24/565) compared to reported deaths in subjects randomized to placebo (3.6%, 16/444).

These deaths seem to be mostly associated with underlying disease. There was one subject (study 302 subject 025201) who died 40 minutes after restarting UT-15C. She had been hospitalized for hypotension, restarted the drug and reported nausea, vomiting and hypotension followed by cardiac arrest and death. It was judged that aspiration contributed to death.

There have been 87 deaths¹ reported (78 during the study and 9 within 30 days of the last dose of UT-15C) in the ongoing, open label extension study TDE-PH-304. The rate of survival has been estimated at 92.6% following one year of treatment with UT-15C.

Clinical Studies in Indications Other than PAH

¹ As of 8-31-2008

There were no deaths reported during the TDE-DU-101² or TDE-DU-201³ studies.

Without long term controlled data, it is not possible to have confidence in the safety of UT-15C use beyond 16 weeks.

7.3.2 Nonfatal Serious Adverse Events

There was only one serious adverse event (esophagitis) reported during the healthy adult volunteer studies.

The table below shows the serious adverse events reported during the controlled clinical trials.

Table 1-22: Serious Adverse Events that occurred in at least three PAH subjects receiving UT-15C (all controlled clinical studies in PAH)

Adverse Event	UT-15C (n=565)	Placebo (n=444)
Right ventricular failure	22 (4%)	7 (2%)
Pulmonary hypertension	6 (1%)	13 (3%)
Pulmonary arterial hypertension	7 (1%)	8 (2%)
Dyspnoea	6 (1%)	6 (1%)
Cardiac failure	5 (<1%)	2 (<1%)
Atrial flutter	3 (<1%)	1 (<1%)
Lower respiratory tract infection	4 (<1%)	1 (<1%)
Syncope	5 (<1%)	5 (<1%)
Renal failure, acute	4 (<1%)	0
Pneumonia	3 (<1%)	8 (2%)

Right heart failure

Right ventricular failure was reported twice as much by the UT-15C group (4%) compared to the placebo group (2%) during the placebo controlled trials. The other events were reported by both groups at a similar rate. In the combination trials, right ventricular failure was reported by 3% of subjects randomized to UT-15C and 1% randomized to placebo (table 1.9.12).

Renal dysfunction

There were 5 (<1%) reports of acute renal failure/renal impairment reported by the UT-15C group compared to no reports by the placebo group in the placebo controlled studies. The five subjects are shown in the table below.

² An Evaluation of the Pharmacokinetics and Safety of Fixed and Escalating Doses of Oral Trepstinil Diethanolamine (UT-15C) Sustained Release Tablets in Patients with Systemic Sclerosis

³ DISTOL-1: Digital Ischemic Lesions in Scleroderma Treated with Oral Trepstinil Diethanolamine: A randomized, doubleblind, placebo-controlled,

Table 1-25: Summary of Treatment-Emergent Serious Adverse Events of Renal Dysfunction in Controlled Clinical Studies in PAH

Study	Subject	SAE Term	Time to event onset (days)	UT-15C Dose	Comment
TDE-PH-301	044101	Renal failure acute	88	0.5 mg BID, continued	Indomethacin, chronic renal failure
			107	1 mg BID, continued	
TDE-PH-301	044102	Renal failure acute	68	2mg BID, stopped temporarily	RHF, diabetes
TDE-PH-301	112104	Renal failure acute	31	5 mg BID, continued	RHF
TDE-PH-302	169201	Renal failure acute	25	2 mg BID, discontinued	RHF, SLE, subject died
TDE-PH-302	178201	Renal impairment	12	continued	RHF, SLE subject died
		Renal impairment	79	5 mg BID	

These cases are complicated by concurrent right heart failure, chronic renal failure, and diabetes.

In the open label trial 304, 40 subjects reported worsening renal function. Events reported by these subjects are shown below.

Table 1-26: Renal Dysfunction Reported as Adverse Events for UT-15C During the Open Label Study in PAH (TDE-PH-304)

	UT-15C N=824
Renal disorder	1 (<1%)
Renal failure	9 (1%)
Renal failure, acute	25 (3%)
Renal failure, chronic	6 (<1%)
Renal impairment	4 (<1%)

Of these events, 19 were reported as serious. These are shown below.

Table 1-27: Summary of Renal Dysfunction Adverse Events for UT-15C During the Open Label Study in PAH (TDE-PH-304)

Subject	Duration of therapy (months)	UT-15C Dose	Comment
025102	26	6 mg BID, continued	RHF, diuretic use
027103	15	14.5 mg BID, discontinued, started on Remodulin	RHF, grossly edematous, ascites
029101	32	13.5 mg BID, continued	Post surgery with chronic renal failure
036801	7	6 mg BID, discontinued	Hypoxemic respiratory failure, pancreatitis
040117	28	6 mg BID, discontinued, died	Chronic RF, worsening PAH, sepsis
040127	0.5	0.5 mg AM, 0.75 mg PM, continued	Volume depletion due to vomiting, diarrhea
046102	25	4 mg BID, continued	Diabetes, Large B-cell lymphoma
046102	60	4.75 mg AM, 5 mg PM	Diabetes, pneumonia, chronic renal failure
112109	11	5.5 mg BID, discontinued	Acute RHF
120102	5	4 mg BID, continued	Acute RHF
005201	15	11 mg AM, 12 mg PM continued	Pneumonia, heart failure, diuresis
009205	11	2 mg BID, continued	Pneumonia, tacrolimus toxicity
036205	33	5.5 mg BID, continued	Volume depletion, diarrhea
046203	26	16 mg BID, discontinued, subject died	Edema refractory to oral diuretics, ibuprofen use, worsening PAH
046205	24	7 mg AM, 7.5 mg PM, continued	Volume depletion, vomiting
046205	36	8 mg AM, 7.5 mg PM, continued	Chronic renal failure, volume depletion, vomiting
069201	4	10 mg BID, discontinued	DVT, gout
127207	9	4 mg AM, 3.5 mg PM, discontinued, subject died	Autopsy evidence of exacerbation of connective tissue disease with obliteration of renal vessels
179208	2	1.75 mg BID, discontinued, subject died	Diarrhea, vomiting, worsening respiratory distress

Most of these events were complicated by volume depletion, right heart failure obliteration of renal vessels, or other serious diseases/conditions.

Vomiting

There were no reports of serious vomiting events. However, subject 131102 study 301 suffered a Mallory Weiss tear following an episode of vomiting and hematemesis five hours after receiving UT-15C 1 mg.

Serious events reported by subjects in controlled trial other than PAH:

- TDE-DU-101 had no serious adverse event report;
- TDE-DU-201 had two reports of pneumothorax compared to none in placebo. The other serious events in this study were reported by less than 2 subjects in the UT-15C group.

Hepatic disorders

There were 2 reports (hepatic ischemia and acute cholecystitis) in the UT-15C group compared to none in the placebo group. Elevated hepatic enzymes reported as a serious event was reported by one subject in the UT-15C group compared to none in the placebo group.

In summary, there is no firm evidence that UT-15C is associated with the occurrence of any serious adverse events with the possible exception of the Mallory Weiss tear. However, there is an increase in the reporting of right heart failure, an event that is expected with PAH. It is unknown if this is a real finding and should be pursued with longer, controlled trials.

7.3.3 Discontinuations for Adverse Events

Healthy Volunteer Studies

In these studies, adverse events that led to dose reduction, discontinuation of study drug, or requiring medical intervention to treat the adverse event included headache, dizziness, nausea, vomiting, decreased white blood cell (WBC) count, chest discomfort and esophagitis. There was one report of hypotension requiring medical attention in TDE-PH-113.

Clinical efficacy trials

The table below shows the number of subjects who discontinued study drug for any reason in one of the three placebo controlled trials.

Number and (percent) discontinued for any reason

Study (#UT-15C/#placebo)	<u>UT-15C</u>	<u>Placebo</u>
301 (174/176)	39 (21)	24 (14)
302 (233/116)	51 (22)	18 (16)
308 (157/153)	<u>25 (16)</u>	<u>15 (10)</u>
Total (564/445)	115 (20)	57 (13)

Nearly twice as many subjects randomized to UT-15C discontinued study drug compared to subjects randomized to placebo. The number of drop outs by reason is shown below for these trials.

Number and (percent) of subjects

	Study 301		Study 302		Study 308	
	UT-15C n=174	Placebo n=176	UT-15C n=233	Placebo n=116	UT-15C n=157	Placebo n=153
Any reason	39 (21)	24 (14)	51 (22)	18 (16)	25 (16)	15 (10)
Adverse	25 (14)	9 (5)	33 (14)	9 (8)	20 (13)	8 (5)

event+						
Clinical worsening	7 (4)	8 (5)	7 (3)	7 (6)	4 (3)	4 (3)
Other	7 (4)	7 (5)	11 (5)	2 (2)	1 (<1)	3 (2)

+includes death

Healthy Volunteer Studies

Other significant adverse events

Other significant adverse events reported during the healthy volunteer studies defined as those adverse events leading to dose reduction, discontinuation of study drug, or requiring medical intervention to treat the adverse event included headache, dizziness, nausea, vomiting, decreased white blood cell count, chest discomfort and esophagitis. There was one report of hypotension with bradycardia requiring medical intervention reported about 5 hours after a single dose of 2.5mg.

Vomiting

Time to vomiting was examined in study TDE-PH-113. Normal volunteer subjects received UT-15C 2.5 mg dose. The time to onset of vomiting ranged from 5 hour to 10 hours with Tmax ranging from 3 to 10 hours.

Controlled PAH trials

Adverse events that that resulted in premature study drug discontinuation during studies 301 and 308 (with background PAH drugs) and 302 (monotherapy) shown below.

Table 1-31: Summary of Adverse Events Resulting in Permanent Study Drug Discontinuation in more than one Subject that Received UT-15C

Adverse Event	Treatment %		
	UT-15C TDE-PH-302 N=233	UT-15C TDE-PH-301 and TDE-PH-308 N=332	Placebo (All Studies) N=444
Headache	7 (3%)	20 (6%)	1 (<1%)
Nausea	6 (3%)	16 (5%)	1 (<1%)
Diarrhoea	4 (2%)	10 (3%)	1 (<1%)
Vomiting	4 (2%)	10 (3%)	1 (<1%)
Worsening pulmonary hypertension/pulmonary hypertension	4 (2%)	7 (2%)	20 (5%)
Pain in extremity	2 (<1%)	6 (2%)	1 (<1%)
Chest discomfort	0	2 (<1%)	0
Myalgia	2 (<1%)	3 (1%)	0
Pain	0	2 (<1%)	1 (<1%)
Dyspnoea	2 (<1%)	3 (1%)	0
Flushing	0	2 (<1%)	0
Pain in jaw	5 (2%)	4 (1%)	0
Right ventricular failure	8 (3%)	2 (<1%)	2 (<1%)
Muscle spasm	1 (<1%)	2 (<1%)	0
Abdominal distension	1 (<1%)	2 (<1%)	0
Dyspepsia	0	2 (<1%)	0
Bone pain	0	2 (<1%)	0
Abdominal pain	3 (1%)	1 (<1%)	2 (<1%)
Cardiac failure	2 (<1%)	1 (<1%)	0
Dizziness	2 (<1%)	0	1 (<1%)

Common adverse events resulting in drug discontinuation included headache, nausea, diarrhea, and vomiting. These adverse events tend to be associated with prostanoid use.

7.3.4 Adverse Events

The table below shows the adverse events reported by at least 10% of subjects who received UT-15C and reported more frequently by them compared to the subjects who received placebo.

Table 1-13: Adverse Events that Occurred in at least 10% of PAH Subjects that Received UT-15C and More Frequent than in Subjects that Received Placebo (studies TDE-PH-301, TDE-PH-302 and TDE-PH-308)

Adverse Event	TDE-PH-302		TDE-PH-301 and TDE-PH-308	
	UT-15C N=233	Placebo N=116	UT-15C N=332	Placebo N=328
Headache	69%	31%	79%	38%
Nausea	39%	22%	56%	27%
Diarrhoea	37%	18%	58%	26%
Vomiting	24%	16%	33%	8%
Flushing	21%	8%	42%	13%
Pain in extremity	19%	8%	24%	9%
Pain in jaw	25%	7%	34%	9%
Dizziness	14%	15%	18%	13%
Fatigue	9%	7%	14%	10%
Myalgia	10%	4%	13%	5%
Dyspnoea	4%	12%	11%	7%

Placebo subtracted incidence rates for the most commonly reported events in the monotherapy trial 302 include headache (38%), nausea (17%), diarrhea (19%), vomiting (8%), flushing (13%), pain in extremity (11%), pain in jaw (18%). These events were not dissimilar to those reported in the studies with background PAH medications (301 and 308).

Adverse events reported in the open label study 304 are shown below.

Table 1-19: Adverse Events occurring in at least 10% of Subjects Receiving UT-15C During the Open Label Study in PAH (TDE-PH-304)

Adverse Event	UT-15C N=824
Headache	72%
Diarrhoea	59%
Nausea	51%
Flushing	39%
Pain in jaw	33%
Vomiting	32%
Pain in extremity	25%
Dizziness	20%
Upper respiratory tract infection	17%
Peripheral oedema	16%
Fatigue	15%
Dyspnoea	15%
Nasopharyngitis	13%
Cough	13%
Pulmonary hypertension	12%
Myalgia	12%
Chest pain	11%
Arthralgia	11%
Abdominal pain	10%
Palpitations	10%

7.3.5 Laboratory Findings

Hematology

All placebo controlled trials

The table below shows the mean change from baseline at endpoint for selected hematology parameters.

Mean change from baseline at endpoint (week 12/16)

	UT-15C	placebo
Erythrocytes (10 ⁶ /uL)	-0.07	0.04
Hematocrit (%)	-0.6	0.6
Hemoglobin (g/dL)	-0.32	0.10

Includes studies 301, 302, 308

Table 1.9.35

Compared to placebo there were decreases in mean change from baseline at endpoint for erythrocytes, hematocrit, and hemoglobin.

There were slightly more increases in shift tables (normal or high at baseline shifting to low or normal at endpoint) in the UT-15C group compared to placebo for erythrocytes, hematocrit, hemoglobin (tables 1.9.36 and 1.9.45).

The table below shows the number of clinically notable hematology parameters reported as adverse events in the placebo controlled trials.

Table 1-36: Clinically Notable Laboratory Hematology Abnormalities Reported as AEs in the Controlled Clinical Studies in PAH

MedDRA Preferred term	UT-15C N=565	Placebo N=444
Haemoglobin increased	1	0
Haemoglobin decreased	2	0
Haematocrit increased	1	0
Haematocrit decreased	2	0
WBC count increased	0	1
WBC count decreased	0	1
Neutrophil count increased	0	1
Platelet function test abnormal	0	1
Platelet count decreased	1	2

There were few of these abnormal reports.

In conclusion, there are signs of a small, subclinical decrease in erythrocytes, hematocrit and hemoglobin in subjects receiving UT-15C.

Chemistry parameters

The mean change from baseline at week 12/16 for potassium in the all placebo controlled trials was lower for the subjects randomized to UT-15C (-0.14 mEq/L) compared to no change in subjects randomized to placebo. (table 1.9.33). This change was not reflected in the shift tables (1.9.34 and 1.9.46) and there was only report of hypokalemia as an adverse event (table 1-39). No other chemistry abnormalities were identified including AST, ALT, bilirubin, serum creatinine.

Urinalysis

There are no large differences between the treatment groups for the presence of blood and/or protein in the urine at week 12/16 in the placebo controlled trials (table 1.9.37).

The table below shows the clinically notable abnormalities reported as adverse events in the controlled studies.

Table 1-40: Clinically Notable Urinalysis Abnormalities Reported as AEs in the Controlled Clinical Studies in PAH

Adverse Event	UT-15C N=565	Placebo N=444
Blood urine present	0	1
Protein urine present	1	0
Proteinuria	4	3
Haematuria	1	2

7.3.6 Vital Signs

Healthy Volunteer Studies

One subject (study TDE-PH-113) received a single dose of UT-15C (2.5 mg) and reported an episode of hypotension that required the administration of IV fluids.

Controlled clinical studies

The is no evidence of clinically relevant chronic effects of UT-15C compared to placebo on blood pressure, heart rate, respiratory rate, temperature, or body weight (table 1.9.39).

The table below displays the serious adverse events suggestive of an adverse effect on blood pressure, by study and treatment group.

The number and (percent) of subjects

	301 [^]		302+		308 [^]	
	UT-15C N=175	Placebo N=175	UT-15C N=233	Placebo N=116	UT-15C N=157	Placebo N=153
syncope	2 (1)	3 (2)	2 (<1)	1 (<)	1 (<1)	2 (1)
hypotension	0	2 (2)	-	-	-	-
presyncope	-	-	1 (<1)	1 (<1)	0	1 (<1)
fall	-	-	-	-	2 (1)	0

[^]table 14.3.1.3

+table 14.3.1.3.2

The reporting of the serious adverse event hypotension or suggestive of hypotension in subjects receiving UT-15C was rare.

Electrocardiograms (ECGs)

See QT review by Dr. Monica Fiszman.

No obvious treatment emergent abnormalities that might suggest an adverse drug effect have been identified with the periodic ECGs.

Dose Dependency for Adverse Events

There are no controlled trials evaluating various doses of UT-15C and reported adverse events.

The initial dose in the efficacy trial TDE-PH-302 was decreased numerous times from 1 mg to 0.125 mg, mainly for such adverse events as headache, nausea and vomiting.

Time Dependency for Adverse Events

Vomiting

Time to vomiting was examined in study TDE-PH-113. Normal volunteer subjects received UT-15C 2.5 mg dose. The time to onset of vomiting ranged from 5 hour to 10 hours with Tmax ranging from 3 to 10 hours.

Drug-Demographic Interactions

The demographic variables examined for this section were age, gender, and race.

Age

There is no evidence that there are differences in type or incidence rates for common adverse events when comparing different age groups (table 1.9.18).

Gender

The table below shows the most commonly reported adverse events by gender in the placebo controlled clinical PAH studies.

Table 1-45: Summary of Adverse Events Occurring in $\geq 10\%$ of Male or Female Subjects in Controlled Clinical Studies in PAH

Adverse Event (Preferred term)	Male		Female	
	UT-15C (n = 126)	Placebo (n = 92)	UT-15C (n = 439)	Placebo (n = 352)
Headache	64%	36%	78%	36%
Diarrhoea	44%	21%	51%	25%
Nausea	30%	24%	54%	26%
Vomiting	17%	4%	33%	12%
Flushing	37%	12%	33%	11%
Pain in jaw	29%	8%	31%	8%
Pain in extremity	21%	1%	22%	10%
Dizziness	14%	10%	17%	14%
Myalgia	8%	2%	13%	5%
Fatigue	9%	10%	13%	9%
Oedema peripheral	10%	9%	8%	7%
Dyspnoea	10%	9%	8%	8%
Nasopharyngitis	11%	9%	6%	11%
Abdominal pain	6%	7%	10%	5%

Overall, there are no obvious clinical differences in type and reporting rate by gender for any of these adverse events.

Race

There is no obvious indication that the incidence rates of adverse event reporting in the controlled clinical studies differ because of the subject's race (table 1.9.19).

Drug-Disease Interactions

The table below shows the most commonly adverse events that were reported more frequently in the UT-15C treatment group according to PAH etiology.

Table 1-46: Summary of Most Common Adverse Events Occurring in $\geq 10\%$ of Subjects by Etiology of PAH in Controlled Clinical Studies in PAH

MedDRA Preferred Term	Idiopathic/Heritable		Collagen Vascular Disease		Other	
	UT-15C (n = 389)	Placebo (n = 305)	UT-15C (n = 142)	Placebo (n = 114)	UT-15C (n = 34)	Placebo (n = 25)
Headache	74%	34%	75%	38%	79%	48%
Dizziness	15%	11%	20%	14%	15%	24%
Diarrhoea	48%	22%	52%	26%	56%	36%
Nausea	47%	26%	56%	23%	41%	40%
Vomiting	28%	10%	32%	9%	29%	20%
Pain in jaw	30%	9%	31%	5%	32%	12%
Pain in extremity	22%	7%	23%	9%	12%	20%
Flushing	35%	12%	31%	10%	24%	8%
Myalgia	9%	4%	17%	7%	15%	0
Arthralgia	6%	3%	11%	5%	15%	8%
Fatigue	11%	8%	15%	13%	6%	12%
Oedema peripheral	8%	6%	11%	11%	0	12%
Dyspnoea	7%	5%	11%	16%	6%	8%
Abdominal pain	9%	6%	7%	6%	15%	0
Chest pain	6%	7%	6%	8%	12%	8%

There is no evidence that adverse events reported during controlled clinical trials were affected by PAH etiology.

Drug-Drug Interactions

Healthy volunteer interaction study with bosentan (Tracleer)

In TDE-PH-105, 24 healthy volunteers were each given the following three treatments following a standardized breakfast and dinner in a randomized sequence: UT-15C SR 1 mg every 12 hours x 4.5 days (A); Tracleer® 125 mg BID x 4.5 days (B); UT-15C SR and Tracleer® x 4.5 days (C). Adverse events occurred more frequently during the combination treatment. The two most frequently reported events in A, B, C were headache (9%, 9%, 50%) and flushing (9%, 0%, 17%), indicating an additive effect of these findings when both agents are given together.

Clinical studies in subjects with PAH

The table below shows the incidence rates for the adverse events that were reported by more than 10% of subjects in the two clinical studies which allowed background PAH therapy.

Table 1-47: Summary of Most Common Adverse Events Occurring in $\geq 10\%$ of Subjects by UT-15C and Background Therapy in Controlled Clinical Studies in PAH

MedDRA Preferred Term	ERA alone %		ERA and PDES-I %		PDES-I alone %		UT-15C mono %	
	UT-15C (n = 81)	Placebo (n = 78)	UT-15C (n = 139)	Placebo (n = 142)	UT-15C (n = 112)	Placebo (n = 108)	UT-15C (n = 233)	Placebo (n = 116)
Headache	77	44	80	35	79	38	69	30
Dizziness	20	22	12	5	24	16	14	14
Diarrhoea	48	31	62	23	61	26	37	18
Nausea	53	33	63	27	48	23	38	22
Vomiting	35	9	35	4	29	13	24	16
Pain in jaw	31	12	41	8	29	6	25	7
Pain in extremity	30	12	24	6	21	9	18	8
Myalgia	16	6	14	4	8	4	10	4
Arthralgia	14	5	9	4	5	4	6	3
Oedema peripheral	12	10	7	8	10	6	8	7
Fatigue	19	5	10	11	17	12	8	7
Flushing	42	18	47	11	35	12	21	8
Dyspnoea	12	9	14	8	6	4	4	12
Upper respiratory tract infection	10	10	9	8	4	9	6	6
Nasopharyngitis	7	15	11	8	6	16	5	6
Abdominal pain	7	5	7	6	4	2	13	8

Most of the adverse events shown above were reported more often by subjects in the combination groups compared to subjects receiving UT-15C alone.

Additional Safety Evaluations

Human Carcinogenicity

There was an agreement between the sponsor and FDA (End of Phase 1 meeting dated 09 November 2005 (b) (4) carcinogenicity program for UT-15C needs to be ongoing at the time of approval of an NDA or MAA. An oral carcinogenicity study in transgenic rasH2 mice was initiated in December 2010, and results will be submitted when available. A dose range-finding study in Sprague Dawley rats has been completed (Study TPU00016), and the oral 2 year UT-15C rat carcinogenicity study protocol was reviewed and accepted by the CAC.

Human Reproduction and Pregnancy Data

Pregnancy was an exclusion criterion for participation in the UT-15C clinical development program.

The sponsor reported (as of 31 August 2011) ten cases of pregnancy during exposure to UT-15C:

- six underwent elective termination,
- one ectopic pregnancy treated surgically,
- one intrauterine fetal death,
- one premature caesarean delivery with infant outcome unknown,
- one caesarean delivery with normal infant.

No neonatal abnormalities were reported.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not evaluated

6.1.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no randomized, controlled trials that were designed to determine, if any, the overdose effect, the drug abuse potential, or the withdrawal/rebound effect of UT-15C.

Overdose

The sponsor discovered three cases coded to the MedDRA High-Level Term overdoseduring a search of the UT-15C safety database (through August 31, 2011). Two cases (UTC-010098 and UTC-005516) involved narcotics overdose. The remaining case (UTC-000577 in study TDE-PH-304) involved the study subject inadvertently increasing her dose from 3 mg twice daily to 5 mg

twice daily. The subject was subsequently hospitalized for diarrhea. Symptoms resolved with therapy and a return to the prescribed UT-15C dosing regimen.

Subject 025201 in TDE-PH-302 reported multiple syncopal episodes while exposed to UT-15C 7 mg BID. Therapy was interrupted for approximately 48 hours then restarted at 6 mg. Forty minutes later, the subject developed nausea, vomiting, and hypotension, went into cardiac arrest and expired after unsuccessful resuscitation. The pathology report stated that the “death was due to a profound episode of vasovagal syncope causing hypotension (acute circulatory failure), probably provoked by the interruption and inappropriate restart of study medication, leading to loss of consciousness, aspiration of stomach content and cardiac arrest. . .”.

Starting dose: study TDE-PH-301 was initiated with a starting dose of 1 mg twice daily. Protocol Amendment 4 lowered the starting dose four fold to 0.5 mg twice daily because of poor tolerability. Subjects who were enrolled when drug initiation was with 1 mg had a higher rate of study drug discontinuation because of adverse events (25%) compared to those subjects starting with 0.5 mg (12%) and 0.25 mg (zero). This is shown in the table below.

Table 1-49: Summary of Discontinuations Due to Adverse Events by Minimum Tablet Strength Available in Study TDE-PH-301

Minimum Tablet Strength Available	AE Discontinuation UT-15C n (%)
Overall (n = 174)	25 (14%)
1 mg (n = 51)	13 (25%)
0.5 mg (n = 100)	12 (12%)
0.25 mg (n = 23)	0

The adverse events associated with high doses of UT-15C include headache, nausea, diarrhea, vomiting, hypotension, dizziness and syncope.

Drug Abuse

There is no known abuse potential for UT-15C, which is neither structurally nor pharmacologically related to other drugs with established abuse potential. The sponsor searched the UT-15C safety database cumulatively through August 31, 2011 for cases captured by the Structured MedDRA Query (SMQ) ‘Drug abuse, dependence and withdrawal’. The search found no cases of drug abuse.

Withdrawal and Rebound

Label for Remodulin® states:

Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided. (b) (4)

The sponsor searched the UT-15C safety database cumulatively through August 31, 2011 and found two cases (UTC-000499 and UTC-002380) that reported exacerbation of symptoms of pulmonary hypertension following abrupt discontinuation of study drug and rebound pulmonary hypertension following general anesthetic, respectively. There is scant evidence of a rebound effect when UT-15C is discontinued.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

While the effects of UT-15C on the ability to drive or operate machinery have not been studied, somnolence, dizziness and vasovagal syncope have been reported as adverse events.

8 Postmarket Experience

UT-15C has not received marketing authorization. There are no post-marketing data for UT-15C.

9 Appendices

Attached

9.1 Literature Review/References

Publications were submitted. They were noncontributory to this review.

9.2 Labeling Recommendations

The NDA is not approvable so here are no labeling recommendations

9.3 Advisory Committee Meeting

Not planned.

Appendix 1

United Therapeutics Corp.

ATTACHMENT TO FORM FDA 3455

NDA 203496

(b) (4)
 (treprostinil diethanolamine) Sustained Release Tablet

Investigators with Financial Interests to Disclose

Studies TDE-PH-301, TDE-PH-302, and TDE-PH-308

Site Number	Investigator	Address	Significant Payments of Other Sorts During These Studies	Comments
002	Robyn J. Barst	Columbia Presbyterian Medical Center New York, NY United States	301, 302	The Significant Payments of Other Sorts made to these investigators were for consulting and ongoing research. These were multi-center studies conducted worldwide. The Significant Payments of Other Sorts made to these investigators did not influence the results of these studies.
010	Robert Bourge	University of Alabama-Birmingham Birmingham, AL United States	301, 302, 308	
036	Roblee Allen	UC Davis Medical Center Sacramento, CA United States	301, 302, 308	
040	Martha Kingman	UT Southwestern Medical Center Dallas, TX United States	301, 302, 308	
041	Jeremy Feldman	Arizona Pulmonary Specialist Phoenix, AZ United States	308	
046	James White	Mary M Parkes Center for Asthma, Allergy and Pulmonary Care Rochester, NY United States	301, 302, 308	
067	Sean Studer	Newark Beth Israel Medical Center Newark, NJ United States	308	

Appendix 2

Study Number: TDE-PH-301

Medical Reviewer's conclusions: This study was designed to evaluate the safety and efficacy of UT-15C administered over 16 weeks to subjects with PAH who were receiving stable background therapy including an ERA and/or a PDE5-I. The dose of study drug was to be titrated until the "optimal" dose was achieved.

The primary endpoint of change in 6MWD at Week 16 trended but did not achieve statistical significance.

There were numerous study subjects randomized to UT-15C who discontinued prematurely, primarily because of study drug intolerability. There were numerous adverse events that were reported significantly more often in the UT-15C group compared to placebo.

Overall, in this study there was a statistically insignificant treatment effect and the drug was found to be difficult for patients to tolerate. In addition, there was no attempt to determine if UT-15C has a dose response.

Title: A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Combination with an Endothelin Receptor Antagonist and/or a Phosphodiesterase-5 Inhibitor in Subjects with Pulmonary Arterial Hypertension

Study Initiation Date: 20 October 2006 (First Subject Enrolled)

Study Completion Date: 17 September 2008 (Last Subject Completed)

Objectives: The primary objective of this study was to assess the effect of treprostiniol diethanolamine sustained release (SR) tablets on exercise capacity compared to placebo (as measured by the change in 6-minute-walk distance (6MWD) from Baseline to Week 16) in subjects with pulmonary arterial hypertension (PAH).

Secondary objectives included evaluation of the effects of UT-15C SR on the following:

- ~ Combined Walk Distance/Borg Dyspnea Score
- ~ Clinical Worsening (defined as:
 1. Death (all causes excluding accident)
 2. Transplantation or atrial septostomy
 3. Clinical deterioration as defined by:
 - a. Hospitalization as a result of PAH, or
 - b. $\geq 20\%$ decrease in 6MWD from Baseline (or too ill to walk) and a decrease in WHO functional class,
and
 - c. Initiation of new PAH specific therapy [(i.e., endothelin receptor antagonist

(ERA), phosphodiesterase-5 inhibitor (PDE5-I), prostacyclin]

- ~ Borg Dyspnea Score
- ~ Dyspnea-Fatigue Index
- ~ World Health Organization (WHO) Functional Class
- ~ Symptoms of PAH
- ~ Safety (adverse events (AEs), clinical laboratory parameters, electrocardiogram (ECG) findings)

Study procedures

This was an international, multi-center, randomized, double-blind, placebo-controlled, parallel group 16-week study in subjects with PAH currently receiving approved oral therapy for the treatment of PAH including an ERA and/or a PDE5-I. Subjects were required to have a Baseline 6MWD of 100-450 meters for inclusion in the study.

After qualifying for study entry, subjects were randomized into the 16-week treatment phase of the study. Subjects were assessed at five clinic visits including Baseline, Week 4, Week 8, Week 12 and Week 16. Subjects initiated treatment with UT-15C SR or placebo in the clinic following randomization and consumption of a 500 calorie meal as required per the protocol. Between visits, subjects were contacted weekly via the telephone to assess AEs, changes in concomitant medications and to make decisions regarding dose titration.

At scheduled clinic visits, subjects were assessed for 6MWD, Borg dyspnea score, WHO functional classification, clinical worsening, signs and symptoms of PAH and the dyspnea-fatigue index.

Safety evaluations included assessment of adverse events throughout the study, ECGs and physical examinations at Baseline and Week 16 and laboratory samples for determination of hematology, chemistry and urinalysis at Baseline, Week 8 and Week 16. Vital signs were also measured at each clinic visit.

Following completion of all study assessments, eligible subjects were able to enter the open-label extension study (TDE-PH-304).

Dosing

Trepstinil diethanolamine tablets are sustained release osmotic tablets designed for release of UT-15C over approximately 12-hours. Initially UT-15C SR tablets were provided as 1 mg and 5 mg strengths for the 16-week Treatment Phase. Subsequently, Amendments 3 and 4 introduced the 0.5 mg and 0.25 mg tablets, respectively. Amendment 4 lowered the starting dose to 0.5 mg and removed the 5 mg tablet strength.

Subjects were randomized 1:1 to receive either UT-15C SR or matching placebo. Titration to the individual subject's optimal dose was conducted in a blinded fashion.

Once all entry criteria were met and random treatment assignment confirmed, the first dose of study drug (1 mg prior to Amendment 4 or 0.5 mg following Amendment 4) was taken by the subject immediately following a meal while at the study site. The subject remained close to the study site for approximately two to six hours for periodic observation and monitoring of possible adverse events. The second dose of study drug was taken the next morning.

At that time, oral dosing of study drug was continued twice daily (every 12 hours +/- 1 hour) immediately following (~10 minutes) breakfast and dinner. Subjects were instructed to take the appropriate amount of 0.25 mg, 0.5 mg, 1 mg and/or 5 mg tablets based upon their prescribed dose. In general, the dose of study drug could be increased in 1 mg increments every 5 days prior to Amendment 4 or 0.5 mg increments every three days after implementation of Amendment 4, in the absence of dose-limiting drug-related adverse events, to ensure the subject received the optimal clinical dose throughout the study. The 0.25 mg strength could be used throughout the 16-week Treatment Phase if a 0.5 mg dose increase was not tolerated and an intermediate dose was required.

The maximum allowable dose of study drug during the 16-week Treatment Phase was 16 mg twice daily. Subjects could not increase their dosing regimen by greater than 0.5 mg at a time and no sooner than every three days. No dose adjustments could be made within 5 days of the Week 16 visit.

Number of Subjects (planned and analyzed): Approximately 300 subjects (randomized 1:1 active:placebo) were planned. A total of 354 subjects were randomized with 350 subjects receiving a dose of study drug and subsequently analyzed.

Diagnosis and Main Criteria for Inclusion:

A subject was eligible to participate in this study if all of the following criteria were met:

1. The subject was between the ages of 12 and 65 years of age at Screening. Protocol Amendment 3 increased the upper age limit from 65 to 70 years.
2. The subject weighed a minimum of 45 kilograms at Screening.
3. The subject, if female, was physiologically incapable of childbearing or practicing an acceptable method of birth control as deemed appropriate by the physician or institution. For women of childbearing potential, a negative serum pregnancy test was required at Screening.
4. The subject had a diagnosis of symptomatic idiopathic or familial PAH (including PAH associated with appetite suppressant/toxin use), PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired \geq 5 years), PAH associated with collagen vascular disease or PAH associated with HIV infection.
5. The subject, if HIV positive, had a CD4 lymphocyte count \geq 200 within 30 days of Baseline and was receiving current standard of care anti-retroviral or other effective medication for treatment of HIV.

6. The subject had a Baseline 6-minute walk distance was between 100 and 400 meters, inclusive. Protocol Amendment 3 changed the Baseline 6-minute walk distance requirement to 150-450 meters.

7. The subject may have benefited from the introduction of additional therapy (i.e., a prostacyclin) as determined by their medical provider.

8. The subject must have been optimally treated with approved oral therapies.

Specifically, the subject:

a. Had been receiving approved PDE5-I or approved ERA therapy alone for at least 90 days and at the current stable dose for 30 days prior to Baseline and was willing to remain on PDE5-I or ERA alone and at the same dose for the duration of the 16-week Treatment Phase

or

b. Had been receiving the combination of approved PDE5-I and approved ERA therapy for at least 90

days prior to Baseline with both treatments at the current stable dose at least 30 days prior to Baseline and was willing to remain on the combination of PDE5-I and ERA at the same dose for the duration of the 16-week Treatment Phase.

9. The subject was optimally treated with conventional pulmonary hypertension therapy (anticoagulant, diuretic, oxygen, digoxin, etc) using the same regimen for at least 30 days prior to Baseline.

10. The subject had previously undergone a cardiac catheterization and been documented to have a mean pulmonary artery pressure (PAPm) > 25 mmHg, a pulmonary capillary wedge pressure (PCWP) or a left ventricular end diastolic pressure (LVEDP) < 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units and absence of unrepaired congenital heart disease.

11. The subject had previously undergone echocardiography with evidence of normal left systolic and diastolic ventricular function and absence of any clinically significant left sided heart disease (i.e., mitral valve stenosis).

12. The subject had a previous chest radiograph, ventilation perfusion scan, high resolution computerized tomography scan or pulmonary angiography that were consistent with the diagnosis of PAH (i.e., low probability of pulmonary embolism; absence of major perfusion defects).

13. In the opinion of the principal investigator, the subject was able to communicate effectively with study personnel and was considered reliable, willing and likely to be cooperative with protocol requirements.

14. The subject voluntarily gave informed consent to participate in the study

Exclusions

A subject was not eligible to participate in this study if any of the following criteria were met:

1. The subject was pregnant or lactating.

2. The subject had received epoprostenol, trepstinil, iloprost, beraprost or any other prostacyclin therapy within 30 days of Baseline (except if used during acute vasoreactivity testing).

3. The subject had a new type of chronic therapy (including but not limited to oxygen, a different category of vasodilator, diuretic, digoxin) for pulmonary hypertension added within 30 days of Baseline.
4. The subject had any PAH medication except for anticoagulants discontinued within 30 days of Baseline.
5. The subject had any disease associated with pulmonary arterial hypertension other than collagen vascular disease, HIV infection or repaired congenital systemic-to-pulmonary shunts (repaired \geq 5 years) (i.e., portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, etc.) or had an atrial septostomy.
6. The subject had a current diagnosis of uncontrolled sleep apnea as defined by their physician.
7. The subject had chronic renal insufficiency as defined by either a Screening creatinine value greater than 2.5 mg/dL (221 μ mol/L) or the requirement for dialysis.
8. The subject had anemia as defined by a Screening hemoglobin value of less than 10 g/dL.
9. The subject had a history or current evidence of left-sided heart disease including previous myocardial infarction or evidence of current left-sided heart disease as defined by PCWPM or LVEDP $>$ 15 mmHg or left ventricular ejection fraction (LVEF) $<$ 40% as assessed by either multigated angiogram (MUGA), angiography or echocardiography or left ventricular (LV) shortening fraction $<$ 22% as assessed by echocardiography or symptomatic coronary artery disease (i.e., demonstratable ischemia either at rest or during exercise).
10. The subject had significant parenchymal lung disease as evidenced by pulmonary function tests done within 6 months of Baseline as defined by any one of the following:
 - a. Total lung capacity $<$ 60% (predicted), or
 - b. If total lung capacity was between 60% and 70% of predicted, a high resolution CT scan must have been performed to document diffuse interstitial fibrosis or alveolitis, or
 - c. Forced expiratory volume/forced vital capacity (FEV/FVC) ratio $<$ 50%
11. The subject had uncontrolled systemic hypertension as evidenced by systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.
12. The subject had a musculoskeletal disorder (i.e., hip replacement, artificial leg, etc.) or any other disease that was likely to limit ambulation, or was connected to a machine that was not portable.
13. The subject had an unstable psychiatric condition or was mentally incapable of understanding the objectives, nature, or consequences of the trial, or had any condition which in the investigator's opinion would constitute an unacceptable risk to the subject's safety.
14. The subject was receiving an investigational drug, or had an investigational device in place (except a Chronicle® device if in place and without complications for 30 days prior to Screening), or had participated in an investigational drug or device study within 30 days prior to Screening.

Efficacy Assessments

Six-Minute Walk Test

The 6-minute walk test was conducted at Screening (optional; served as a practice test if the subject had not previously performed the 6-minute walk test), Baseline prior to starting study drug but at least 6 hours after the practice test and during the Treatment Phase at Weeks 4, 8, 12 and 16. During these visits, the 6-minute walk test was administered two to five hours after the subject's morning dose of study drug and appropriate background therapy(ies). With the implementation of Amendment 4, the 6-minute walk test was administered three to six hours after the morning dose of study drug to correlate with the peak concentration of UT- 15C.

Statistical Methods:

Using an allocation ratio of 1:1 between UT-15C SR and placebo, a fixed sample size of approximately 278 subjects was needed to provide at least 90% power at a significance level of 0.01 (two-sided hypothesis) to detect a 35 meter between-treatment difference in the change from Baseline in distance traversed during the 6- Minute Walk, assuming a standard deviation of 75 meters. Missing Week 16 6MWD values were imputed according to the statistical analysis plan.

RESULTS

Disposition of subjects

There were 354 subjects enrolled with 350 subjects (174 active and 176 placebo). Three subjects (112110, 124102 and 136104) randomized to the active group and one subject (006106) randomized to the placebo group subjects did not receive a dose of study drug. Three subjects (023101, 041101 and 041102) were enrolled but were not included in the analysis population because they were withdrawn from the study following a temporary drug recall (UT-15C 1 mg tablets) in June 2006. The table below shows the number of subjects who completed the study and those who discontinued prematurely, by reason.

Table 10-1 Disposition of Study Subjects

Study Disposition	Treatment n (%)	
	Oral Treprostinil n = 174	Placebo n = 176
Completed Study	153 (88)	167 (95)
Discontinued Study Prematurely	21 (12)	9 (5)
Consent Withdrawn	13 (7)	3 (2)
Death	3 (2)	2 (1)
Lost to Follow-up	2 (1)	1 (<1)
Other	2 (1)	3 (2)
Protocol Violation	1 (<1)	0 (0)

More than twice as many subjects randomized to treprostinil (21, 12%) prematurely discontinued study drug compared to those randomized to placebo (9, 5%). The primary reason for discontinuation was consent withdrawn (three times more in the treprostinil group compared to placebo group). The consent withdrawn category is usually a withdrawn because of an adverse event.

Demographics

The demographics of the subjects are shown below by treatment group.

Table 11-1 Summary of Baseline Demographics

Characteristic	Active (n=174)	Placebo (n=176)
Age in Years: mean (range)	51.1 (17-75)	49.5 (15-71)
Gender: Male/Female (n)	26/148	36/140
Race: n (%)		
Caucasian	159 (91)	155 (88)
African American	8 (5)	12 (7)
Asian	6 (3)	8 (5)
Native American	3 (2)	2 (1)
PAH Etiology: n (%)		
IPAH/FPAH	113 (65)	119 (68)
CVD	49 (28)	43 (24)
Repaired CHD	11 (6)	11 (6)
HIV	1 (<1)	3 (2)
Background PAH Therapy: n (%)		
ERA	55 (32)	51 (29)
PDE5-I	45 (26)	43 (24)
Both	74 (43)	82 (47)
Baseline WHO Functional Class: II/III (n)	41/127	31/139
Baseline 6MWD: Mean ± SD (m)	346.1 ± 71.4	345.4 ± 75.5

Subjects were around 50 years of age (range 15-75 years), most were white (90%) and female (82%). The majority (66%) was diagnosed with idiopathic or familial PAH, 26% were diagnosed with PAH related to collagen vascular disease, 6% had PAH related to a repaired congenital heart defect and 1% subjects had PAH related to HIV infection.

Background PAH therapy included an ERA alone (30%), PDE5-I alone (25%), or both (45%). Most subjects (76%) were WHO functional class III and mean baseline 6MWD was 346 meters.

The demographics of the two treatment groups were reasonably well balance at baseline.

Efficacy Results

The table below shows how missing data or subject droupouts were imputed for missing 6MWD for the primary endpoint.

Table 11-18 Handling of Dropouts or Missing Data

Event	Value Used	
	Nonparametric Analysis	Parametric Analysis
Death within 16 weeks (excluding accidents); regardless of reason for study drug termination	Lowest rank	Value corresponding to overall poorest relative change ^a
Premature Termination of Study Drug:		
Clinical deterioration	Lowest rank	Value corresponding to overall poorest relative change ^a
Transplantation or atrial septostomy	Lowest rank	Value corresponding to overall poorest relative change ^a
Accident or AE unrelated to disease	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward
Lost to follow-up	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward
Protocol violation	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward
Consent withdrawn	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward
Missing Data for Subjects Still Receiving Study Drug:		
Too clinically ill to perform 6-minute walk test	Lowest rank	Value corresponding to overall poorest change ^a
Data missing for any other reason	Last rank obtained prior to assessment carried forward	Last rank obtained prior to assessment carried forward

^aTo impute a value corresponding to the poorest change:

$$\text{Value}_i = \text{Baseline}_i \times \min_j[\text{Value}_j/\text{Baseline}_j] \quad (\text{for all non-missing values } j \text{ for the visit})$$

The primary measure of efficacy was the effect of treprostinil, compared to placebo, on exercise capacity as measured by the change in 6MWD from Baseline at Week 16 (at peak effect⁴).

The treatment effect was determined using the Hodges-Lehman method to estimate the median difference between treatment groups in the change in 6MWD from Baseline.

Table 11-4 Summary of Hodges-Lehmann Estimate of Treatment Effect

Time Period	Median 6MWD (meters)		Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
	Active n = 174	Placebo n = 176		
Baseline	363	363	-	-
Week 4	371	363	4 (-2.4, 12)	0.238
Week 8	379	369	9 (0, 18)	0.051
Week 12	378	366	13 (3, 23)	0.015*
Week 16	381	367	11 (0, 22)	0.072

* Statistically significant

⁴ The 6MWD was assessed between 2 and 6 hours after the morning dose of study drug and background therapy(ies).

The treatment effect ranged from 4 m (week 4) to 13 m (week 12). The primary efficacy endpoint of change in 6MWD from Baseline to Week 16 between treatment groups was 11 meters which failed to meet statistical significance (Hodges-Lehmann; $p = 0.072$).

Dosing

The table below shows the H-L estimate of median treatment effect at Week 16 by lowest dosing strength available at randomization.

Table 11-11 Hodges-Lehmann Median Placebo Corrected Change in Peak 6MWD at Week 16 from Baseline by Lowest Dose Strength Available at Randomization

Smallest Dose Strength Available (mg)	Number of Subjects n active/n placebo	Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
0.25	23/26	29.5 (1, 73)	0.085
0.5	100/99	7 (-7, 21)	0.327
1	51/51	5 (-16, 28)	0.853

Subjects taking the 0.25 mg dose walked further (placebo corrected change in 6MWD of 29.5 m) compared to subjects taking 0.5 mg (7 m) and 1 mg (5 mg). According to this study, the higher the dose of UT-15C the smaller the treatment effect.

Background therapy

Background PAH therapy and walk distance at week 16 is shown below.

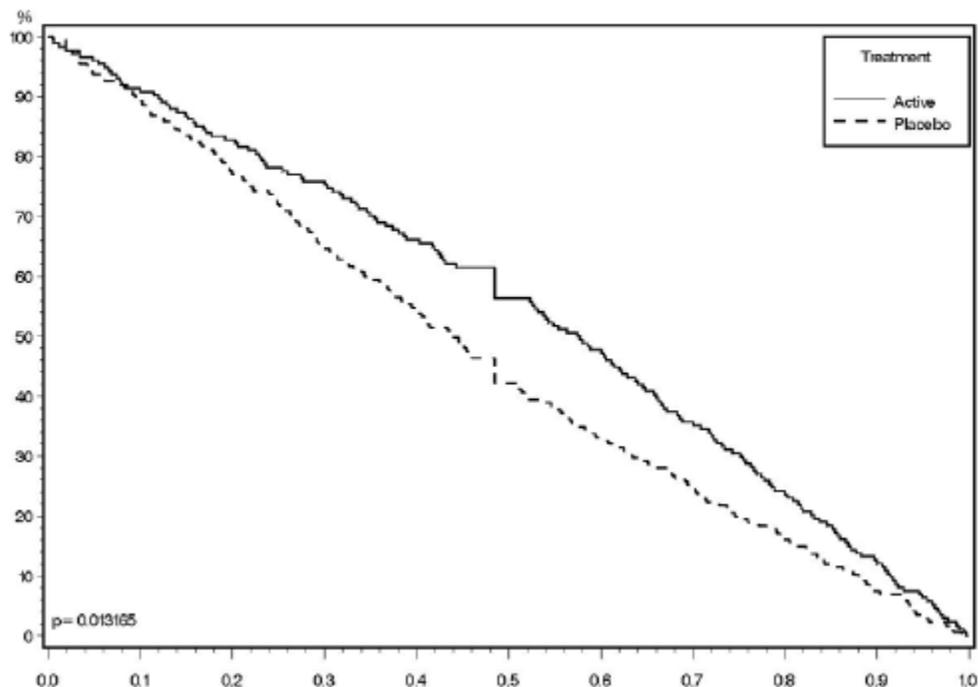
Table 11-12 Hodges-Lehmann Median Placebo Corrected Change in Peak 6MWD at Week 16 from Baseline by Background PAH Therapy

Background PAH Therapy	Number of Subjects n active/n placebo	Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
ERA	55/51	5 (-12, 24)	0.615
PDE5-I	45/43	17 (-6, 40)	0.230
ERA and PDE5-I	74/82	10 (-6, 28)	0.209

The change in walk distance ranged from 5 m (ERA as background therapy) to 17 m (PDE5-I as background therapy).

Secondary endpoints at Week 16 included combined 6-minute walk distance and Borg dyspnea score ($p = 0.013$).

Figure 11-1 Combined Six-Minute Walk Distance and Borg Dyspnea Score

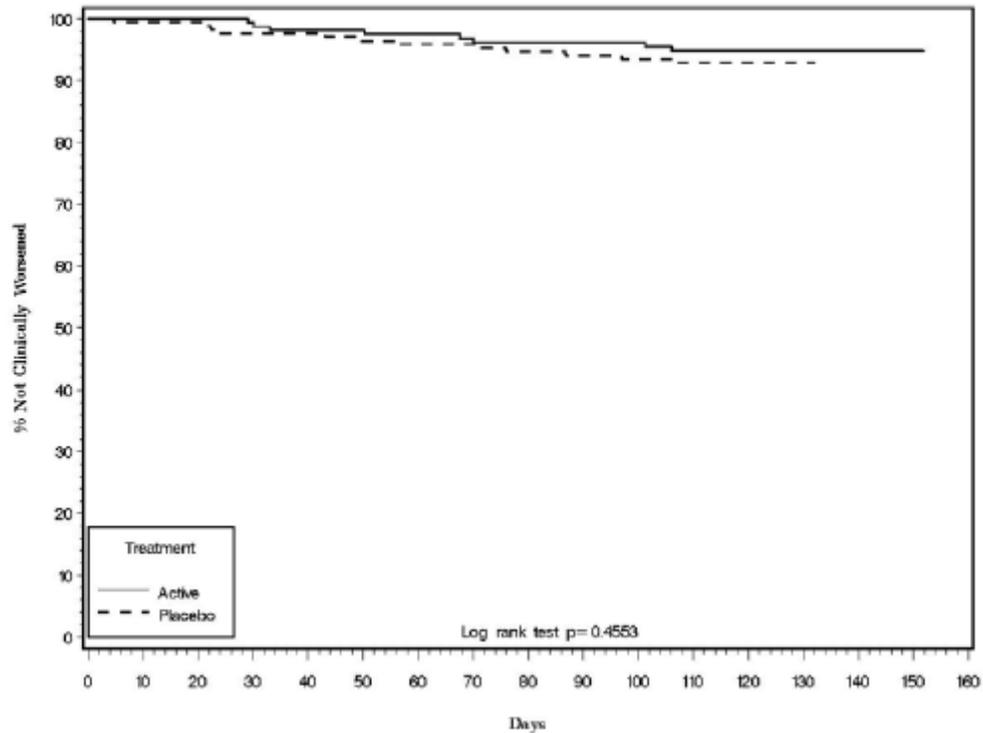


The time to clinical worsening is shown below. There was no difference between UT-15C and placebo ($p = 0.455$).

Table 11-13 Summary of Clinical Worsening

Category	Clinical Worsening n (%)	
	Active n = 174	Placebo n = 176
No Clinical Worsening	166 (95)	164 (93)
Clinical Worsening	8 (5)	12 (7)
Death	0 (0)	1 (<1)
Transplantation or atrial Septostomy	1 (<1)	1 (<1)
PAH Hospitalization	5 (3)	8 (5)
Twenty Percent Decrease in 6MWD and Decrease in WHO Functional Class	2 (1)	2 (1)

Figure 11-2 Time to Clinical Worsening



Most subjects were WHO functional class III at baseline. There were few changes in class by week 16.

Table 11-15 Summary World Health Organization Functional Class by Treatment Group

WHO Functional Classification	Treatment (n Baseline/ n Week 16)	
	Active n = 174	Placebo n = 176
I	2/2	1/1
II	41/58	31/48
III	127/103	139/114
IV	4/11	5/13

Borg dyspnea score, shown below changed little by week 16 in the UT-15C group.

Table 11-14 Mean Borg Dyspnea Scores

Time Period	Mean Score	
	Active n = 174	Placebo n = 176
Baseline	4.2	4.3
Week 4	4.1	4.4
Week 8	4.3	4.5
Week 12	4.1	4.6
Week 16	4.2	4.6

The mean dyspnea-fatigue score, shown below, changed little in the UT-15C.

Table 11-16 Mean Dyspnea-Fatigue Index Scores

Time Period	Mean Score	
	Active n = 174	Placebo n = 176
Baseline	5.7	5.5
Week 4	5.7	5.5
Week 8	5.7	5.5
Week 12	5.6	5.3
Week 16	5.7	5.1

In conclusion, there is little evidence of a treatment effect with treprostinil in subjects who are taking background PAH drugs.

Safety

Dosing instructions:

The study was initiated with subjects administered a 1 mg twice daily starting dose with dose increases in 1 mg increments. A 5 mg tablet strength was available at study start; however, Protocol Amendment 4 removed this tablet strength. Additional tablet strengths of 0.5 and 0.25 mg were made available to subjects at sequentially during the study.

The final dosing instructions for subjects required that study drug be initiated at 0.5 mg twice daily with dose escalation of an additional 0.5 mg twice daily every three days if clinically indicated based upon adverse events and symptoms of PAH. Doses were maximized throughout the Treatment Phase up to a maximum dose of 16 mg BID at the end of 16-weeks. The 0.25 mg strength, if available, was used throughout the 16-week

Treatment Phase if a 0.5 mg dose increase was not tolerated and an intermediate dose was required. Study drug was to be administered with the morning and evening doses of background therapy immediately following breakfast and dinner.

The table below shows the mean dose of study drug at each clinic visit.

Table 12-1 Mean Study Drug Dose at Each Scheduled Visit

Study Visit (n = Active /Placebo)	Study Drug Dose Achieved Mean Dose ± SD (mg)	
	Active	Placebo
Week 4 (n = 166/170)	2.6 ± 1.7	5.0 ± 2.5
Week 8 (n = 156/163)	3.2 ± 2.3	7.9 ± 4.0
Week 12 (n = 147/158)	3.5 ± 2.8	10.3 ± 5.0
Week 16 (n = 140/154)	3.5 ± 2.9	11.0 ± 5.3

The mean dose ± SD of UT-15C achieved during the study at Week 16 was 3.5 ± 2.9 mg (range of 0.25 – 16 mg) twice daily as compared to 11.0 ± 5.3 (range of 0.5 – 23 mg) in the placebo group. This indicates that subjects found UT-15C difficult to tolerate.

The table below shows the maximum dose achieved among study completers.

Table 12-3 Maximum Dose Achieved Among Study Completers

Maximum Dose Achieved by Week 16 (mg)	Subjects Completing Study n (%)	
	Active n = 140	Placebo n = 154
> 0 - 1	34 (24)	6 (4)
>1 - 2	20 (14)	0
>2-4	54 (39)	20 (13)
>4-6	12 (9)	18 (12)
>6-8	12 (9)	9 (6)
>8-10	3 (2)	8 (5)
>10	5 (4)	93 (60)

Subjects randomized to placebo were able to tolerate “higher” placebo doses compared to subjects randomized to UT-15C. Doses of UT-15C greater than 4 mg were uncommon, i.e., were hard to tolerate, in the subjects randomized to UT-15C.

The table below shows the maximum dose achieved grouped by treatment and background PAH therapy (includes only study completers).

Table 12-4 Mean Week 16 Dose by Background Therapy for Study Completers

Background Therapy (n = Active /Placebo)	Week 16 Study Drug Dose Achieved Mean Dose ± SD (mg)	
	Active	Placebo
Total (n = 140/154)	3.5 ± 2.9	11.0 ± 5.3
ERA (n = 42/ 5)	3.6 ± 2.5	10.1 ± 5.2
PDE5-I (n = 36/39)	3.8 ± 3.9	10.6 ± 5.2
Both (n = 62/70)	3.2 ± 2.5	11.8 ± 5.3

Tolerability of UT-15C (or lack of it) was independent of concomitant PAH therapy.

Duration of treatment:

Subjects received UT-15C for a mean ± SD of 100 ± 32 days (range of 2 – 152 days) compared to placebo subjects who received study drug longer (mean of 104 ± 26 days and range of 1 – 132 days).

Serious safety

Deaths

There were 5 reported deaths (3 randomized to UT-15C and 2 randomized to placebo. An additional death (placebo) was reported 2 months after the subject was discontinued from study.

Deaths of subjects randomized to UT-15C

Subject 011101 was a 60 year old female who reported a history of pulmonary hypertension (listed for lung transplantation), chronic obstructive pulmonary disease, coronary artery disease, four vessel coronary artery bypass surgery, congestive heart failure, breast cancer with left mastectomy, type-II diabetes mellitus, acute respiratory distress syndrome, psoriasis, hyperlipidemia, lacunar cerebral infarct and depression.

She suffered an episode of syncope about one month after start of UT-15C 5mg bid. Upon exam, she was found to be anemic, with low magnesium, had some right and left sided heart failure requiring diuresis, and low oxygen saturation. Dose of study drug was lowered to 4 mg bid. One month later she had a repeat episode of syncope. She was found to have **severe carotid stenosis**. Her dose of sildenafil was decreased to 10 mg tid.

Approximately 5 days before she died, she was hospitalized because of a **syncopal episode**. She had another event while hospitalized and became unresponsive. She was weaned from the ventilator and died about 4 months after start of study drug. The investigator considered the syncopal episodes “not in proportion to [her degree of] pulmonary hypertension.”

Subject 112102 was a 50 year old female with a history of CREST syndrome, scleroderma esophagitis, pulmonary fibrosis, gastro-esophageal reflux, right heart failure and atrial septostomy. Concomitant PAH medications included bosentan and sildenafil. And she was titrated up to a total daily dose of 3 mg UT-15C. The subject was hospitalized 4 days after start of study drug because of worsening pulmonary hypertension. Her medication was down titrated to a final dose of 1 mg prior to discontinuation about 1 month after starting drug. Three days later she reported “a secondary event of hyperparathyroidism due to intravenous Zometa for the treatment of osteoporosis.” Approximately 2 weeks later she suffered a **respiratory arrest** while in transit to a local hospital and died.

Subject 145102 was a 22 year old female with unknown medical history. Concomitant medications included sildenafil and Coumadin. She started study medication 0.5 mg once daily. Approximately 2 months later, the subject was hospitalized for vomiting and nausea. An echocardiogram revealed severe right ventricular dysfunction. After a right heart catheterization showing low cardiac output, she had severe hypotension, and reported an inguinal hematoma and a large drop in hemoglobin. Three days later she developed elevated liver enzymes, with a peak GOT of 462 and peak GPT of 595. Liver enzymes returned to normal after 4 days. Approximately two weeks after hospitalization she was started on epoprostenol therapy with mild clinical improvement. The next day she became severely **hypotensive with respiratory failure and cardiac arrest** and died a short time later.

Deaths of subjects randomized to placebo

Subject 004107 was a 50 year old female with a medical history that included atrial septal defect repair, sick sinus syndrome, supraventricular tachycardia, syncope and pacemaker insertion. The subject's concomitant medications included bosentan, sildenafil, warfarin, digoxin, diltiazem, furosemide, metolazone, spironolactone, potassium chloride, seretide and salbutamol. One day after starting study drug, the subject was hospitalized for worsening pulmonary arterial hypertension, syncope and increasing right heart failure. She was treated with diuresis and rest. She died 3 days later.

Subject 014103 was a 54 year old female who had suffered a fall and was found to have bilateral subdural hematomas which led to her death. Concomitant medications included coumadin. She had been taking placebo for about 4 months.

Adverse events leading to discontinuation

There were more subjects randomized to UT-15C who dropped out because of an adverse event (18%, 31/174) compared to placebo subjects (11%, 19/176).

Table 12-10 Summary of Adverse Events Resulting in Permanent Study Drug Discontinuation in > 1 Active Subject

Adverse Event	Treatment n (%)	
	Active n = 174	Placebo n = 176
Any event	31 (18%)	19 (11%)
Headache	12 (7%)	0*
Nausea	11 (6%)	1 (<1%)*
Diarrhea	7 (4%)	1 (<1%)*
Vomiting	7 (4%)	1 (<1%)*
Worsening pulmonary hypertension	6 (3%)	8 (5%)
Extremity pain	4 (2%)	1 (<1%)
Chest discomfort	3 (2%)	0
Myalgia	3 (2%)	0
Pain	2 (1%)	1 (<1%)
Dyspnea	2 (1%)	0 (<1%)
Flushing	2 (1%)	0

* p<0.05

The subjects in UT-15C dropped out more often than their placebo counterparts because of headache, nausea, diarrhea, and vomiting (all statistically significantly worse than placebo). The drop out rates for events including extremity pain, chest discomfort and myalgia were greater in the UT-15C group compared to placebo.

There is probably a dose related component to the adverse events. The table below shows study drug discontinuation in relation to the availability of the 0.25, 0.5 and 1 mg tablet strengths.

Table 12-11 Summary of Discontinuations Due to Adverse Events by Minimum Tablet Strength Available

Minimum Tablet Strength Available	AE Discontinuation UT-15C SR n (%)
Overall (n = 174)	25 (14%)
1 mg (n = 51)	13 (25%)
0.5 mg (n = 100)	12 (12%)
0.25 mg (n = 23)	0

Compared to the 0.25 mg starting dose that had no discontinuations because of adverse event, 25% and 12% of subjects who had started with the 1 mg or 0.5 mg strength discontinued study drug because of adverse events, respectively.

Serious adverse events

The serious adverse events reported by at least one subject randomized to UT-15C are shown below by treatment group.

Table 12-9 Serious Adverse Events Occurring in at Least 1 Active Subject

Adverse Event	Treatment n (%)	
	Active n = 174	Placebo n = 176
Any event	32 (18%)	33 (19%)
Worsening pulmonary hypertension	9 (5%)	8 (5%)
Right ventricular failure	6 (3%)	2 (1%)
Acute renal failure	3 (2%)	0
Syncope	2 (1%)	3 (2%)
Atrial flutter	2 (1%)	1 (<1%)
Dyspnea	1 (<1%)	3 (2%)
Lower respiratory tract infection	1 (<1%)	1 (<1%)
Aortic stenosis	1 (<1%)	0
Cardiac arrest	1 (<1%)	0
Cardiac failure	1 (<1%)	0
Congestive cardiac failure	1 (<1%)	0
Hemorrhagic diarrhea	1 (<1%)	0
Hepatitis	1 (<1%)	0
Secondary hyperparathyroidism	1 (<1%)	0
Hypoxia	1 (<1%)	0
Increased INR	1 (<1%)	0
Intestinal obstruction	1 (<1%)	0
Abnormal LFT	1 (<1%)	0
Low cardiac output syndrome	1 (<1%)	0
Mallory-Weiss syndrome	1 (<1%)	0
Myalgia	1 (<1%)	0
Pulmonary hemorrhage	1 (<1%)	0
Spinal osteoarthritis	1 (<1%)	0
Tibia fracture	1 (<1%)	0
Bradycardia	1 (<1%)	0
Large intestinal hemorrhage	1 (<1%)	0
Central line infection	1 (<1%)	0
Increased hepatic enzyme	1 (<1%)	0
Streptococcal infection	1 (<1%)	0

There were 9 reports in the UT-15C group of heart failure (includes right ventricular failure, cardiac failure, congestive cardiac failure, low cardiac output syndrome) compared to 2 placebo reports. There was one report of cardiac arrest in the UT-15C group but none in placebo.

There were 3 reports of liver abnormality (includes hepatitis, abnormal LFT, and increased hepatic enzyme) by the UT-15C group compared to 0 reports by the placebo group.

There was one report of Mallory-Weiss syndrome in the UT-15C group. Subject 131102 experienced vomiting and haematemesis. She was hospitalized and diagnosed with a Mallory Weiss tear. The event occurred about 5 hours after taking an increased dose of UT-15C (increased to 1 mg).

This event goes along with the increased vomiting reporting rate in the drop outs and indicates the vomiting could be extreme.

There were 3 reports of acute renal failure in the UT-15 group compared to 0 in the placebo group.

All adverse events

The adverse events reported by at least 3% of the UT-15C group are shown below.

Table 12-5 Summary of Adverse Events Occurring in $\geq 3\%$ of Subjects Receiving Active Therapy and More Frequently than in Placebo Patients

Adverse Event	Treatment n (%)	
	Oral Treprostinil n = 174)	Placebo n = 176
Any Event	173 (99%)	157 (90%)*
Headache	150 (86%)	65 (37%)*
Nausea	112 (64%)	60 (34%)*
Diarrhea	106 (61%)	48 (27%)*
Flushing	85 (49%)	27 (15%)*
Vomiting	76 (43%)	14 (8%)*
Pain in jaw	74 (43%)	21 (12%)*
Pain in extremity	54 (31%)	17 (10%)*
Dizziness	30 (17%)	28 (16%)
Fatigue	25 (14%)	17 (10%)
Myalgia	24 (14%)	6 (3%)*
Arthralgia	18 (10%)	4 (2%)*
Pain	17 (10%)	6 (3%)*
Palpitations	17 (10%)	9 (5%)
Insomnia	15 (9%)	7 (4%)
Back pain	13 (7%)	10 (6%)
Dyspnea	13 (7%)	12 (7%)
Decreased appetite	13 (7%)	2 (1%)*
Abdominal distension	11 (6%)	10 (6%)
Rash	10 (6%)	8 (5%)
Constipation	9 (5%)	8 (5%)
Dyspepsia	9 (5%)	8 (5%)
Musculoskeletal pain	9 (5%)	3 (2%)
Abdominal pain	8 (5%)	5 (3%)
Anxiety	8 (5%)	4 (2%)
Migraine	8 (5%)	0*
Chest discomfort	7 (4%)	3 (2%)
Presyncope	7 (4%)	4 (2%)
Bronchitis	6 (3%)	5 (3%)
Anorexia	6 (3%)	4 (2%)
Dry mouth	6 (3%)	4 (2%)
Hot flush	6 (3%)	4 (2%)
Chills	6 (3%)	3 (2%)
Right ventricular failure	6 (3%)	3 (2%)
Sinusitis	6 (3%)	3 (2%)
Influenza like illness	6 (3%)	2 (1%)
Abdominal discomfort	5 (3%)	3 (2%)

Gastroesophageal reflux disease	5 (3%)	2 (1%)
Erythema	5 (3%)	1 (<1%)
Feeling hot	5 (3%)	0

* p < 0.05

Significantly more subjects randomized to UT-15C reported adverse events (173/174, 99%) compared to subjects randomized to placebo (90%).

The events that were reported statistically significantly more often by the subjects randomized to UT-15C compared to placebo include headache (86% vs 37%), nausea (64% vs. 34%), diarrhea (61% vs.27%), flushing (49% vs. 15%), vomiting (43% vs. 8%), jaw pain (43% vs. 12%), extremity pain (31% vs. 10%), myalgia (14% vs. 3%), arthralgia (10% vs. 2%), pain NOS (10% vs. 3%), decreased appetite (7% vs. 1%), and migraine (5% vs. 0%).

Clinical Laboratory parameters

Hematology

The table below shows those hematology values that showed a decrease from baseline at week 16 in the mean for the UT-15C group compared to the placebo group.

Mean change from baseline at week 16

	UT-15C	placebo
RBC count 10 ¹² /L	-0.06	0.04
Hemoglobin g/dl	-0.26	0.13
Hematocrit	-0.7	0.5
Lymphocyte count 10 ⁹ /L	-0.1	0.01
Monocytes %	-0.14	0.06

From table 14.3.4.2

At week 16 in the UT-15C group there were mean decreases in RBC count, hb/hct, lymphocyte count and monocytes.

Chemistry

There were no chemistry parameters that showed a clinically significant change in the UT-15C group that was not similar to the change shown in the placebo group. Table 14.3.4.4.

Individual laboratory abnormalities

The table below shows the laboratory abnormalities reported as adverse events, UT-15C group only.

Table 12-12 Adverse Events Related to Laboratory Parameters in the Active Group

Subject Number	Adverse Event (Preferred Term)	Intensity/Relationship to Study Drug	Action Taken
006105	Blood potassium decreased	Mild/Not Attributable	None
006108	Blood carbonate decreased	Mild/Not Attributable	None
009105	Hypokalemia	Mild/Not Attributable	None
009109	Hypokalemia	Moderate/Not Attributable	None
009109	Pancytopenia	Moderate/ Not Attributable	None
010106	Hypokalemia	Mild/Not Attributable	None
011101	Iron deficiency anemia	Moderate/Not Attributable	None
011101	Hypomagnesaemia	Moderate/Not Attributable	None
016104	Blood lactate dehydrogenase increased	Mild/Possibly Attributable	None
024106	Hypokalemia	Severe/Not Attributable	None
026102	Liver function test abnormal	Moderate/Not Attributable	None
037102	Anemia	Moderate/Not Attributable	None
039101	Anemia	Moderate/Possibly Attributable	None
040111	Liver function test abnormal	Severe/Not Attributable	None
040122	Hypokalemia	Mild/Not Attributable	None
111109	Anemia	Moderate/Not Attributable	None

112102	Hypophosphatemia	Severe/Not Attributable	None
112102	Iron deficiency anemia	Moderate/Not Attributable	None
112102	Electrolyte imbalance	Mild/Not Attributable	None
112104	International normalized ratio increased	Mild/Not Attributable	None
112104	Liver function test abnormal	Moderate/Not Attributable	None
112108	Liver function test abnormal	Mild/Not Attributable	None
114101	Iron deficiency	Moderate/Not Attributable	None
115103	Iron deficiency	Mild/Not Attributable	None
120102	Hypokalemia	Mild/Not Attributable	None
122103	Hepatic enzyme increased	Moderate/Not Attributable	None
131102	Serum ferritin decreased	Moderate/Not Attributable	None
140101	Hypokalemia	Mild/Not Attributable	None

There was one report of pancytopenia (009109). The subject's values are shown below.

Treatment: Active, Subject: 009109

	Baseline 25MAR08 {Day 0; Baseline}	Week 8 28MAY08 {Day 64; Week 8}	Week 16 28JUL08 {Day 125; Week 16}
RBC Count [3.9-5.5 10 ¹² /L]	4.0	4.0	4.0
Hemoglobin [11.5-15.8 g/dL]	10.8 L	10.1 L	11.2 L
Hematocrit [34-48%]	36	32 L	36
Platelet Count [130-394 10 ⁹ /L]	126 L	181	117 L
WBC Count [3.80-10.70 10 ⁹ /L]	5.02	3.87	5.47
Neutrophil Count [1.96-7.23 10 ⁹ /L]	3.71	2.73	3.56
Lymphocyte Count [0.80-3.00 10 ⁹ /L]	0.75 L	0.59 L	1.31
Monocyte Count [0.12-0.92 10 ⁹ /L]	0.10 L	0.49	0.55
Eosinophil Count [0.00-0.57 10 ⁹ /L]	0.15	0.04	0.05
Basophil Count [0.00-0.20 10 ⁹ /L]	0.10	0.01	0.00
Neutrophils (relative) [40.5-75.0%]	74.0	70.6	65.0
Lymphocytes (relative) [15.4-48.5%]	15.0 L	15.3 L	24.0
Monocytes (relative) [2.6-10.1%]	2.0 L	12.6 H	10.0
Eosinophils (relative) [0.0-6.8%]	3.0	1.1	1.0
Basophils (relative) [0.0-2.0%]	2.0	0.4	0.0
Sodium [135-145 mmol/L]	141	140	138
Potassium [3.4-5.4 mmol/L]	3.6	3.1 L	3.7
Chloride [94-112 mmol/L]	105	104	102
Bicarbonate [17.0-30.6 mmol/L]	24.7	20.3	23.7
Calcium [8.3-10.6 mg/dL]	9.0	8.7	8.9
Albumin [3.3-4.9 g/dL]	3.3	3.5	3.6
Total Bilirubin [0.2-1.2 mg/dL]	0.6	0.5	0.5
Alkaline Phosphatase [35-123 IU/L]	181 H	194 H	278 H
Lactate Dehydrogenase [53-234 IU/L]	182	158	147
ALT (SGPT) [6-34 IU/L]	17	16	19
AST (SGOT) [9-34 IU/L]	28	27	22
Creatinine [0.4-1.1 mg/dL]	0.9	0.9	1.0
BUN/Urea [4-24 mg/dL]	18	14	20

There is little laboratory evidence for this event.

There were 5 reports of liver enzyme abnormalities. These were mild to moderate elevations.

The adverse events reported by the UT-15C group related to blood heart or heart rate include decreased weight (four reports), hypotension (three reports), increased temperature (two reports), orthostatic hypotension (one report), tachycardia (one report), increased heart rate (one report) and irregular heart rate (one report).

ECGs

There are no obvious ECG abnormalities that can be attributed to UT-15C in this study. There was no obvious effect seen on heart rate.

Appendix 3

Clinical trial review Protocol TDE-PH-302

Medical Reviewer's conclusions: The efficacy findings in this study are unreliable because of the high number of drop outs in the UT-15C group and the use of log rank when data points are missing. There is no dose response information (the minimum effective dose is unknown), this agent is difficult for subjects to tolerate (one case involved a report of a Mallory Weiss tear after a bout of nausea and vomiting) and a death occurred forty minutes after dosing when the patient reported nausea, vomiting, and hypotension followed by cardiac arrest.

Title of the Study: A 12-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects with Pulmonary Arterial Hypertension

Study Dates: April 29, 2011-October 24, 2006

Location of Study Sites: USA, Canada, Europe, China, India, Israel, Mexico, and Puerto Rico

Objectives: The primary objective of this study was to assess the effect of UT-15C sustained release tablets on exercise capacity compared to placebo as measured by the change in 6-minute-walk distance from baseline to week 12 in subjects with PAH.

Secondary objectives included

- ~ Combined Walk Distance/Borg Dyspnea Score
- ~ Clinical Worsening
- ~ Borg Dyspnea Score
- ~ Dyspnea-Fatigue Index
- ~ World Health Organization (WHO) Functional Class
- ~ Symptoms of PAH

Safety data includes adverse events, clinical laboratory parameters, ECG findings, physical examinations, vital signs.

Methodology:

This was an international, multi-center, randomized, double-blind, placebo-controlled, 12-week study in subjects with PAH who were not receiving approved oral therapy such as an endothelin receptor antagonist and/or a phosphodiesterase-5 inhibitor for the treatment of PAH.

After qualifying for study entry, subjects were randomized 2: 1 (UT-C15: placebo) into the 12-week Treatment Phase of the study. Subjects were assessed at five clinic visits including Baseline, Week 4, Week 8, Week 11 and Week 12.

At Weeks 4, 8, and 12, subjects were assessed for 6MWD, Borg dyspnea score, WHO functional classification, clinical worsening, signs and symptoms of PAH, and the dyspnea-fatigue index. At Week 11, subjects were assessed for 6MWD, Borg dyspnea score, and clinical worsening.

Main entry criteria:

- between the ages of 12 and 65 years of age at Screening. Protocol Amendment 3 increased the upper age limit from 65 to 70 years. Protocol Amendment 6 increased the upper age limit from 70 to 75 years.
- a diagnosis of symptomatic idiopathic or heritable PAH (including PAH associated with appetite suppressant/toxin use), PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired for at least 5 years), PAH associated with collagen vascular disease or PAH associated with human immunodeficiency virus (HIV) infection.
- baseline 6MWD between 100 and 450 meters (original criterion was 100 to 400 meters), inclusive. Protocol Amendment 3 changed the Baseline 6MWD requirement to 150-450 meters. Protocol Amendment 5 reduced the upper limit of the Baseline 6MWD to 400 meters. Protocol Amendment 6 increased the lower limit of the Baseline 6MWD to 200 meters. Protocol Amendment 8 increased the upper limit of the Baseline 6-MWD to 425 meters.
- optimally treated with conventional pulmonary hypertension therapy (anticoagulant, diuretic, oxygen, digoxin, etc) using the same regimen for at least 14 days prior to Baseline. Amendment 8 clarified this criterion by adjusting it to read: The subject was optimally treated with conventional pulmonary hypertension therapy (oral vasodilators, oxygen, digoxin, etc) with no additions, discontinuations, or dose changes for at least 14 days prior to Baseline (excluding anticoagulants) Diuretics may have been adjusted, but not discontinued or added, within 14 days of Baseline.
- documented by cardiac catheterization to have a mean pulmonary artery pressure (PAPm) greater than 25 mmHg, a pulmonary capillary wedge pressure (PCWP) or a left ventricular end diastolic pressure (LVEDP) less than or equal to 15 mmHg and pulmonary vascular resistance (PVR) greater than 3 Wood units and absence of unrepaired congenital heart disease.
- previously undergone echocardiography with evidence of normal left systolic and diastolic ventricular function and absence of any clinically significant left sided heart disease (e.g., mitral valve stenosis).

Main Criteria for Exclusion:

- The subject had received a prostacyclin (except if used during acute vasoreactivity testing), endothelin receptor antagonist, or phosphodiesterase-5 inhibitor within 30 days of Baseline.
- The subject had any PAH medication except for anticoagulants discontinued within 14 days of Baseline.

- The subject had any disease associated with PAH other than collagen vascular disease, HIV infection, or repaired congenital systemic-to-pulmonary shunts (repaired for at least 5 years) (e.g., portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, etc.) or had an atrial septostomy.
- The subject had a history or current evidence of left-sided heart disease including previous myocardial infarction or evidence of current left-sided heart disease as defined by a PCWP or LVEDP greater than 15 mmHg or left ventricular ejection fraction (LVEF) less than 40% as assessed by either multigated angiogram (MUGA), angiography or echocardiography or left ventricular (LV) shortening fraction less than 22% as assessed by echocardiography or symptomatic coronary artery disease (i.e., demonstrable ischemia either at rest or during exercise). Protocol Amendment 6 removed the shortening fraction assessment. Amendment 8 changed the criterion to exclude subjects who had ischemic heart disease (defined as either symptomatic or requiring anti-anginal therapy or experienced a myocardial infarction with the previous three years), or left ventricular dysfunction as evidenced by a mean PCWP (or a left ventricular end diastolic pressure) greater than 15 mmHg or LVEF less than 40% as assessed by either MUGA, angiography, or echocardiography. Patients with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (i.e. right ventricular hypertrophy and/or dilation) were not excluded.
- The subject had significant parenchymal lung disease as evidenced by pulmonary function tests done within 6 months of Baseline as defined by any one of the following:
 - a. Total lung capacity less than 60% (predicted), or
 - b. If total lung capacity was between 60% and 70% of predicted, a high resolution computed tomography (CT) scan must have been performed to document diffuse interstitial fibrosis or alveolitis, or
 - c. Forced expiratory volume/forced vital capacity (FEV/FVC) ratio less than 50%

Dosing The original protocol instructed investigators to start dosing with 1 mg BID and then increase the dose every five days. (Maximum allowed dose was 12 mg bid.) The subjects were not able to tolerate this starting dose so Amendment 4 changed the starting dose to 0.5 mg BID and allowed dose increases every three days. Again, the protocol was amended (5) to decrease the starting dose to 0.25 mg BID. Then, at the discretion of the study investigator, doses could be increased in 0.25 mg increments every three days during the first four weeks of the study and then either 0.25 mg or 0.5 mg increments after Week 4 as tolerated. Amendment 6 introduced the 0.125 mg tablet that could be used throughout the 12-week Treatment Phase if a 0.25 mg dose increase was not tolerated and an intermediate dose was required. A total of 228 subjects (151 UT-15C and 77 placebo) had access to the 0.25 mg.

Efficacy:

Primary Endpoint:

Change from Baseline in 6MWD at Week 12 assessed between 3 and 6 hours after the morning dose of study drug (peak drug concentration).

Secondary Endpoints:

The 6MWD measured at weeks 4, 8 and 11 (trough drug concentration).

Other secondary endpoints included the changes from baseline in the Borg dyspnea score, WHO functional class, dyspnea fatigue index, signs and symptoms of PAH, as well as an assessment of clinical worsening as defined by the following:

1. Death (all causes excluding accident)
 2. Transplantation or atrial septostomy
 3. Clinical deterioration as defined by:
 - a. Hospitalization as a result of PAH, or
 - b. Greater than or equal to 20% decrease in 6-minute walk distance from Baseline (or too ill to walk) and a decrease in WHO functional class
- And
- c. Initiation of new PAH specific therapy (i.e., ERA, PDE5-I, prostacyclin)

Data Monitoring

Data for the first 171 subjects randomized into the study were recorded on a paper Case Report Form (CRF) and collected by clinical monitors. Data for subjects randomized afterward were recorded using an electronic data capture system; InForm version 4.6 from Phase Forward (Waltham, MA).

Results

The study was conducted in North America, Europe, Israel, India, and China.

A total of 349 were enrolled in the study with all 349 subjects (233 active and 116 placebo) receiving at least one dose of study drug. One subject (041201) was enrolled but is not included in the overall population. This subject was withdrawn from the study following a temporary drug recall (UT-15C 1 mg tablets) in June 2006.

Demographics

The table below shows the demographic data for the two treatment groups.

Table 14.1.4.2
 Summary of Demographic Information for the Entire Study Population

Variable	Statistic or Category	Treatment		p-value
		Active	Placebo	
Age	n	233	116	0.247255a
	Mean	40.6	42.5	
	SD	14.0	13.5	
	SE	0.9	1.3	
	Median	40.0	42.0	
	Lower Qrt1	29.0	32.0	
	Upper Qrt1	52.0	59.0	
	Min.	12	19	
	Max.	73	68	
Age Category	n	233	116	0.298699f
	<16	2 (<1%)	0	
	16-64	221 (95%)	107 (92%)	
Sex	n	233	116	0.511830f
	Female	172 (74%)	90 (78%)	
Ethnicity	n	233	116	0.882784f
	Hispanic/Latino	43 (18%)	20 (17%)	
Race	n	233	115	0.255512f
	American Indian/Alaska Native	16 (7%)	12 (10%)	
	Asian	110 (47%)	55 (48%)	
	Black/African American	10 (4%)	1 (<1%)	
	White	96 (41%)	47 (41%)	
Weight (kg)	n	233	114	0.894844a
	Mean	68.50	68.14	
	SD	20.85	21.07	
	SE	1.37	1.97	
	Median	63.70	64.00	
	Lower Qrt1	52.00	51.70	
	Upper Qrt1	80.00	80.00	
	Min.	40.5	40.0	
	Max.	151.4	137.5	

Mean age was around 40 years (with the range from 12 to 73). Most subjects were female (75%) and either Asian (47%) or white (40%). The two groups were fairly well balanced.

Geographic distribution

There were 105 subjects from USA/Canada, 92 from India, 71 from China, and 81 from other countries.

History of PAH

Table 14.1.5.2
 Summary of PAH History for the Entire Study Population

Variable	Type or Category	Treatment		p-value
		Active	Placebo	
Years since PAH diagnosis	n	233	116	0.638146a
	Mean	0.999	0.945	
	SD	2.668	3.078	
	SE	0.175	0.286	
	Median	0.118	0.110	
	Lower Qrt1	0.033	0.022	
	Upper Qrt1	0.736	0.795	
	Min.	0.00	-1.59	
	Max.	29.92	29.75	
Etiology	n	233	116	0.976536f
	Idiopathic or familial	171 (73%)	89 (76%)	
	Collagen vascular disease	45 (19%)	22 (19%)	
	HIV infection	3 (1%)	1 (<1%)	
	Congenital heart defect	13 (6%)	5 (4%)	
	Other	1 (<1%)	0	

The mean period of time between diagnosis and starting study was about 1 year for both treatment groups.

The majority of subjects (around 75%) had a PAH etiology of idiopathic/familial. The second most frequent etiology was collagen vascular disease (19%) followed by congenital heart defect (5%), and HIV infection (1%). The two treatment groups were fairly well balanced.

The walk distance data at baseline is shown below by treatment group.

Table 14.1.7.2
 Summary of Randomisation Information for the Entire Study Population

Variable	Statistic or Category	Treatment		p-value
		Active	Placebo	
6MWD Stratum	n	233	116	1.000000f
	>350m	111 (48%)	55 (47%)	
	<=350m	122 (52%)	61 (53%)	
6MWD at Baseline	n	233	116	0.593371a
	Mean	332.3	325.2	
	SD	71.6	77.1	
	SE	4.7	7.2	
	Median	347.0	338.5	
	Lower Qrt1	289.0	265.5	
	Upper Qrt1	387.0	383.5	
	Min.	117	131	
Max.	468	447		

The mean 6MWD at baseline was somewhat longer for the UT-15C group (332.3 m) compared to placebo (325.2 m). The difference was not statistically significant. Around half the subjects walked 350 m or less at baseline.

WHO Functional class at baseline: no. (%) of subjects

	UT-15C N=233	Placebo N=116
Class I/II	90 (39)	43 (37)
Class III/IV	143 (61)	73 (63)

The majority of subjects were WHO functional class III or IV. The treatment groups were balanced.

The most common concomitant drugs are shown below by treatment groups.

Table 14.1.9.1.2
 Summary of Concomitant Medications Ongoing At Baseline For the Entire Study Population

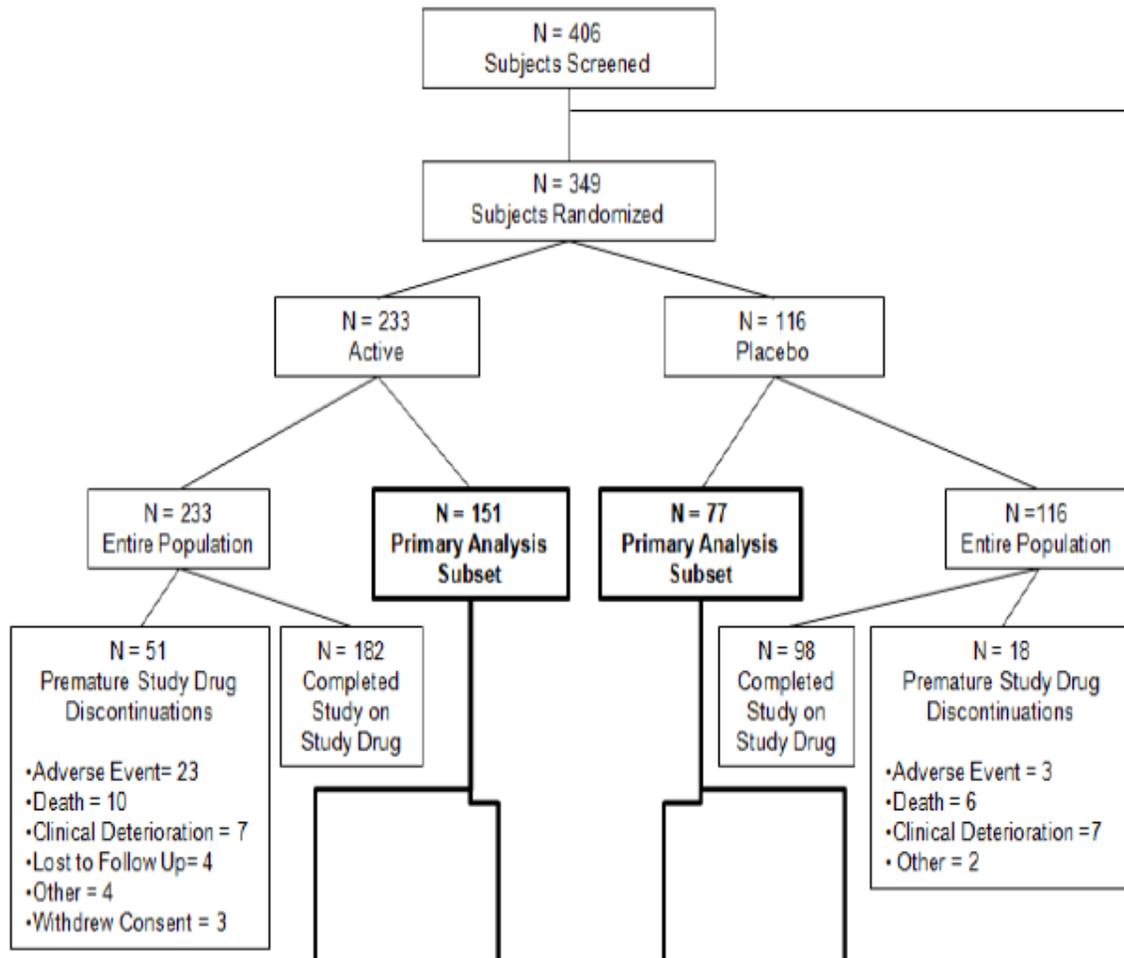
WHODD Medication Name:	Treatment		Fisher's Exact Test p-value
	Active	Placebo	
** Any Medication **	211/233 (91) [1160]	110/116 (95) [640]	0.211
FUROSEMIDE	78/233 (33) [78]	39/116 (34) [39]	>.250
DIGOXIN	63/233 (27) [63]	33/116 (28) [33]	>.250
OXYGEN	34/233 (15) [34]	16/116 (16) [16]	>.250
SPIRONOLACTONE	32/233 (14) [32]	20/116 (17) [20]	>.250
POTASSIUM CHLORIDE	38/233 (16) [38]	11/116 (9) [11]	0.102
WARFARIN	32/233 (14) [32]	16/116 (14) [16]	>.250
ACENOCOUMAROL	29/233 (12) [29]	16/116 (16) [16]	>.250
TORASEMIDE	31/233 (13) [31]	12/116 (10) [12]	>.250
ACETYLSALICYLIC ACID	27/233 (12) [27]	12/116 (10) [12]	>.250
OMEPRAZOLE	22/233 (9) [22]	15/116 (13) [15]	>.250
PREDNISONE	22/233 (9) [22]	8/116 (8) [8]	>.250
LEVOTHYROXINE SODIUM	20/233 (9) [20]	8/116 (7) [8]	>.250
OSYROL-LASIX	16/233 (7) [16]	12/116 (10) [12]	>.250
HYDROCHLOROTHIAZIDE	23/233 (10) [23]	4/116 (3) [4]	0.035*

Most subjects took additional medication. The most commonly used drugs were furosemide, digoxin, and spironolactone. Oxygen was also frequently used by study subjects.

Disposition

A summary of subject disposition for both treatment groups is shown below.

Figure 10-1 Disposition of All Subjects



A greater percentage of subjects randomized to UT-15C stopped study drug early (22%, 51/233) compared to subjects randomized to placebo (16%, 18/116).

Overall, a higher percentage of placebo subjects (88%) agreed to rollover into the open label follow up study compared to UT-15C subjects (76%). (from table 14.1.3.1.2.)

Of the subjects who stopped drug prematurely, eleven UT-15C subjects and 2 placebo subjects were reported to have discontinued for other/lost to follow up/consent withdrawn. The CRFs for these subjects were reviewed and the findings are discussed below.

UT-15C subjects

Subject 200232 Reason given: lost to follow up week 8 (last visit week 4). Adverse events reported were lower extremity edema, facial edema, weakness of legs. PAH

related events that appeared or worsened between randomization and end of study included general edema, hypoxia, and loss of consciousness. 6MWD went from 350 m at baseline to 337 week 4. Fatigue score went from 0 at baseline to 2 at week 4. Dizziness and syncope went from 1 to 0 and chest pain went from 0 to 1. Dose was decreased from 1.75 mg BID to 0.25 mg BID and then increased to 2.0 BID up to 2.75 BID. Revise reason for study drug discontinuation to clinical worsening. Reviewer assessment: clinical worsening.

Subject 200225 Reason given: lost to follow up. Adverse events reported were headache, fatigue, rash. WHO class went from II to III, dyspnea-fatigue index went from 7 to 6, PAH symptoms did not change, 6MWD went from 390 m baseline to 450 m week 8 to 440 week 11. Dose was decreased and then increased three times. Reviewer assessment: adverse events/drug intolerability.

Subject 200245 Reason given: lost to follow up. No adverse events reported. PAH symptoms no change, dyspnea/fatigue index improved (6 to 8), WHO class improved (III to II). Drug titrated without interruption up to 2.5 BID. Reviewer assessment: lost to follow up

Subject 060204 Reason given: lost to follow up. Subject did not return after baseline visit. Reported "upset stomach" when dose was increased from 0.25 mg bid to 0.5 mg bid. Reviewer assessment: adverse event/drug intolerability.

Subject 174223 Reason given: other (subject decided to go for non medical alternative treatment). Adverse events reported were dizziness, restlessness, headache, dyspnea on exertion, dry skin, decreased memory, dry throat, numbness of extremities, loss of taste, loss of appetite. Dose was decreased and then increased three times. WHO classification was unchanged from baseline and walk distance increased from 297 m to 360 m. Reviewer assessment: adverse events/drug intolerability.

Subject 115207 Reason given: consent withdrawn. Adverse events reported were abdominal pain, diarrhea, leg pain, nausea. Dose down titrated and then increased then stopped. Reviewer assessment: adverse events/drug intolerability.

Subject 013201 Reason given: other. Subject had unblinded study drug (peeled back label) prior to week 4 assessment. Adverse events reported lung cramps (sic), sinusitis, left knee pain, headache, nausea, rash, left ear pain, tinnitus, diarrhea, vomiting. Reviewer assessment: adverse events/drug intolerability.

Subject 020210 Reason given: consent withdrawn. Adverse events reported were headache, vomiting, dizziness, facial redness, muscle pain, flatulence, diarrhea, insomnia. Reviewer assessment: adverse events/drug intolerability.

Subject 041204 Reason given: consent withdrawn. On day of withdrawal, subject complained of chest pain and was admitted to hospital. Adverse events included body

aches, constipation, asthma exacerbated, chest wall strain. Dyspnea developed but fatigue improved at week 4. Walk distance went from 432 m to 473 week 4. Dose was stopped and restarted. Reviewer assessment: adverse events/drug intolerability.

Subject 171201 Reason given: other (mistakenly unblinded during ivrs, labels are undisturbed). No adverse events reported. Dyspnea-fatigue index became less severe at week 12 (magnitude of pace went from major to moderate), symptom of dyspnea improved, 336 m at baseline to 400 week 12. Reviewer assessment: subject should not be classified as premature discontinuation.

Subject 026204 Reason given: other. Subject stopped taking study drug for “unknown reason.” WHO class went from III at baseline to IV at week 8. Two days later the subject died (listed as pulmonary embolism/pulmonary edema). Adverse events include headache, dizziness, nausea, facial flushing, jaw pain, abdominal cramping, diarrhea, restless legs, metallic taste, renal insufficiency. Reviewer assessment: clinical worsening/death.

Placebo subjects

Subject 036214 Reason given: other. Subject mistakenly stopped study drug early but completed last visit. Subject has week 12 values. Reviewer assessment: subject should not be classified as premature discontinuation.

Subject 041205 reason given: other. Clinical worsening was recorded as reason for drop out on CRF page 37. Walk distance went from 301 m at baseline to 91 m week 8. Nearly all symptoms of CHF grew worse at week 8. Reviewer assessment: clinical worsening.

The reasons for dropping out for many of these subjects should be re-classified. As discussed in the next section, missing data or subject dropouts were imputed for values for the primary endpoint of change in 6MWD at Week 12.

Doses of study drug

The mean doses of study drug at each visit are shown below by treatment group.

Table 4-8 Mean Study Drug Dose at Each Scheduled Visit for the ITT Population (study TDE-PH-302)

Study Visit (n = UT-15C /Placebo)	Study Drug Dose Achieved Mean ± SD Dose (mg)	
	UT-15C	Placebo
Week 4 (n =223/113)	2.6 ± 1.6	3.3 ± 1.9
Week 8 (n = 204/104)	3.5 ± 2.2	4.8 ± 2.8
Week 12 (n =189/99)	3.6 ± 2.2	5.1 ± 3.1

Efficacy results

The primary endpoint of the study was change in 6MWD from Baseline to Week 12 as measured by the 6MWD recorded 3 to 6 hours following the last dose of UT-15C at Week 12. The primary analysis, nonparametric analysis of covariance (NP-ANCOVA), adjusted for Baseline walk, compared this endpoint between treatment groups for subjects in the primary analysis population. Treatment effect was determined using the Hodges-Lehmann method to estimate the median difference between treatment groups for change from Baseline in 6MWD.

At week 12, there were 81% of randomized UT-15C subjects (189/233) and 85% of randomized placebo subjects (99/116) still taking study drug (table 14.1.10.2).

The table below displays how missing data or subject dropouts were imputed for values for the primary endpoint of change in 6MWD at Week 12.

Table 11-16 Handling of Premature Termination of Study Drug and Missing Data for Primary Endpoint

Event	Value Used	
	Nonparametric Analysis	Parametric Analysis
Death within 12 weeks (excluding accidents); regardless of reason for study drug termination	Lowest rank	Value corresponding to overall poorest relative change ^a
Premature Termination of Study Drug:		
Clinical deterioration	Lowest rank	Value corresponding to overall poorest relative change ^a
Transplantation or atrial septostomy	Lowest rank	Value corresponding to overall poorest relative change ^a
Accident or AE unrelated to disease	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward
Lost to follow-up	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward
Protocol violation	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward
Consent withdrawn	Last rank obtained prior to termination carried forward	Last observation obtained prior to termination carried forward

Event	Value Used	
	Nonparametric Analysis	Parametric Analysis
Missing Data for Subjects Still Receiving Study Drug:		
Too clinically ill to perform 6-minute walk test	Lowest rank	Value corresponding to overall poorest change ^a
Data missing for any other reason	Last rank obtained prior to assessment carried forward	Last rank obtained prior to assessment carried forward

^aTo impute a value corresponding to the poorest change:

$$\text{Value}_i = \text{Baseline}_i \times \min_j[\text{Value}_j/\text{Baseline}_j] \text{ (for all non-missing values } j \text{ for the visit)}$$

6MWD

The primary efficacy objective was to assess the effect of UT-15C on exercise capacity as measured by the change in 6MWD from Baseline to Week 12 population.

Table 11-3 Summary of Hodges-Lehmann Estimates of Treatment Effect for Entire Study Population

Time Period	Median 6MWD (meters)		Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
	Active n = 233	Placebo n = 116		
Baseline	347	339	—	—
Week 4	358	340	+14.0 (+4, +25)	0.0025
Week 8	360	340	+20.0 (+7, +34)	0.0008
Week 11*	351	327	+17.0 (+3, +33)	0.0025
Week 12	370	330	+25.5 (+10, +41)	0.0001

* 6MWT conducted at trough drug level (8 -13 hrs post dose of UT-15C)

There were statistically significant mean treatment effects at weeks 4, 8, 11, and 12 that ranged from 14 m (week 4) to 25.5 m (week 12, p=0.0001). The walk distance at week 11 was to have been conducted at trough drug concentration. The mean treatment effect at week 11 was 17m (p=0.0025).

Overall, the 14-26 m improvement in walk distance seen in the UT-15C group is not unreasonable. The TRIUMP 1 study with treprostinil given by inhalation showed a similar effect (20 m). The studies with the injection showed smaller effect size (10 m for the pooled analysis).

The table below shows the summary of subject accountability for entire study population for the week 12 walk test.

Table 14.2.1.4
 Summary of Further Information Pertaining to Peak Six-Minute Walk Data for the Entire Study Population
 [Assessment: Week 12]

Variable	Category	Treatment	
		Active	Placebo
Current Status	n	233	116
	In study	174 (75%)	98 (84%)
	Death	14 (6%)	9 (8%)
	Clinical deterioration	7 (3%)	6 (5%)
	Adverse event	8 (3%)	1 (<1%)
	Adverse event, no F/U	13 (6%)	0
	Consent withdrawn	3 (1%)	0
	Lost to follow-up	3 (1%)	0
	Lost to follow-up, no F/U	1 (<1%)	0
	Discontinued for other reasons	1 (<1%)	2 (2%)
	In study, too ill to walk	3 (1%)	0
	In study, unblinded, no F/U	2 (<1%)	0
	In study, other	4 (2%)	0
Handling of Data	n	233	116
	Observation present	174 (75%)	98 (84%)
	Lowest rank used	24 (10%)	15 (13%)
	Average placebo rank used	16 (7%)	0
	Last rank carried forward	19 (8%)	3 (3%)
6MWT at Peak [Study Drug]?	n	174	98
	No	15 (9%)	12 (12%)
	Yes	159 (91%)	86 (88%)
6MWD Change >=	n	233	116
	0 m	162 (70%)	59 (51%)
	10 m	134 (58%)	53 (46%)
	20 m	121 (52%)	44 (38%)
	30 m	108 (46%)	38 (33%)
	40 m	86 (37%)	29 (25%)
	50 m	78 (33%)	24 (21%)
	60 m	67 (29%)	18 (16%)
	70 m	52 (22%)	13 (11%)
	80 m	42 (18%)	13 (11%)
	90 m	36 (15%)	11 (9%)
	100 m	29 (12%)	8 (7%)

Overall, 59 subjects (25%) in the UT-15C group did not have the week 12 walk test compared to 18 subjects (11%) in the placebo group. The average rank assigned to these subjects was 0.42. The average rank was 0.24 for the placebo subjects.

Of the 59 subjects with no week 12 6MWD, 9 (all UT-15C) were still in the trial but did not perform the walk test for a variety of reasons⁵:

- Subjects 051212, 115201, 178201 were handled as worst rank;

⁵ Email from Rex Mauthe dated 5-14-2012

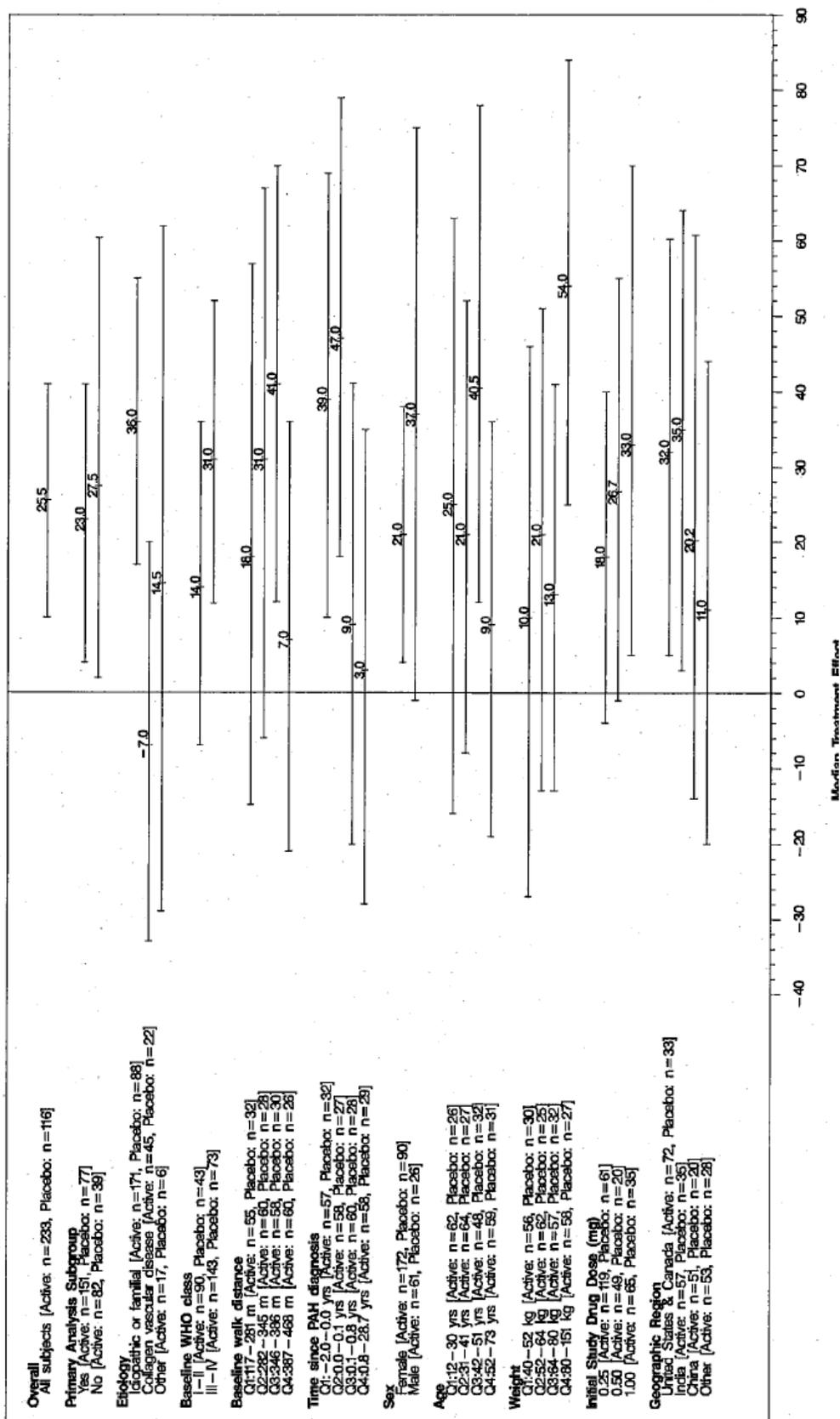
- Subjects 013201, 171201 were assigned neutral values per the SAP after being accidentally unblended;
- Subject 127209 had a late Week 12 6MWT (i.e., Day 120) that was excluded from the analysis;
- Subjects 060206 & 174244 missed their Week 12 6MWT for clearly documented reasons unrelated to PAH (lower extremity ulcer pain & family matters, respectively), so they had Week 8 values carried forward;
- Subject 171207 apparently missed the Week 12 assessment due to confusion at the site; only the Week 11 trough test was performed rather than both the Week 11 trough & Week 12 peak tests, so the subject's Week 8 value was carried forward.

When the 59 UT-15C subjects are given worst rank, then the p value becomes 0.92. When the 18 placebo subjects are assigned worst rank as well, the p value becomes 0.21. This finding casts doubt upon the reliability of the original results.

Subgroups

The figure below shows the outcome of the 6MW by subgroup.

Figure 14.2.1.2
 Plot of Six-Minute Walk Distance Outcome for Various Subgroups for the Entire Study Population



The covariates that demonstrate an interaction with treatment include baseline 6MWD (346-386 m better than the other distances), disease etiology (idiopathic/familial better than collagen vascular/other) and baseline WHO functional class (III/IV better than I/II).

Secondary endpoints

Borg dyspnea score

The Borg score was assessed immediately following the 6-minute walk test using a rating scale from 0-10. The investigators were given these instructions:

Following the walk, the person administering the test will obtain a rating of dyspnea using the Borg Scale.

The person will use the following dialogue [with the subject]:

"I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg Scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3; and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represents the greatest shortness of breath you have ever experienced in your life, and if you feel more short of breath than you have ever been in your life before, choose a number greater than 10 that represents how short of breath you feel. If one of the numbers does not exactly represent how short of breath you are, then you can choose a fraction between.

The results at week 12 are shown below.

Table 14.2.4.1.2
 Summary of the Borg Score for the Entire Study Population
 [Assessment: Week 12]

Variable	Statistic or Category	Treatment		p-value
		Active	Placebo	
Baseline	n	233	116	
	Median	3.00	4.00	0.010452a
	Lower Qrt1	2.00	2.25	
	Upper Qrt1	5.00	6.00	
	Min.	0.0	0.0	
	Max.	10.0	10.0	
	Mean	3.51	4.22	0.008482b
SD	2.32	2.45		
SE	0.15	0.23		
Follow-up	n	233	116	
	Median	3.00	4.00	
	Lower Qrt1	2.00	2.00	
	Upper Qrt1	5.00	7.00	
	Min.	0.0	0.0	
	Max.	10.0	10.0	
	Mean	3.62	4.72	
SD	2.88	3.00		
SE	0.19	0.28		
Change from Baseline	n	233	116	0.102440a
	Median	0.00	0.00	
	Lower Qrt1	-1.00	-1.00	
	Upper Qrt1	1.00	2.00	
	Min.	-7.0	-7.0	
	Max.	10.0	8.0	
	H-L Estimate (95% CI)		0.00 (-1.00, 0.00)	
	Mean	0.11	0.50	0.210965b
SD	2.76	2.66		
SE	0.18	0.25		
Handling of Data	n	233	116	
	Observation present	174 (75%)	98 (84%)	
	Worst Score of 10.0 used	24 (10%)	15 (13%)	
	Baseline observation used	16 (7%)	0	
	Last observation carried forward	19 (8%)	3 (3%)	

The baseline means were higher (i.e., worse) for the placebo group (4.22) compared to the UT-15C group (3.51) with the p value equal to 0.008. The mean change from baseline at week 12 was clinically but not statistically worse for the placebo group (0.50) compared to UT-15C (0.11).

Clinical worsening

Time to clinical worsening was defined as the time from randomization to the first of death (except due to accidental causes), transplantation, atrial septosomy, or hospitalization because of PAH. Subjects were also considered to have experienced clinical worsening if they had a 20% or greater decrease in 6MWD from baseline or were too ill to walk with a decrease in WHO functional class and had started a new PAH therapy including either an ERA, a PDE5-1 or a prostacyclin.

The table below shows the results by treatment group.

Table 14.2.2.2
 Summary of Clinical Worsening For the Entire Study Population

Variable	Category	Treatment		p-value
		Active	Placebo	
Clinical Worsening	n	233	116	0.3572
	No	211 (91%)	101 (87%)	
	Yes	22 (9%)	15 (13%)	
Clinical worsening event	n	233	116	
	No clinical worsening (censored)	211 (91%)	101 (87%)	
	Death	13 (6%)	8 (7%)	
	Clinical deterioration	9 (4%)	5 (4%)	
	>=20% decrease 6MWD, worsened WHO class & new PAH medication	0	2 (2%)	

There was a higher percentage of placebo subjects with clinical worsening (13%) compared to UT-15C group (9%). This difference was not statistically significant.

World Health Organization Functional Class

The table shows the percent of subjects for WHO functional class at baseline and at week 12.

Table 14.2.3.1.2
 Summary of WHO Functional Class for the Entire Study Population
 [Assessment: Week 12]

Variable	Statistic or Category	Treatment		p-value
		Active	Placebo	
Baseline	n	233	116	0.515313a
	I	7 (3%)	1 (<1%)	
	II	83 (36%)	42 (36%)	
	III	142 (61%)	70 (60%)	
	IV	1 (<1%)	3 (3%)	
Shift from Baseline	n	233	116	
	I->I	200 (86%)	100 (86%)	
	I->II	1 (<1%)	1 (<1%)	
	I->III	1 (<1%)	0 (<1%)	
	I->IV	1 (<1%)	1 (<1%)	
	II->I	6 (3%)	3 (3%)	
	II->II	84 (36%)	34 (29%)	
	II->III	12 (5%)	5 (4%)	
	II->IV	1 (2%)	1 (2%)	
	III->I	38 (16%)	12 (10%)	
	III->II	97 (42%)	45 (39%)	
	III->III	17 (7%)	13 (11%)	
	III->IV	1 (<1%)	2 (2%)	
	IV->III	0	1 (<1%)	
Change from Baseline	n	233	116	0.275309a
	Median	0.0	0.0	
	Lower Qrt1	0.0	0.0	
	Upper Qrt1	0.0	0.0	
	Min.	-1	-1	
	Max.	2	2	
	H-L Estimate (95% CI)		0.0 (0.0, 0.0)	
	Mean	0.0	0.1	
	SD	0.6	0.6	
	SE	0.0	0.1	
Handling of Data	n	233	116	
	Observation present	179 (77%)	88 (84%)	
	Worst Class of IV used	21 (9%)	15 (13%)	
	Baseline observation used	16 (7%)	0	
	Last observation carried forward	18 (8%)	3 (3%)	

At baseline, the two treatment groups were similar regarding the percent of subjects by WHO functional class with around 60% of subjects being classified as WHO III.

At week 12, most subjects did not change from their baseline category. There were 36 (15%) UT-15C subjects who got worse compared to 21 (18%) placebo subjects. The overall changes were not significantly different.

Dyspnea-Fatigue Index

Each of the three components of the dyspnea-fatigue index were rated on a scale of 0 to 4 with 0 being the worst condition and 4 being the best condition for each component. The dyspnea-fatigue index was computed by summing the three component scores. The median index values remained unchanged at all post-baseline assessments compared to baseline values and changes did not differ between treatment groups at Week 12.

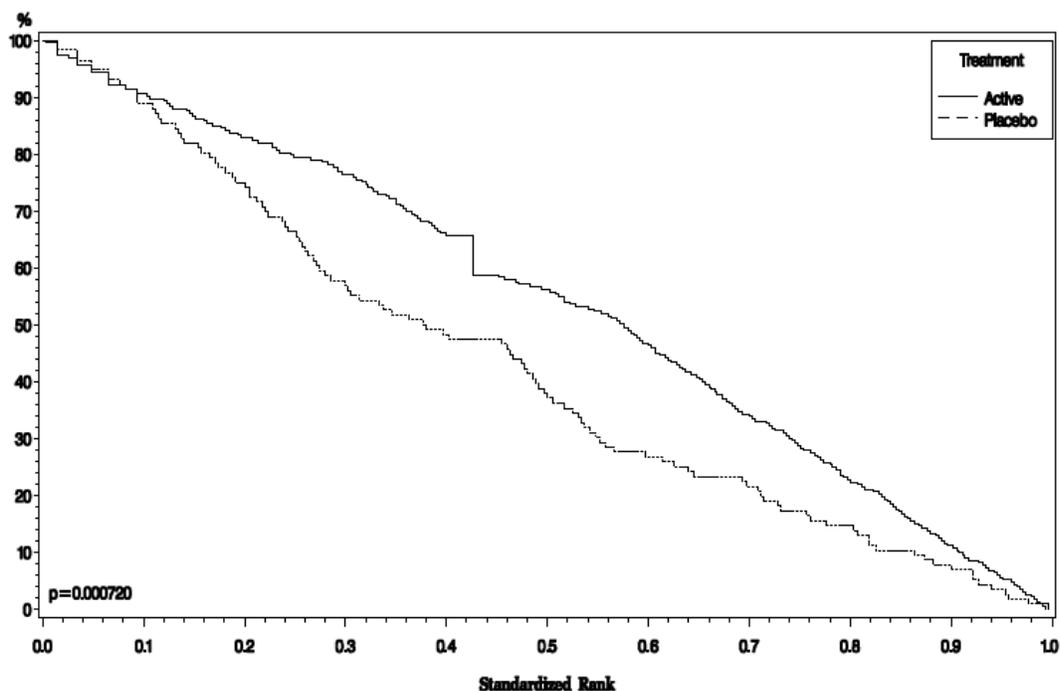
Symptoms of Pulmonary Arterial Hypertension

Symptoms of PAH including fatigue, dyspnea, edema, dizziness, syncope, chest pain, and orthopnea were assessed at Baseline and at Weeks 4, 8, and 12. Each symptom was given a severity grade value of 0 to 3. There was no observed treatment effect on symptoms of PAH for the entire population.

6MWD and Borg dyspnea score at week 12

According to the study protocol, at the end of 6 minute walk test, the tester called “stop” while simultaneously stopping the watch and then measuring the distance walked. The Borg Dyspnea Rating was then administered. This was an attempt to determine how subjects “feel when carrying out their usual activities of daily living.”

Figure 14.24.2
Plot of the Combined Six-Minute Walk Distance and Borg Score Ranks for the Entire Study Population
[Assessment: Week 12]



Safety

Investigators were instructed by the protocol (appendix G) not to report “expected events attributable to the progression of PAH.”

APPENDIX G: Expected Adverse Events Listing for UT-15C Clinical Studies

Part A: Expected Events Attributable to the Progression of PAH

Any event that is associated with the progression of a subject’s PAH should NOT be recorded as an adverse event in the case report form as the most relevant PAH symptoms will be evaluated and recorded as an efficacy endpoint and all other events will be captured as disease related events.

Abdominal pain	Fatigue
Anorexia	Heart failure (including exacerbation of)
Ascites	Hypoxia
Cardiovascular collapse	Loss of consciousness
Chest pain	Nausea
Cool extremities	Orthopnea
Cor pulmonale	Pallor
Cough	Palpitations/cardiac arrhythmia
Cyanosis	Paroxysmal nocturnal dyspnea
Dizziness	Pulmonary hypertension (exacerbation of)
Dyspnea at rest	Sudden death
Dyspnea at exertion	Syncope/presyncope
Edema	Tachycardia
Exercise intolerance	Weight loss/gain
Hemoptysis	Vasovagal reaction
	Vomiting

Extent of exposure

Subjects randomized to UT-15C were exposed for a mean + SD of 76.1 + 24.5 (range 2 – 146 days) and subjects randomized to placebo were exposed for an average of 76.6 + 19.6 (range 3 – 103 days).

The mean + SD dose of UT-15C achieved for the entire study population at Week 12 was 3.6 ± 2.2 (range 0.25 – 12 mg) BID in the active group as compared to 5.1 ± 3.1 (range 0.5 – 17 mg) in the placebo group.

All adverse events

All adverse events reported by at least 3% of the subjects randomized to UT-15C and reported more often by this group than the placebo group are shown below.

Table 12-8 Summary of Adverse Events Occurring in at Least 3% of Subjects Receiving Active Therapy and More Frequently than in Placebo Patients from the Entire Study Population

Adverse Event	Treatment n (%)	
	UT-15C n = 233	Placebo n = 116
Any Event	219 (94%)	106 (91%)
Headache	160 (69%)	36 (31%) [†]
Nausea	91 (39%)	25 (22%) [†]
Diarrhea	86 (37%)	21 (18%) [†]
Pain in jaw	59 (25%)	8 (7%) [†]
Vomiting	57 (24%)	19 (16%)
Flushing	50 (21%)	9 (8%) [†]
Pain in extremity	44 (19%)	9 (8%) [†]
Abdominal pain	31 (13%)	9 (8%)
Myalgia	24 (10%)	5 (4%)
Fatigue	20 (9%)	8 (7%)
Decreased appetite	19 (8%)	5 (4%)
Peripheral edema	18 (8%)	8 (7%)
Insomnia	17 (7%)	5 (4%)
Arthralgia	15 (6%)	4 (3%)
Hypokalemia	15 (6%)	4 (3%)
Back pain	14 (6%)	4 (3%)
Right ventricular failure	13 (6%)	4 (3%)
Pain	13 (6%)	0 (0%) [†]
Abdominal distention	11 (5%)	4 (3%)
Erythema	11 (5%)	1 (<1%)
Rash	11 (5%)	0 (0%) [†]
Upper abdominal pain	10 (4%)	4 (3%)
Dyspepsia	10 (4%)	3 (3%)
Gastritis	9 (4%)	2 (2%)
Abdominal discomfort	9 (4%)	1 (<1%)
Urinary tract infection	7 (3%)	2 (2%)
Neck pain	7 (3%)	1 (<1%)
Hemoptysis	6 (3%)	2 (2%)
Tachycardia	6 (3%)	1 (<1%)
Frequent bowel movements	6 (3%)	0 (0%)

[†] p < 0.05

The events that were statistically significantly higher in the UT-15C group compared to placebo include headache, nausea, diarrhea, pain in jaw, flushing, pain in extremity, pain and rash.

Serious safety

The serious adverse events reported by more than one subject receiving UT-15C are shown below.

Table 12-14 Summary of Serious Adverse Events Occurring in More Than One Subject Receiving UT-15C from the Entire Study Population

Adverse Event	Treatment n (%)	
	UT-15C n = 233	Placebo n = 116
Any event	41 (18%)	26 (22%)
Right ventricular failure	13 (6%)	4 (3%)
Pulmonary hypertension	6 (3%)	9 (8%) [†]
Cardiac failure	3 (1%)	2 (2%)
Pneumonia	3 (1%)	1 (<1%)
Death	2 (<1%)	2 (2%)
Chest pain	2 (<1%)	1 (<1%)
Dyspnea	2 (<1%)	1 (<1%)
Syncope	2 (<1%)	1 (<1%)
Pulmonary embolism	2 (<1%)	0 (0%)

[†] p < 0.05

The percentage of UT-15C subjects reporting right ventricular failure (6%) was twice the percentage of placebo subjects (3%). The other events were similar for both treatment groups except pulmonary hypertension that was reported by more placebo subjects (8%) compared to UT-15C subjects (3%).

Deaths

There were 24 reported deaths during the 12 week study including 15 deaths in UT-15C and 9 deaths in the placebo group. Additionally, one subject in the active group (subject number 178201) died after completing the Week 12 visit but prior to enrollment in the open-label extension study (TDEPH- 304).

The 24 subjects who were randomized and subsequently died are shown in the table below. A discussion of each of these deaths follows the table.

Table 14.3.2.1.2
 Listing of Deaths for the Entire Study Population

Subject	Random- ization	First Dose	Last Dose	Reason for Stopping Study Drug	D/C	Reason for Study Discontinuation	Date of Death	Day of Death	Cause of Death:
Treatment: Active									
025201	29JAN07	29JAN07	03APR07	Death	03APR07	Death	03APR07	65	"ASPIRATION"
026204	21OCT08	21OCT08	09JAN09	Other	11JAN09	Death	11JAN09	83	"PULMONARY EMBOLISM / PULMONARY EDEMA"
029201	27NOV06	27NOV06	17DEC06	Clinical Deterioration	11JAN07	Consent Withdrawn	01FEB07	67	Progression of disease under study
115201	07MAY07	07MAY07	22JUL07	Clinical Deterioration	26JUL07	Death	26JUL07	81	Progression of disease under study
115203	09SEP07	09SEP07	11SEP07	Adverse Event	17SEP07	Death	17SEP07	9	"NON SMALL CELL LUNG CARCINOMA"
117201	27MAR07	27MAR07	09APR07	Death	09APR07	Death	09APR07	14	"CARDIOGENIC SHOCK"
127201	05NOV07	05NOV07	08NOV07	Adverse Event	11NOV07	Death	11NOV07	7	"BACTERIAL INFECTION OF SUBCUTANEOUS TISSUE"
169201	31JAN11	31JAN11	01MAR11	Death	02MAR11	Death	02MAR11	31	"ACUTE RENAL FAILURE, PRIMARY PULMONARY HYPERTENSION, RIGHT HEART FAILURE AND SCLERODERMA"
169202	31JAN11	31JAN11	22MAR11	Death	22MAR11	Death	22MAR11	51	Progression of disease under study
174219	22FEB10	22FEB10	26APR10	Death	27APR10	Death	27APR10	65	Progression of disease under study
174236	25JAN11	25JAN11	12APR11	Death	12APR11	Death	12APR11	78	Progression of disease under study
176202	21AUG10	21AUG10	26SEP10	Death	26SEP10	Death	26SEP10	37	Progression of disease under study
200205	01NOV10	01NOV10	18JAN11	Death	19JAN11	Death	19JAN11	80	"SEVERE PNEUMONIA AND HEART FAILURE"
200218	06DEC10	06DEC10	30DEC10	Death	30DEC10	Death	30DEC10	25	"UNKNOWN DEATH"
200242	21JAN11	21JAN11	03APR11	Death	04APR11	Death	04APR11	74	Progression of disease under study
Treatment: Placebo									
020211	26APR07	26APR07	21JUN07	Adverse Event	28JUN07	Death	28JUN07	64	Progression of disease under study
046211	29JUN09	29JUN09	05JUL09	Death	06JUL09	Death	06JUL09	8	"CARDIOVASCULAR COLLAPSE"
127203	06DEC07	06DEC07	10JAN08	Death	10JAN08	Death	10JAN08	36	Progression of disease under study
127204	11DEC07	11DEC07	07FEB08	Clinical Deterioration	14FEB08	Death	14FEB08	66	Progression of disease under study
174234	22JAN11	22JAN11	25JAN11	Death	25JAN11	Death	25JAN11	4	Progression of disease under study
176201	16APR10	16APR10	23APR10	Death	24APR10	Death	24APR10	9	"CHEST PAIN"
178205	15SEP10	15SEP10	04NOV10	Death	05NOV10	Death	05NOV10	52	Progression of disease under study
200215	30NOV10	30NOV10	17DEC10	Adverse Event	24DEC10	Consent Withdrawn	24DEC10	25	"ACUTE RIGHT HEART FAILURE"
200228	29DEC10	29DEC10	08FEB11	Death	08FEB11	Death	08FEB11	42	"DIEFROM UNKNOW REASON"

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Subject 025201 was a 60 year old female with a medical history that included hypertension, anemia, glaucoma, celiac sprue, methazolamide allergy and elevated liver function tests. Concomitant medications included timolol maleate, bisoprolol fumarate, amlodipine/benazepril HCL and multiple dietary supplements.

The patient was randomized to treprostinil diethanolamine and received up to 7 mg twice daily. About 5 weeks later, the subject reported hypotension and bisoprolol was discontinued. A month later, amlodipine/benazepril was discontinued because of re-elevated LFTs. Approximately 2 months after starting drug the subject reported a syncopal episode with nausea and vomiting and worsening PAH. Later that evening she was hospitalized for hypotension. The next day she was transferred to the study institution for further care. She had not received study medication for two days but received an evening dose (6 mg) on the day she died. **Forty minutes after dosing the patient reported nausea, vomiting, and hypotension. She went into cardiac arrest and died** after unsuccessful resuscitation.

Death report stated that submitted information indicating that death was due to a profound **vasovagal syncope** causing hypotension (acute circulatory failure), leading to loss of consciousness, **aspiration** of stomach content and **cardiac arrest** in a patient who had moderately severe pulmonary arterial hypertension.

Subject 026204 was a 52 year old female with a medical history that included systemic sclerosis secondary to pulmonary arterial hypertension (PAH) diagnosed in 2008, hypothyroidism, gastroesophageal reflux disease (GERD) and abdominal pain. Concomitant medications included levothyroxine, omeprazole and calcium. The patient received treprostinil diethanolamine up to 2 mg BID for about 81 days and discontinued drug 2 days before death.

About 3 weeks before death, the subject reported **abdominal discomfort**. Study drug dose was tapered 0.25 mg BID. The results of a repeat echocardiogram confirmed severe pulmonary arterial hypertension and it was recommended that she start epoprostenol therapy. She declined and decided to stop taking study drug. On the day she died (study day 83), the subject reported chills, anorexia and diarrhea (treated with loperamide) as well as increased joint pain, shortness of breath, palpitations, rapid heart rate and increased weakness. She became **cyanotic** and had a **near-syncopal episode** at home. The paramedics gave her nitroglycerin for chest tightness and her blood pressure was low. Upon arrival to the emergency room she had abdominal tenderness, diffuse myalgias, mottled skin and scleroderma present in all extremities. She was febrile, blood pressure 03/74 mm Hg, pulse 102 beats per minute, and respirations 32 breaths per minute, pH of 7.28 (normal range 7.35–7.45), pCO₂ of 42.9 (normal range 35–45), and a white blood count of 17,400/mcl.

A chest computed tomography (CT) confirmed bilateral pulmonary emboli. pressure dropped acutely, and she had **progressive bradycardia followed by cardiac shock**. The cause of death was pulmonary embolism and pulmonary edema. No autopsy was performed.

Subject 029201 was a 44 year old female with a medical history that included pulmonary hypertension, hypothyroidism, cor pulmonale, chronic kidney disease and clostridium difficile colitis. Concomitant medications included warfarin, furosemide, potassium, digoxin, levothyroxine, calcium, and rabeprazole. The patient was receiving UT-15C 2 mg BID for about 3 weeks when she presented with shortness of breath, lethargy, and increased swelling of her extremities. She was hospitalized for right heart failure. She verbalized noncompliance with her medications for many days due to anxiety, abdominal pain and intermittent nausea which existed prior to study drug initiation. She reportedly had been compliant with all doses of blinded study drug during Week 1 of study participation, but started to miss doses after study medication was increased to 2 mg. The subject was found to have a severely dilated, hypocontractile right ventricle with severe right ventricular overload and increased pulmonary artery pressure in comparison to her previous study. Study drug was discontinued and she placed on IV treprostinil sodium. She continued to deteriorate and developed renal failure and hyponatremia. She was determined to be in "**end-stage**" heart failure, was weaned off of IV treprostinil sodium and transferred to hospice care and died about one month later.

Subject 115201 was a 59 year old female with a medical history that included scleroderma, hypothyroidism, depression, constipation, and reflux. Concomitant medications included furosemide, spironolactone, omeprazole, levothyroxine. The patient received UT-15C 3 mg bid for about 10 weeks and then discontinued for worsening of PAH. The subject was hospitalized with **significant weakness, significant respiratory deterioration and worsening edema** of the legs and right

hand. She reported peripheral cyanosis of the digits, mild dyspnea and tachypnea. Subcutaneous trepstinil sodium was started with initial clinical improvement. About 4 days after the study drug was stopped the patient was **found pulseless**. CPR attempts failed. No autopsy was performed.

Subject 115203 was diagnosed with **adenocarcinoma** of the lung. He had been taking UT-15C for two days. He discontinued the study drug, was hospitalized and died a short time later.

Subject 117201 was a 53 year old female with a medical history that included pulmonary hypertension, essential hypertension and hypothyroidism. Reported serious adverse events included atrial flutter, right heart failure and cardiogenic shock. Concomitant medications included furosemide, enalapril, levothyroxine sodium.

The patient started UT-15C 2 mg bid and was admitted to hospital about 12 days later with abdominal pain and nausea. An electrocardiogram (ECG) showed new atrial flutter. The patient received IV verapamil and metoprolol. She developed **cardiogenic shock with extreme bradycardia/complete atrioventricular block**. Resuscitation attempts were unsuccessful. Cause of death was recorded as cardiogenic shock and atrial flutter.

Subject 127201 was a 35 year old female with a medical history that included systemic lupus erythematosus associated with cryoglobulinaemia and skin ulceration of right cruris. Reported serious adverse events were bacterial infection of subcutaneous tissue and heart failure which led to study drug withdrawal (UT- 15C 1 mg bid was taken for 3 days). The patient had been hospitalised earlier for treatment of her collagen vascular disease. During hospitalisation, the patient developed a bacterial infection of subcutaneous tissue. Study drug was started in the hospital. Two days later, the patient complained of an infected chronic penetrating ulcer on the lateral aspect of her right ankle. Intravenous antibiotics were administered and cultures revealed multiple organisms. She **suddenly collapsed with loss of consciousness and sinus bradycardia that progressed to cardiac arrest**. Cardiopulmonary resuscitation was ineffective and she died 6 days after starting study drug. The autopsy report stated the cause of death was **pulmonary edema and serious right ventricular failure**.

Subject 169201 was a 55 year old female with a medical history that included systemic lupus erythematosus. Subject received UT-15C 2 mg bid. Concomitant medications included tramadol, multivitamin, calcium carbonate/Vitamin D3, rabeprazole, hydroxychloroquine, alprazolam, torsemide, furosemide, Himalayan ayurvedic supplement, codeine linctus and calcium supplement. About one month after starting study drug was hospitalized for **complaints of general weakness, vomiting and reduced appetite**. The study drug dosage was interrupted and she was treated with torsemide, hydroxychloroquine, 'MSET' and pantoprazole. The patient was diagnosed with **acute renal failure**. UT-15C was restarted. She was transferred to intensive care unit and was scheduled for dialysis. She died that day. No autopsy was performed.

Subject 169202 was a 62 year old male with a medical history that included for gastroenteritis, fatigue, and pulmonary arterial hypertension. Concomitant medications included digoxin, isosorbide mononitrate, clopidogrel, frumil, torasemide, metolazone, Vibact, calcium + pantothenate + folic + lactobacillus + acidophilus + niacinamide + thiamine + mononitrate + vitamin B12 + vitamini B2 + Vitamin B6 + Vitamin C and Senil Forte).

Hhe received UT-15C up to 5 mg bid.

About one month after randomization, the subject reported loose stools, stomach upset, and decreased urine output. One week later he reported **complaints of weakness, with continued abdominal discomfort**, and pain in leg, loose motions and decrease in urine output. At clinic visit blood pressure was 90/60 mm Hg, heart rate of 76 beats per minute. The patient was advised to reduce the dose of diuretics. The subject continued to report **fatigue, severe asthenia**, giddiness, and blood pressure of 90/60 mm Hg and heart rate of 72 beats per minute. The patient was examined and advised to reduce study drug dose and be admitted to hospital if his condition did not improve. That evening the subject **collapsed** and was brought to hospital where he was declared dead upon arrival. The patient was diagnosed with a worsening of PAH. An autopsy was not performed.

Subject 174219 was a 37-year-old, 40.5-kg, Asian female with a medical history significant for pulmonary arterial hypertension. Concomitant medications included amiloride, furosemide, sparacide, rabeprazole, domperidone, ondansetron, Vitamin B Complex, sucralfate. She received UT-15C 0.5 mg bid.

Approximately 63 days after initiating study drug, the patient **suddenly developed chest discomfort and collapsed and died** on the way to the hospital. No autopsy was performed.

Subject 174236 was a 41 year-old, 41.3-kg, Asian female with medical history being significant for primary pulmonary hypertension. Concomitant medications included Lanoxin (digoxin), Lasix (furosemide), Aldactone (spironolactone), Ranidom (ranitidine), Nise (nimesulide), and Tryptomer (amyltriptiline hydrochloride).

She received UT-15C 1.75 mg once daily. Non serious adverse events included headache, abdominal distension, gastritis, hypokalemia. On day 77 she complained of **breathlessness** to her husband and was taken to local hospital where she died. No autopsy was performed. Death certificate listed cause of death as **severe PAH with moderate tricuspid regurgitation with complete heart block**.

Subject 176202 was a 37-year-old, 55-kg, Asian female with a medical history that included left ventricular dysfunction and bronchospasm. Concomitant medications included digoxin, furosemide, etofylline, theophylline, rabeprazole and dompericlone.

Prior to the patient's death, she underwent tests that confirmed moderate to **severe PAH and moderate tricuspid regurgitation**, good left ventricular function, and concentric left ventricular hypertrophy. She received UT-15C 0.5 mg bid which was downtitrated to 0.25 bid after reporting **abdominal pain**.

Approximately 36 days after initiating study drug, the patient **died at home**. It was unknown if an autopsy was performed and no death certificate was provided.

Subject 200205 was a 32 year old, 50 kg, Asian male with a medical history significant for bronchiectasis since childhood. Concomitant medications included furosemide, Hydrodiuril (hydrochlorothiazide), potassium chloride, simvastatin, Diltrazam (diltiazem hydrochloride), digoxin and oxygen. He received UT-15C 1.75 mg bid. Approximately 5 weeks after initiating study drug, the patient began suffering fever and cough and tests showed severe pulmonary arterial hypertension and right heart enlargement. He was admitted to hospital due to feeling increased chest distress and shortness of breath upon exertion and diagnosed with **pneumonia and heart failure**.

The study drug dosage was increased to 2.0 mg twice daily and increased again to 2.75 mg twice daily. The pneumonia and heart failure were resolved and the patient was discharged from hospital. Two weeks later the subject was readmitted to hospital with chest distress and **pneumonia and heart failure**.

He was given bi-level positive airway pressure assisted ventilation. He suffered **cardiac arrest** and resuscitation was ineffective. No autopsy was performed, and the cause of death was determined to be heart failure.

Subject 200218 was a 21-year-old, 60-kg, Asian female whose medical history was significant for systemic lupus erythematosus. Concomitant medications included furosemide, torasemide, potassium chloride, digoxin, prednisone, hydroxychloroquine and ranitidine. The subject received UT-15C up to 1.5 mg bid. No serious adverse events were reported. Approximately 24 days after initiating study drug, the patient was resting at home when she **suddenly experienced palpitations, and then died** before the ambulance arrived. No autopsy was performed.

Subject 200242 was a 22 year-old, 59-kg, Asian female with an unknown medical history. Concomitant medications included hydrochlorothiazide, furosemide, digoxin, potassium chloride, and oxygen treatment. She received UT-15C 4.0 mg, twice a day. Seventy days after starting drug subject reported **hemoptysis**. She was admitted to the hospital and treated with antibiotics and hemostatic therapy (not further specified). Treatment with dopamine was initiated without relief. Her coagulation studies showed a **prolonged PT**. She was also **hypoxic**. She was treated with ceftizoxime, cyclosporine injection, aminomethyl benzoic acid, dopamine, desmopressin acetate, oxygen treatment, pituitrin, dyphylline, dexamethasone, furosemide, doxofylline, methylprednisone, heart pill of musk (Chinese traditional medicine), torasemide,

amiodarone, coraminum, lobeline, adrenaline, norepinephrine, and isoprenaline. A short time later she became **comtose** and was discharged to home. She died that day. An autopsy was not performed.

Study drug discontinuations for adverse events

The table below shows the number of subjects who were withdrawn from study drug because of an adverse event (only events reported by more than one subject in the UT-15C group).

Table 12-16 Summary of Adverse Events Resulting in Permanent Study Drug Discontinuation in More Than One Active Subject From the Entire Study Population

Adverse Event	Treatment n (%)	
	UT-15C n = 233	Placebo n = 116
Any event	36 (15%)	13 (11%)
Right ventricular failure	8 (3%)	1 (<1%)
Headache	7 (3%)	1 (<1%)
Nausea	6 (3%)	0 (0%)
Jaw pain	5 (2%)	0 (0%)
Pulmonary hypertension	4 (2%)	8 (7%) [†]
Diarrhea	4 (2%)	0 (0%)
Vomiting	4 (2%)	0 (0%)
Abdominal pain	3 (1%)	0 (0%)
Cardiac failure	2 (<1%)	0 (0%)
Dizziness	2 (<1%)	0 (0%)
Dyspnea	2 (<1%)	0 (0%)
Myalgia	2 (<1%)	0 (0%)
Extremity pain	2 (<1%)	0 (0%)

A higher percentage of subjects in the UT-15C group (15%) stopped the study drug because of an adverse event compared to the placebo group (11%). The most common reasons were right ventricular failure, headache, and nausea. The placebo group withdrew primarily because of pulmonary hypertension (7% compared to UT-15C 2%). This analysis could be flawed because the investigators were instructed not to report events associated with pulmonary hypertension as adverse events but as efficacy endpoints.

Clinical Laboratory values

Hematology

The parameters RBC count, hemoglobin and hematocrit in the UT-15C group showed small decreases in the mean change from baseline at week 12. The placebo group showed small increases for these parameters (table 14.3.4.2). There were also numerically more shifts in the UT-15C group from normal to low and/or high to low or

from high to normal at week 12 for RBC count, hemoglobin, and hematocrit (table 14.3.4.3).

There were 3 subjects who reported anemia as an adverse event: 036211, 065202, 200231.

The values for RBC, hemoglobin and hematocrit for each of these subjects are shown in the tables below.

Appendix 16.2.8
 Listing of Laboratory Data

Parameter [Normal Range]:

Treatment: Active, Subject: 036211

	Baseline 26AUG09 [Day 1; Baseline]	Week 12 16NOV09 [Day 83; Week 12]
RBC Count [4.1-5.6 10 ¹² /L]	4.9	4.4
Hemoglobin [11.6-16.4 g/dL]	14.9	13.0
Hematocrit [34-48%]	46	38

Appendix 16.2.8
 Listing of Laboratory Data

Parameter [Normal Range]:

Treatment: Active, Subject: 065202

	Screen 20DEC10 [Day -15; Baseline]	Baseline 06JAN11 [Day 1; Baseline]	Week 8 02MAR11 [Day 57; Week 8]	Week 8 07MAR11 [Day 62; Week 8]	Week 12 30MAR11 [Day 85; Week 12]
RBC Count [3.9-5.5 10 ¹² /L]	4.1	4.3	3.9	3.8 L	4.0
Hemoglobin [11.5-15.8 g/dL]	11.8	12.3	10.9 L	10.7 L	10.9 L
Hematocrit [34-48%]	34	37	32 L	32 L	33 L

Appendix 16.2.8
 Listing of Laboratory Data

Parameter [Normal Range]:

Treatment: Active, Subject: 200231

	Screen 04JAN11 [Day -1; Baseline]	Baseline 06JAN11 [Day 1; Baseline]	Baseline 15FEB11 [Day 41; --]	Baseline 18FEB11 [Day 44; Week 8]	Week 8 08MAR11 [Day 62; Post D/C]
RBC Count [4.1-5.6 10 ¹² /L]	4.3	4.4	4.6	4.8	4.8
Hemoglobin [11.6-16.4 g/dL]	10.1 L	10.5 L	10.0 L	10.3 L	12.2
Hematocrit [34-48%]	33 L	36	34	36	41

There were 2 subjects who reported hemoglobin and hematocrit decreased as an adverse event: 065202, 069201. Their values for RBC, hemoglobin and hematocrit are shown below.

Appendix 16.2.8
 Listing of Laboratory Data

Parameter [Normal Range]:

Treatment: Active, Subject: 066202

	Screen 20DEC10 [Day -15; Baseline]	Baseline 05JAN11 [Day 1; Baseline]	Week 8 02MAR11 [Day 57; Week 8]	Week 8 07MAR11 [Day 62; Week 8]	Week 12 30MAR11 [Day 85; Week 12]
RBC Count [3.9-5.5 10 ¹² /L]	4.1	4.3	3.9	3.8 L	4.0
Hemoglobin [11.5-15.8 g/dL]	11.8	12.3	10.9 L	10.7 L	10.9 L
Hematocrit [34-48%]	34	37	32 L	32 L	33 L

Appendix 16.2.8
 Listing of Laboratory Data

Parameter [Normal Range]:

Treatment: Active, Subject: 069201

	Baseline 05OCT10 [Day 1; Baseline]	Week 8 29NOV10 [Day 56; Week 8]	Week 12 27DEC10 [Day 84; Week 12]
RBC Count [4.0-5.8 10 ¹² /L]	3.7 L	3.8 L	3.3 L
Hemoglobin [12.5-17.0 g/dL]	12.5	13.0	11.1 L
Hematocrit [37-51%]	40	38	32 L

Changes in platelet counts were similar for the two treatment groups.

There are some indications that UT-15C could cause a decrease in RBC count/hemoglobin/hematocrit in some subjects. The drug effect, if real, is probably small.

Chemistry

The mean changes for blood chemistry values were similar for the UT-15C and placebo treatment groups (table 14.3.4.4) as were the shift changes (table 14.3.4.5). Adverse events pertaining to blood chemistry were uncommonly reported (see below)

Reported adverse events related to chemistry values are shown below.

No. and (%) of subjects reporting event

	UT-15C n=233	Placebo n=116
hypokalemia	15 (6)	4 (3)
hepatic function abnormal	2 (<1)	0
hyperbilirubinemia	1 (<1)	1 (<1)
renal failure [^]	3 (1)	1 (<1)
ALT abnormal	1 (<1)	0
AST abnormal ^{^^}	2 (1)	0
jaundice	1 (<1)	0

[^]includes acute

^{^^}includes increased

Table 14.3.1.1.2

Hypokalemia was reported twice as often by the UT-15C group (6%) compared to placebo (3%). The change from baseline at week 12 for potassium levels showed a greater decline (-0.19 mmol/L) for the UT-15C group compared to placebo (-0.02 mmol/L).

No subject reported a serious adverse event related to a laboratory value.

Urinalysis

Changes in the urine for blood and/or protein seemed similar for the two treatment groups (table 14.3.5).

Vital signs

A summary of vital signs is shown in the table below.

Mean change from baseline at week 12

	UT-15C n=183	Placebo n=97
weight	0.33 kg	0.46 kg
pulse	1.9 bpm	0.5 bpm
systolic bp	-3.0 mmHg	1.9 mmHg
diastolic bp	-2.8 mmHg	2.0 mmHg

Table 14.3.7

There is a small increase in heart rate and a larger decrease in blood pressure in the UT-15C group compared to placebo.

The table below shows the number and percent of subjects who reported a serious event that could have been related to blood pressure or heart rate or rhythm.

No. and (%) of subjects reporting serious adverse event

	UT-15C n=233	Placebo n=116
syncope	2 (<1)	1 (<1)
atrial flutter	1 (<1)	0
SVT	1 (<1)	0

Table 14.3.1.3.2

There were few subjects in either group reporting these events.

Percent (%) of subjects reporting event

	UT-15C n=233	Placebo n=116
Syncope [^]	2	6
Tachycardia	3	<1
Hypotension	2	0
Atrial flutter	<1	0

[^]less than 1% reported as serious

Table 14.3.7

While it is likely that UT-15C has an effect of lowering blood pressure, there is little evidence that this drug produces serious hypotensive episodes.

Appendix 4

Title: Interim Report #1: An Open Label Extension Trial of UT-15C Sustained Release Tablets in Subjects with Pulmonary Arterial Hypertension

Study Drug: UT-15C (trepstinil diethanolamine)

Indication: Pulmonary Arterial Hypertension (PAH)

Study Number: TDE-PH-304

Study Initiation Date: 16 January 2007 (First Subject Enrolled)

Study Completion Date: Ongoing - Data cut-off for first interim report: 31 August 2011

Objectives:

The primary objective of this study is to provide UT-15C for eligible subjects who participated in phase 3 protocols TDE-PH-301, TDE-PH-302, TDE-PH-308 or other eligible study protocols conducted for the UT-15C product development program.

Secondary objectives include the following:

- Assess the long-term safety of UT-15C in these subjects through assessment of adverse events (AEs) and clinical laboratory parameters.
- Assess the effect of continued therapy with UT-15C on exercise capacity as assessed by the six minute walk test (6MWT) after one year of treatment.

Methodology:

This is an international, multi-center, open-label study designed to provide UT-15C for eligible subjects who participated in protocols TDE-PH-301, TDE-PH-302, TDE-PH-308, or other eligible study protocols conducted for the UT-15C product development program (e.g. TDE-PH-202).

Subjects randomly allocated to receive UT- 15C in protocols TDE-PH-301, TDE-PH-302, or TDE-PH-308 and enrolled in this open-label study will have completed visits at months 6, 12, 24, 36 and yearly visits thereafter, if applicable.

Subjects randomly allocated to receive placebo in protocols TDE-PH-301, TDE-PH-302, or TDE-PH-308 will have completed visits at months 3, 6, 12, 24, 36 and yearly visits thereafter, if applicable.

A 6MWT and Borg dyspnea score were conducted at the visit occurring 12 months after the subject's first exposure to UT-15C. Adverse events were reported continuously.

Number of Subjects (planned and analyzed):

A total of 833 subjects were enrolled prior to 31 August 2011. Nine subjects from study PH-202 had been enrolled in this open-label study at the time of data cut-off, however, TDE-PH-202 is currently recruiting subjects and data from these subjects were not included in this interim report. Therefore, data from 824 subjects were included in these data analyses.

Diagnosis and Main Criteria for Inclusion:

A subject was eligible to participate in this study if all of the following criteria were met:

1. The subject remained on study drug and completed all assessments during the Treatment Phase of the previous study (TDE-PH-301, TDE-PH-302, TDE-PH-308, or other eligible study protocols conducted for the UT-15C product development program (e.g. TDE-PH-202)), or the subject permanently discontinued study drug during the Treatment Phase of the previous study due to clinical worsening. Subjects must have completed premature termination assessments prior to discontinuing study drug, completed all remaining scheduled study visits and received placebo during the Treatment Phase of the previous study. Protocol amendment 4 included the TDE-PH-308 study as a source for subjects to enter the open-label study which increased the total sample size to approximately 900.
2. The subject voluntarily provided written informed consent to participate in the study.
3. The subject, if a female of childbearing potential agreed to continue practicing an acceptable method of birth control as deemed appropriate by the physician or institution (i.e., surgical sterilization, approved hormonal contraceptives, barrier methods [such as a condom or diaphragm] used with a spermicide, an intrauterine device, abstinence, or partner(s) with a vasectomy).

Exclusions:

1. The subject permanently discontinued study drug during the previous study (TDE-PH-301, TDE-PH-302, TDE-PH-308 or other eligible study protocols conducted for the UT-15C product development program (e.g. TDE-PH-202)) because of treatment related adverse events.
2. The subject permanently discontinued study drug during the Treatment Phase of the previous study because of clinical worsening (as defined in those study protocols) and did not undergo premature termination assessments prior to discontinuing study drug, and/or did not complete all remaining study visits through the final scheduled visit.
3. The subject permanently discontinued study drug during the Treatment Phase of the previous study due to clinical worsening, completed premature termination assessments prior to discontinuing study drug, completed all remaining scheduled study visits AND received UT-15C during the Treatment Phase of the previous study (TDE-PH-301, TDE-PH-302, TDE-PH-308, or TDE-PH-202).
4. The subject must not have developed any concurrent illness or condition during the conduct of the previous study, including but not restricted to, sleep apnea, chronic renal insufficiency, anemia, uncontrolled systemic hypertension or left sided heart disease, unless their physician considered that entry into this study would not be detrimental to their overall health.

Dosing and duration of treatment

Subjects randomly allocated to receive UT-15C during the Treatment Phase of the previous study (TDE-PH-301, TDE-PH-302, or TDE-PH-308) initiated therapy in this study at the same dose they received at the final visit for the preceding study.

For subjects randomly allocated to receive placebo during the Treatment Phase of the previous study (TDE-PH- 301, TDE-PH-302, or TDE-PH-308), the final dosing

instructions as specified by protocol Amendment 4 required that study drug be initiated at 0.25 mg twice daily.

Dose escalations were allowed with increments of either 0.25 mg or 0.5 mg BID every three days. There was no upper dosing limit specified.

Duration of Treatment:

The study will continue until either UT-15C becomes commercially available or the study is discontinued by the sponsor.

Other PAH medications

Concomitant PAH medication (endothelin receptor antagonists and phosphodiesterase type 5 inhibitors) could be added, deleted, or dose adjusted as deemed clinically necessary by the investigator during the study. Additional prostanoid therapies administered by any route of administration were not allowed.

Criteria for Evaluation:

Efficacy:

A six minute walk test (6MWT) and corresponding Borg dyspnea score were assessed at the study visit occurring 12 months after the subject first received UT-15C, if applicable.

Safety:

AE reports are being collected throughout the study at regularly scheduled clinic visits and via telephone contact between the site and each subject on a regular basis. Clinical laboratory parameters (hematology, chemistry, and urinalysis) are collected routinely during study visits.

Results

Disposition

As of August 31, 2011, there were 87 reported deaths that occurred while on study drug or within 30 days of discontinuation.

Demography

The table below shows the demographic parameters for the 824 subjects by baseline study. For subjects who received placebo in the base study, baseline values were defined as the value collected at the subject's respective final visit in protocol TDE-PH-301, TDE-PH-302, or TDE-PH-308. For subjects who received UT-15 during the base study, baseline values were defined as the value collected during each subject's baseline visit prior to receiving their first dose of UT- 15C.

Table 11-1 Summary of Baseline Demographics

Characteristic	TDE-PH-301 and TDE-PH-308 n = 543	TDE-PH-302 n = 279	De Novo n = 2	Overall n = 824
Age in Years: mean (range)	50 (16–76)	41 (12–69)	55 (44–66)	47 (12–76)
Gender: Male/Female (n)	107 / 436	77 / 202	0 / 2	184 / 640
Race: n (%)				
American Indian / Alaska Native	10 (2)	25 (9)	0 (0)	35 (4)
Asian	82 (15)	138 (50)	0 (0)	220 (27)
Caucasian	420 (77)	105 (38)	0 (0)	525 (64)
African American	36 (7)	9 (3)	0 (0)	45 (5)
Native Hawaiian / Pacific Islander	1 (<1)	0 (0)	0 (0)	1 (<1)
Ethnicity: n (%)				
Hispanic	30 (6)	47 (17)	0 (0)	77 (9)
Non-Hispanic	513 (94)	232 (83)	0 (0)	745 (90)
Missing	0 (0)	0 (0)	2 (100)	2 (<1)
PAH Etiology: n (%)				
IPAH/HPAH	359 (66)	214 (77)	0 (0)	573 (70)
CVD	152 (28)	49 (18)	0 (0)	201 (24)
Repaired CHD	24 (4)	14 (5)	0 (0)	38 (5)
HIV infection	8 (1)	2 (<1)	0 (0)	10 (1)
Missing	0 (0)	0 (0)	2 (100)	2 (<1)
WHO Functional Classification: n (%)				
I	5 (<1)	7 (3)	0 (0)	12 (1)
II	157 (29)	116 (42)	0 (0)	273 (33)
III	369 (68)	156 (56)	0 (0)	525 (64)
IV	11 (2)	0 (0)	0 (0)	11 (1)
Missing	1 (<1)	0 (0)	2 (100)	3 (<1)

^a Subjects were instructed to designate all race(s) that applied.

- Mean age for these subjects was 47.1 years (range 12–76 years);
- 78% were female;
- 70% were diagnosed with idiopathic or heritable PAH;
- 24% were diagnosed with PAH associated with collagen vascular disease;
- 16% and 23% were on background ERA or PDE5-I therapy, respectively;
- at baseline, the mean time since PAH diagnosis was 2.8 years.

Dosing

The mean bid dosing at months 6, 12, 24, and 36 are shown below.

Table 12-1 Mean Twice Daily Dose of UT-15C at Each Study Visit

Study Visit	Previous Study							
	TDE-PH-301 and TDE-PH-308		TDE-PH-302		De Novo		Overall	
	N	Mean ± SD (mg)	N	Mean ± SD (mg)	N	Mean ± SD (mg)	N	Mean ± SD (mg)
Month 6	360	3.5 ± 2.9	201	4.0 ± 2.6	2	2.7 ± 1.1	563	3.7 ± 2.8
Month 12	230	4.0 ± 3.3	130	4.6 ± 2.8	2	3.3 ± 0.4	362	4.2 ± 3.1
Month 24	145	4.8 ± 3.8	76	5.4 ± 3.4	1	2.5	222	5.0 ± 3.7
Month 36	99	5.5 ± 4.0	52	5.2 ± 3.8	1	2.5	152	5.3 ± 3.9

The mean bid doses ranged between 3.7 mg (month 4) up to 5.3 mg (month 36).

Duration of exposure

The table below shows the duration of exposure as of August 31, 2011 for the 824 subjects enrolled in the extension study.

Table 12-3 Exposure to UT-15C

Duration of Exposure to UT-15C	Number of Subjects in Study Exposed to UT-15C at Given Time Point N (%)
Total Subjects Exposed*	822 (>99)
≥3 months	736 (90)
≥6 months	605 (74)
≥12 months	363 (44)
≥24 months	216 (26)
≥36 months	154 (19)
≥48 months	42 (5)

*Subjects 006109 and 050102 were not exposed to UT-15C and not included in this analysis

At 12 months, there had been 363 subjects exposed to UT-15C. A total of 42 subjects had received the drug for at least 48 months.

Efficacy results

Efficacy was assessed by the effect of UT-15C on exercise capacity as measured by the change in 6MWD and by the change in Borg dyspnea score from baseline to Month 12. Data from subjects who discontinued treatment for any reason prior to 12 months timepoint were not included in the efficacy analyses. Additionally, 242 (29%) subjects who had not yet received UT-15C for 12 months and had not yet completed the corresponding assessment were not included in the efficacy analyses.

The results are shown here for completeness only, interpretation of the change in 6MWD is limited by the lack of a control group, subject discontinuations, and the possible addition of other PAH therapy (including ERAs and PDE5-Is).

Table 11-3 Summary of Mean Six-Minute Walk Distance Change at Month 12

Previous Study Enrollment		Baseline	Month 12
TDE-PH-301 and TDE-PH-308	N	214	215
	Mean 6MWD (meters)	361	387
	Mean Change (meters)	—	+25.6
TDE-PH-302	N	122	122
	Mean 6MWD (meters)	336	362
	Mean Change (meters)	—	+25.9
De Novo	N		2
	Mean 6MWD (meters)	N/A	222
	Mean Change (meters)	—	N/A
Overall	N	336	339
	Mean 6MWD (meters)	352	377
	Mean Change (meters)	—	+25.7 ^a

^a n=336; subjects 040806, 041401, and 041402 did not have a Baseline value recorded for 6MWD

There were 37 subjects were started PAH-approved background therapy after their enrollment into study 304. Their walk distances at baseline and at 12 months are shown below along with the results for the 299 subjects who did not start other PAH therapy.

Table 11-4 Summary of Median Six-Minute Walk Distance Change at Month 12 by Addition of PAH-Approved Background Therapy

		Baseline	Month 12
Additional PAH-approved background therapy added since Baseline N = 37	Median 6MWD (meters)	370	366
	Median Change (meters)	—	+20
No additional PAH- approved background therapy added since Baseline N = 299	Median 6MWD (meters)	366	388
	Median Change (meters)	—	+24

The gain for all groups is between 20 and 26 meters. However, as stated before, these data are unreliable.

Borg scores

The Borg dyspnea score was assessed immediately following the 6MWT using a rating scale from 0 (best condition) to 10 (worst condition).

Table 11-5 Mean Borg Dyspnea Scores

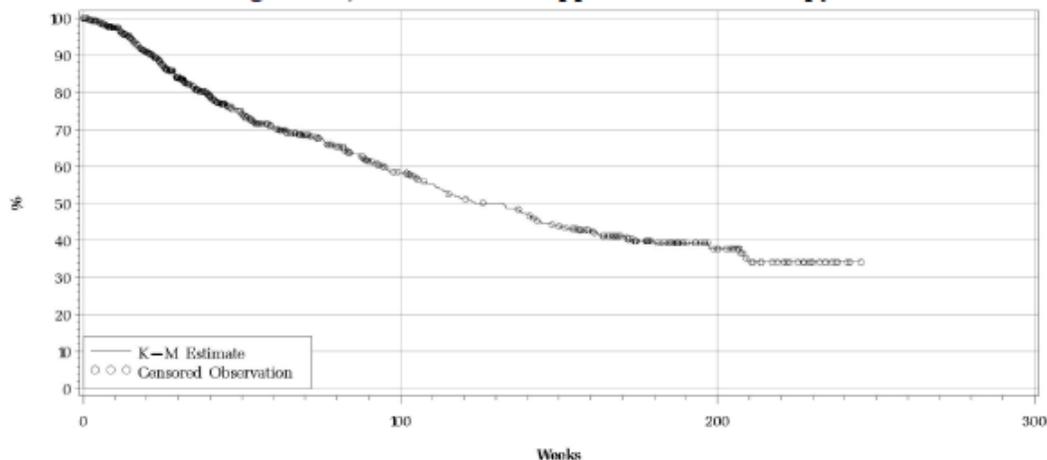
Previous Study Enrollment		Baseline	Month 12
TDE-PH-301 and TDE-PH-308	N	214	217
	Mean	4.01	3.69
	Mean Change	—	-0.34
TDE-PH-302	N	122	121
	Mean	3.84	2.84
	Mean Change	—	-1.00
De Novo	N	0	2
	Mean	N/A	6.00
	Mean Change	—	N/A
Overall	N	336	340
	Mean	3.95	3.40
	Mean Change	—	-0.58

Overall, the subjects decreased their scores. As with the walk data, these results are unreliable.

Time to death

The figure below shows the Kaplan-Meier analysis of death, discontinuation because of disease progression, or the addition of another PAH therapy (but remained in the study).

Figure 11-3 Kaplan-Meier Analysis of Death, Discontinuation due to Disease Progression, or Addition of Approved PAH Therapy

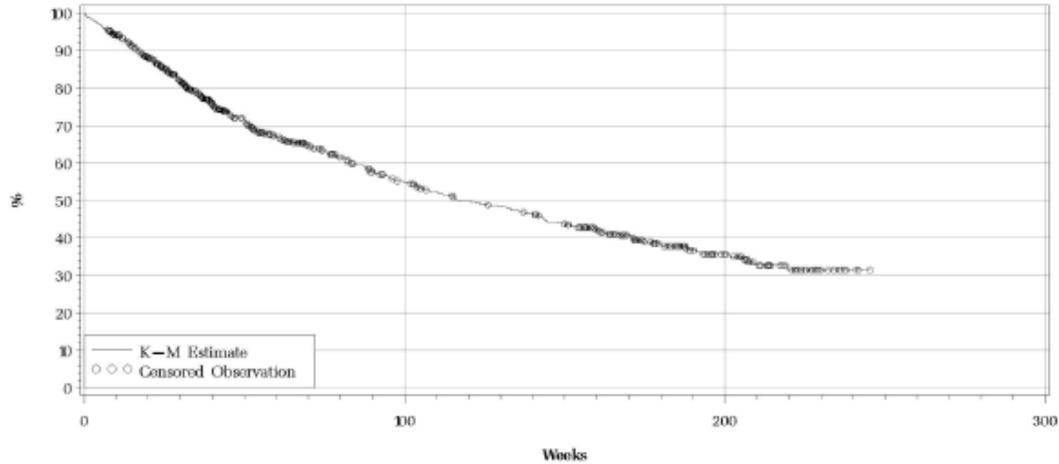


Weeks	0	33	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	247
# Events	0	34	99	138	171	188	199	215	227	243	249	263	270	274	278	278	281	283	283	283
# Censored	2	71	105	204	329	365	390	409	422	426	428	431	438	456	476	495	512	523	534	541
# Pts Remaining	822	719	560	422	324	271	235	200	175	155	147	130	116	94	70	51	31	18	7	0

Overall, approximately 73.0%, 57.5%, and 42.8% of subjects died, discontinued because of disease progression, or had another PAH therapy added at 1, 2, and 3 years following initiation of UT-15C treatment, respectively.

The figure below shows the Kaplan-Meier analysis for discontinuation of UT-15C treatment for any reason.

Figure 11-4 Kaplan-Meier Analysis of Discontinuation of UT-15C Treatment for Any Reason

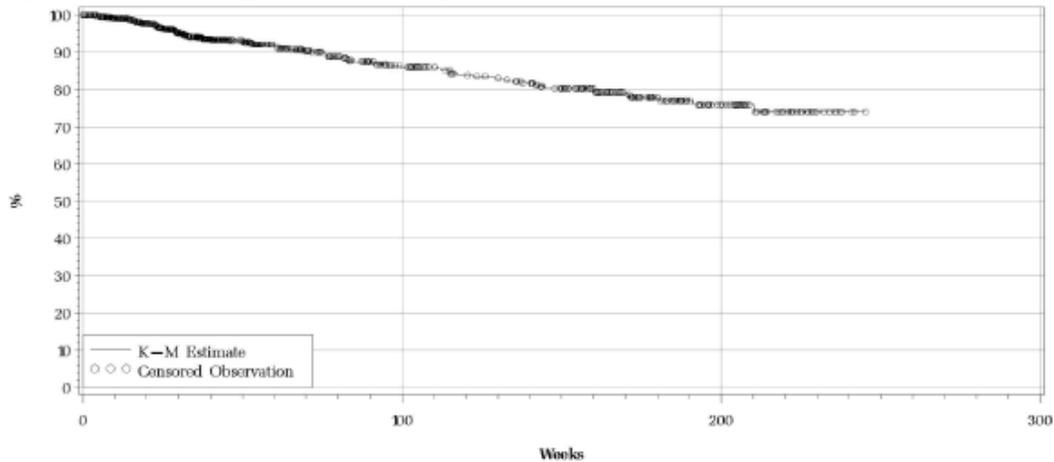


Weeks	0	31	26	39	52	65	78	91	104	117	130	143	156	169	182	195	208	221	234	247
# Events	2	61	123	174	213	233	248	270	284	299	305	317	327	334	342	346	349	351	351	351
# Censored	0	27	99	133	247	279	301	313	322	328	329	334	341	367	303	434	434	449	465	473
# Pts Remaining	822	736	602	457	304	312	275	241	238	197	190	173	156	123	89	64	41	24	8	0

Event-free estimates were 69.6%, 53.7%, and 42.8 after receiving 1, 2, and 3 years of UT-15C therapy, respectively.

The Kaplan-Meier survival curve is shown below.

Figure 11-1 Kaplan-Meier Analysis of Survival

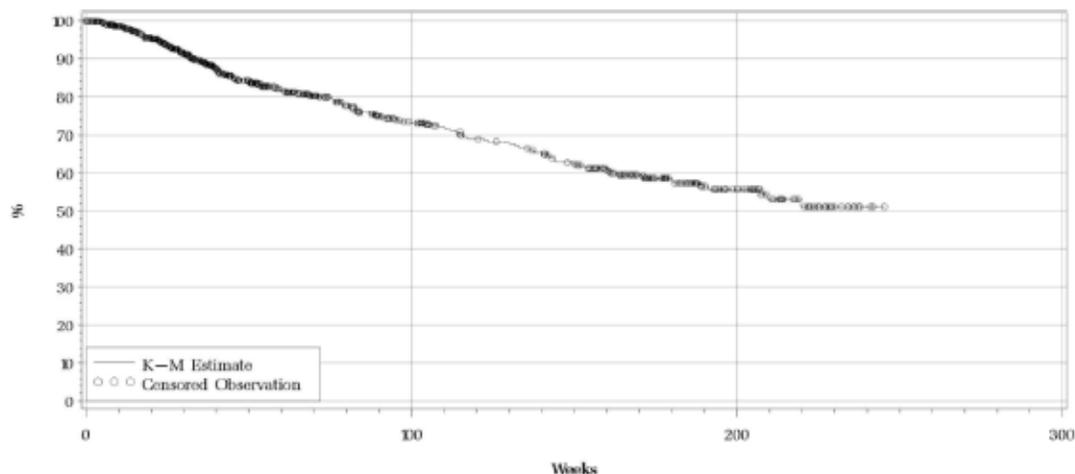


Weeks	0	8	27	42	46	53	59	63	67	71	74	79	80	82	85	86	86	87	87	87
# Events	0	8	27	42	46	53	59	63	67	71	74	79	80	82	85	86	86	87	87	87
# Censored	2	80	105	325	413	459	490	518	539	556	560	572	588	619	650	674	697	733	729	737
# Pts Remaining	822	736	602	457	305	312	275	243	238	197	190	173	156	123	89	64	41	24	8	0

The 1, 2, and 3 year survival estimates for this study population were approximately 92.6%, 86.0%, and 80.3%, respectively.

The figure below shows the Kaplan-Meier analysis of progression free survival.

Figure 11-2 Kaplan-Meier Analysis of Progression Free Survival



Weeks	0	31	61	91	121	151	181	211	241	271	300
# Events	0	17	51	80	101	121	141	161	181	201	221
# Censored	2	71	171	287	359	400	426	449	467	477	480
# Pts Remaining	822	736	602	457	364	312	275	241	219	197	180

Of those subjects alive at 1, 2, and 3 years after initiation of UT-15C therapy, 83.7%, 73.1%, and 61.3% of subjects, respectively, were alive and had not experienced disease progression.

Safety

Serious safety

Deaths

As of August 31, 2011, there were 87 reported deaths in subjects either on UT-15C or within 30 days of stopping the drug. Of the 87 deaths,

-50 (57%) were judged to be the result of disease progression.

- Of the remaining 37 deaths,
- 10 sudden or unexplained death,
- 3 sepsis or probable sepsis,
- 3cardiogenic shock,
- 2 right heart failure,
- 2 pneumonia,

-2 gastrointestinal bleed,
 -2 pulmonary embolism or suspected,
 -3 sudden cardiac death or pulseless electrical activity arrest,
 -2 surgical complications,
 -and 1 each for variceal hemorrhage, subdural hematoma with possible rebound PAH, enterocolitis, heart failure, progression of underlying disease, respiratory failure, scleromiositis, and combination of pneumonia, acute respiratory distress syndrome, and sepsis.

Regarding PAH background therapy, about half (43) of the deaths occurred in subjects who had been enrolled in the study that required either ERA or PDE5-I, or both as background therapy and the other deaths (44) were from the study that did not allow other PAH drugs.

Serious non lethal adverse event

The treatment-emergent serious adverse events SAEs reported for this study through 01 August 1, 2011 are shown in the table below (limited to those events reported by more than one subject).

Table 12-5 Summary of Serious Adverse Events Occurring in at Least 1% of Subjects in the Overall Study Population

Adverse Event	Previous Study N (%)			Overall N= 824
	TDE-PH-301 And TDE-PH-308 N= 543	TDE-PH-302 N= 279	De Novo N= 2	
Any event	229 (42)	108 (39)	1 (50)	338 (41)
Pulmonary hypertension	65 (12)	15 (5)	0	80 (10)
Right ventricular failure	42 (8)	17 (6)	0	59 (7)
Pneumonia	11 (2)	10 (4)	1 (50)	22 (3)
Chest pain	15 (3)	6 (2)	0	21 (3)
Dyspnea	12 (2)	5 (2)	1 (50)	18 (2)
Acute renal failure	10 (2)	8 (3)	0	18 (2)
Syncope	13 (2)	5 (2)	0	18 (2)
Headache	6 (1)	6 (2)	0	12 (1)
Anemia	9 (2)	2 (<1)	0	11 (1)
Cardiac failure	5 (<1)	6 (2)	0	11 (1)

Serious adverse events were reported by 41% of the study population. The most common serious adverse events reported during the study include pulmonary

hypertension, right ventricular failure, pneumonia, and chest pain. Acute renal failure was reported by 18 subjects and serious anemia was reported by 11 subjects.

Adverse Events

The adverse events reported by at least 8% of subjects are shown below.

Number and (percent) of subjects

Adverse Event	Previous Study N (%)			
	TDE-PH-301 And TDE-PH-308 N = 543	TDE-PH-302 N= 279	De Novo N= 2	Overall N=824
Any Event	535 (99)	273 (98)	2 (100)	810 (98)
Headache	396 (73)	195 (70)	2 (100)	593 (72)
Diarrhea	343 (63)	143 (51)	2 (100)	488 (59)
Nausea	299 (55)	117 (42)	1 (50)	417 (51)
Flushing	235 (43)	89 (32)	1 (50)	325 (39)
Pain in jaw	203 (37)	70 (25)	1 (50)	274 (33)
Vomiting	164 (30)	99 (35)	0	263 (32)
Pain in extremity	138 (25)	63 (23)	2 (100)	203 (25)
Dizziness	111 (20)	54 (19)	0	165 (20)
Upper respiratory tract infection	93 (17)	43 (15)	1 (50)	137 (17)
Peripheral edema	85 (16)	43 (15)	0	128 (16)
Fatigue	84 (15)	43 (15)	0	127 (15)
Dyspnea	85 (16)	35 (13)	1 (50)	121 (15)
Nasopharyngitis	71 (13)	36 (13)	0	107 (13)
Cough	59 (11)	44 (16)	0	103 (13)
Pulmonary hypertension	78 (14)	24 (9)	0	102 (12)
Myalgia	61 (11)	39 (14)	0	100 (12)
Chest Pain	59 (11)	34 (12)	0	93 (11)
Arthralgia	58 (11)	30 (11)	0	88 (11)
Abdominal pain	43 (8)	39 (14)	1 (50)	83 (10)
Palpitations	65 (12)	18 (6)	0	83 (10)
Upper abdominal pain	50 (9)	25 (9)	0	75 (9)
Insomnia	41 (8)	25 (9)	0	66 (8)
Pain	43 (8)	22 (8)	1 (50)	66 (8)
Abdominal distension	41 (8)	23 (8)	0	64 (8)
Right ventricular failure	45 (8)	18 (6)	0	63 (8)
Syncope	39 (7)	24 (9)	0	63 (8)
Back pain	40 (7)	22 (8)	0	62 (8)
Nasal congestion	49 (9)	12 (4)	1 (50)	62 (8)

The most commonly reported event was headache (72%), followed by diarrhea (59%), nausea (51%), flushing (39%), pain in jaw (33%), and vomiting (32%).

Discontinuations because of adverse event

There were 186 subjects who reported an adverse event that resulted in permanent study drug discontinuation. The events that were reported by at least 1% of study subjects are shown below.

Table 12-8 Summary of Adverse Events that Resulted in Permanent Discontinuation of UT-15C in at Least 1% of Subjects in the Overall Study Population

Adverse Event	Previous Study N (%)			
	TDE-PH-301 and TDE-PH-308 N= 543	TDE-PH-302 N= 279	De Novo N= 2	Overall N=824
Any event	136 (25)	50 (18)	0	186 (23)
Pulmonary hypertension	45 (8)	7 (3)	0	52 (6)
Headache	23 (4)	11 (4)	0	34 (4)
Nausea	19 (3)	6 (2)	0	25 (3)
Diarrhea	11 (2)	6 (2)	0	17 (2)
Right ventricular failure	11 (2)	5 (2)	0	16 (2)
Vomiting	7 (1)	9 (3)	0	16 (2)
Dyspnea	4 (<1)	5 (2)	0	9 (1)

The most commonly reported events were pulmonary hypertension (52 subjects) followed by headache (34 subjects) and nausea (25 subjects).

Laboratory parameters

The table below shows the laboratory values that were reported as adverse events.

Table 12-9 Adverse Events Related to Laboratory Parameters Occurring in at Least 1% of the Overall Study Population

Adverse Event (Preferred Term)	Previous Study N (%)			
	TDE-PH-301 and TDE-PH-308 N= 543	TDE-PH-302 N=279	De Novo N= 2	Overall N= 824
Hypokalemia	36 (7)	22 (8)	0 (0)	58 (7)
Anemia	31 (6)	10 (4)	0 (0)	41 (5)
Hyponatremia	8 (1)	9 (3)	0 (0)	17 (2)
Thrombocytopenia	6 (1)	9 (3)	0 (0)	15 (2)
Iron deficiency anemia	11 (2)	1 (<1)	0 (0)	12 (1)
Liver function test abnormal	8 (1)	3 (1)	0 (0)	11 (1)
Blood creatinine increased	9 (2)	1 (<1)	0 (0)	10 (1)
Blood potassium decreased	10 (2)	0 (0)	0 (0)	10 (1)
Aspartate aminotransferase increased	7 (1)	2 (<1)	0 (0)	9 (1)
Blood lactate dehydrogenase increased	7 (1)	2 (<1)	0 (0)	9 (1)

Hypokalemia (7%) and anemia (5%) were the most commonly reported laboratory adverse events. There were 11 subjects who reported anemia as a serious adverse event (table 12-5).

Vital signs and physical findings

These were not collected during this study.

Appendix 5

Clinical trial review **Protocol TDE-PH-308**

Medical Reviewer's conclusions: This study (as was TDE-PH-301) was designed to evaluate the safety and efficacy of UT-15C administered over 16 weeks to subjects with PAH who were receiving stable background therapy including an ERA and/or a PDE5-I. The dose of study drug was to be titrated until the "optimal" dose was achieved.

The primary endpoint of change in 6MWD at Week 16 trended but did not achieve statistical significance.

There were numerous study subjects randomized to UT-15C who discontinued prematurely, primarily because of study drug intolerability. There were numerous adverse events that were reported significantly more often in the UT-15C group compared to placebo.

Overall, in this study there was a statistically insignificant treatment effect and the drug was found to be difficult for patients to tolerate. In addition, there was no attempt to determine if UT-15C has a dose response.

Title: A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects with Pulmonary Arterial Hypertension

Study Dates: June 15, 2009 (First Subject Enrolled) through July 22, 2011 (Last Subject Completed).

OBJECTIVES

Study objectives

The primary objective of this 16-week study was to assess the effect of UT-15C sustained release (SR) tablets on exercise capacity compared to placebo (as measured by the change in 6MWD from Baseline to Week 16) in subjects with PAH. The 6MWD was measured at peak drug concentration (3-6 hours after morning dose).

The secondary objectives of this study were to evaluate the effect of UT-15C on the following parameters:

-Clinical Worsening required one of the following:

- Death (all causes excluding accident)
- Transplantation
- Atrial septostomy
- Hospitalization as a result of right heart failure

- Greater than or equal to a 20% decrease in six-minute walk distance from Baseline (or too ill to walk) AND addition of an inhaled prostacyclin analogue, endothelin receptor antagonist (ERA), or phosphodiesterase type-5 inhibitor (PDE5-I)
- Initiation of parenteral prostacyclin therapy (i.e., epoprostenol, iloprost, or trepstinil) for the treatment of PAH

-Combined Walk Distance / Borg Dyspnea Score

-Serum N-terminal pro-BNP

-World Health Organization (WHO) Functional Classification

-Borg Dyspnea Score

-Quality of Life (CAMPHOR)⁶

-Quality of Life (CAMPHOR)

-Dyspnea-Fatigue Index

-Symptoms of PAH

-Biomarkers

Methodology:

This was an international, multi-center, randomized, double-blind, placebo-controlled, 16-week study in subjects with PAH currently receiving approved oral therapy for the treatment of PAH including an ERA and/or a PDE5-I. Subjects were required to have a Baseline 6MWD of 150 to 400 meters for inclusion in the study. Amendment 2 increased the upper limit of the Baseline 6MWD to 425 meters.

After qualifying for study entry, subjects were randomized into the 16-week Treatment Phase of the study. Subjects were assessed at five clinic visits including Baseline, Week 4, Week 8, Week 12 and Week 16. Subjects initiated treatment with UT-15C or placebo following randomization. Between visits, subjects were contacted weekly via the telephone to assess adverse events, changes in concomitant medications and to make decisions regarding study drug dose titration.

At Baseline, Weeks 4, 8, 12 and 16, subjects were assessed for 6MWD, clinical worsening, WHO functional classification, Borg dyspnea score, dyspnea-fatigue index, and signs and symptoms of PAH. Subjects were assessed for serum NT pro-BNP at Baseline, Week 8 and Week 16, and quality of life (CAMPHOR) at Baseline and Week 16. Biomarker samples were collected at Baseline, Week 8 and Week 16. Safety evaluations included assessment of adverse events throughout the study, assessment of laboratory samples for determination of hematology, chemistry, and urinalysis at Baseline, Weeks 8, and Week 16, ECGs, and physical examinations at Baseline and Week 16. Vital signs were also measured at each clinic visit.

⁶ The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is a health related quality of life instrument validated for PAH [McKenna 2006] that assesses impairment (symptoms), disability (activities) and quality of life. This assessment was to be conducted at Baseline prior to the initiation of study drug and at Week 16 in countries with access to a validated version of the CAMPHOR questionnaire based on language availability

Following completion of all study assessments, eligible subjects were able to enter the open-label extension study (TDE-PH-304).

Randomization

The study was randomized 1:1 active to placebo. All subjects were to be randomized using a centrally administered stratified permuted block randomization, stratified by type of background therapy (ERA, PDE-5 inhibitor, or both) which was to be balanced across the two treatment groups. Subjects will also be stratified by Baseline 6-Minute Walk distance (≤ 350 meters and > 350 meters). Block sizes were to be variable and not disclosed to investigators so that no inferences could be made about possible treatment assignments of current or future subjects. An interactive voice response system (IVRS) will be utilized for the central randomization procedure.

Pertinent inclusion criteria

- between the ages of 18 and 75 years of age at screening.
- weighs a minimum of 40 kilograms with a body mass index less than 40 kg/m²
- if female, is physiologically incapable of childbearing or practicing an acceptable method of birth control.
- has a diagnosis of symptomatic idiopathic or familial PAH, PAH associated with collagen vascular disease, PAH associated with HIV infection, or PAH associated with appetite suppressant or toxin use.
- if HIV positive, has a CD4 lymphocyte count ≥ 200 cells/mm³ within 30 days of Baseline and is receiving current standard of care antiretroviral or other effective medication for treatment of HIV.
- has a baseline 6-Minute Walk distance between 150 and 400 meters, inclusive,
- has received an approved PDE-5 inhibitor and/or an approved ERA for at least 90 days and at the current stable dose for 30 days prior to Baseline and is willing to remain on a PDE-5 inhibitor and/or an ERA and at the same dose for the duration of the 16-week Treatment Phase.
- is optimally treated with conventional pulmonary hypertension therapy (oral vasodilators, oxygen, digoxin, etc) with no additions, discontinuations, or dose changes for at least 14 days prior to Baseline (excluding anticoagulants).
- has previously undergone a cardiac catheterization and been documented to have a mean pulmonary artery pressure (PAPm) > 25 mmHg, a pulmonary capillary wedge pressure (PCWP) or a left ventricular end diastolic pressure (LVEDP) < 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units and absence of unrepaired congenital heart disease prior to study initiation. In the event that a reliable PCWP or LVEDP are unable to be obtained during right heart catheterization, subjects with normal left heart function and absence of clinically relevant mitral valve disease on echocardiography are eligible for enrollment.
- has previously undergone echocardiography with evidence of normal left systolic and diastolic ventricular function, and absence of any clinically significant left sided heart disease (e.g. mitral valve stenosis).

-has a previous chest radiograph, ventilation perfusion scan, high resolution computerized tomography scan, or pulmonary angiography that are consistent with the diagnosis of PAH (i.e., low probability of pulmonary embolism; absence of major perfusion defects).

- has pulmonary function tests done within 6 months of Baseline with the following:

a. Total lung capacity (TLC) \geq 60% (predicted); if the TLC is between 60% and 70% of predicted, a high resolution CT scan must be performed to rule out diffuse interstitial fibrosis or alveolitis.

b. Forced expiratory volume/forced vital capacity (FEV/FVC) ratio \geq 50%

Selected exclusion criteria

-received epoprostenol, treprostinil, iloprost, beraprost, or any other prostacyclin therapy within 30 days of Baseline (except if used during acute vasoreactivity testing).

-has previously received UT-15C SR.

-has had previous intolerance or significant lack of efficacy to an oral or parenteral prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.

- has any disease associated with PAH other than collagen vascular disease, HIV infection, or appetite suppressant / toxin use (e.g. portal hypertension, chronic thromboembolic disease, pulmonary venoocclusive disease, etc.) or has had an atrial septostomy.

- has a current diagnosis of uncontrolled sleep apnea as defined by their physician.

-has chronic renal insufficiency as defined by either a Screening creatinine value greater than 2.5 mg/dL (221 μ mol/L) or the requirement for dialysis.

-has liver function tests (AST or ALT) greater than three times the upper limit of normal at Screening.

-has anemia as defined by a Screening hemoglobin value of less than 10 g/dL, active infection, or any other condition that would interfere with the interpretation of study assessments.

-has a history or current evidence of left-sided heart disease including previous myocardial infarction, or evidence of current left-sided heart disease as defined by PCWPM or LVEDP $>$ 15 mmHg or left ventricular ejection fraction (LVEF) $<$ 40% as assessed by either multigated angiogram (MUGA), angiography or echocardiography, or symptomatic coronary artery disease (i.e., demonstrable ischemia either at rest or during exercise).

-has uncontrolled systemic hypertension as evidenced by systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.

-has a musculoskeletal disorder (e.g. hip replacement, artificial leg, etc.) or any other disease that is likely to limit ambulation, or is connected to a machine that is not portable.

Drug dosage, administration and schedule

Once all entry criteria had been met and random treatment assignment confirmed, the first dose of study drug (0.25 mg) should have been taken by the subject. At this time,

oral dosing of study drug was to be initiated at 0.25 mg twice daily following breakfast and dinner. Prior to the Week 4 visit, each dose of study drug should have been adjusted in 0.25 mg increments. Following the Week 4 visit throughout the remainder of the study, each dose of study drug may have been adjusted in either 0.25 or 0.5 mg increments. If available, 0.125 mg tablets may have been utilized for dose titration at anytime throughout the course of the study if 0.25 mg dose increments were not tolerated. Doses of study drug should have been increased as tolerated up to 16 mg bid.

Dosing and administration of adjunctive medications

If the subject was receiving a PDE-5 inhibitor, the subject must have been on PDE-5 inhibitor therapy for at least 90 days and on the same dose for at least 30 days prior to Baseline. The minimum dose of sildenafil used in the study should have been 20 mg three times daily. If the subject was receiving an ERA, the subject must have been on ERA therapy for at least 90 days and on the same dose for at least 30 days prior to Baseline. The dose and frequency of background therapy was not be reduced during the study unless it was considered medically necessary.

Results

Disposition of subjects

A total of 313 subjects were randomized and 310 subjects (157 active and 153 placebo) receiving at least one dose of study drug. One subject was incorrectly randomized by the research site (Site 128). The site realized the randomization error, and consequently, re-randomized the subject as 128801. Two subjects (071801 and 128801) were randomized to the placebo group but did not receive a dose of study drug.

A summary of subject disposition for 310 subjects (subjects who were randomized and presumably took at least one dose of study drug) is shown below.

Table 10-1 Disposition of Study Subjects Who Discontinued Study Drug Prematurely

Study Disposition	Treatment n (%)	
	UT-15C n = 157	Placebo n = 153
Completed Study on Study Drug	132 (84)	138 (90)
Discontinued Study Drug Prematurely	25 (16)	15 (10)
Adverse Event	18 (11)	5 (3)
Clinical Worsening	4 (3)	4 (3)
Death	2 (1)	3 (2)
Withdrew Consent	1 (<1)	2 (1)
Lost to Follow-up	0 (0)	1 (<1)

A total of 40 subjects (25 UT-15C and 15 placebo) prematurely discontinued study drug. The most common reason for discontinuation was adverse event in the UT-15C (18

subjects compared to 5 placebo subjects). There were 5 deaths (2 UT-15C and 3 placebo).

More placebo subjects (138, 90%) agreed to enter the open label extension study TDE-PH-304 compared to the UT-15C subjects (122, 78%).

Demographics

The demographics for the study subjects are shown below by treatment group.

Table 11-1 Summary of Baseline Demographics

Characteristic	UT-15C (n =157)	Placebo (n =153)
Age in Years: mean (range)	51.5 (18–76)	50.4 (20–75)
Gender: Male/Female (n)	38/119	31/122
Race: n (%) #		
Caucasian	105 (67)	96 (63)
Asian	41 (26)	44 (29)
African American	11 (7)	9 (6)
Native American	3 (2)	4 (3)
Native Hawaiian	1 (<1)	0 (0)
PAH Etiology: n (%)		
IPAH/HPAH	104 (66)	99 (65)
CVD	48 (31)	49 (32)
Repaired CHD	3 (2)	1 (<1)
HIV	2 (1)	4 (3)
Background PAH Therapy: n (%)		
ERA	25 (16)	28 (18)
PDE5-I	67 (43)	65 (42)
Both	65 (41)	60 (39)
Baseline WHO Functional Classification:		
II/III/IV (n)	43/110/3 *	37/115/0 **
Baseline 6MWD:		
Mean ± SD (m)	329.4 ± 69.2	336.8 ± 63.5

Subjects were instructed to designate all race(s) that applied.

* Baseline WHO functional classification was not recorded for Subject 126802.

** Baseline WHO functional classification was not recorded for Subject 126804.

The 310 study subjects had a mean age of 51 years (range 18 to 76 years), most were female and white. The most common PAH etiology was idiopathic or heritable PAH (65%) followed by PAH related to collagen vascular disease (31%).

Background PAH therapy included ERA (17%), PDE5-I (42%) or both (40%).

The population was mostly WHO functional class III with only 3 subjects identified as class IV. Mean baseline 6MWD was 330 m for the UT-15C and somewhat longer (337 m) for the placebo group.

The groups were fairly well balanced at baseline.

Efficacy

The primary endpoint of the study was change in 6MWD from Baseline to Week 16 as measured by the 6MWD recorded three to six hours following the last dose of UT-15C at Week 16.

A non-parametric analysis of covariance (NP-ANCOVA), adjusted for baseline walk and PAH-approved background therapy, compared this endpoint between treatment groups for subjects in the ITT population. Magnitude of treatment effect was determined using the Hodges-Lehmann (H-L) method to estimate the median difference between treatment groups for change from Baseline in 6MWD.

Imputations used for missing primary efficacy data are as follows:

- The lowest rank was assigned for death within 16 weeks (excluding accidents), discontinuation due to clinical deterioration, transplantation or atrial septostomy and for subjects too ill due to their PAH to perform the 6MWT.
- Mean placebo rank (for NP-ANCOVA) or value corresponding to the geometric mean relative change for the placebo group was assigned to subjects who withdrew prior to any follow-up 6MWT.
- Last rank carried forward (for NP-ANCOVA) or last observation carried forward (for summary statistics) were assigned to subjects who withdrew prematurely or who did not perform the 6MWT due to any other reason not mentioned above.

The mean walk distances at baseline and weeks 4, 8, 12, and 16 along with the treatment effects are shown in the table below.

Table 11-2 Summary of Hodges-Lehmann Estimates of Treatment Effect

Time Period	Median 6MWD (meters)		Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
	UT-15C n = 157	Placebo n = 153		
Baseline	359	355	—	—
Week 4	360	369	+3 (-4, +10)	0.364
Week 8	352	366	+1 (-9, +11)	0.804
Week 12	361	360	+6.4 (-5, +19)	0.228
Week 16	370	365	+10 (-2, +22)	0.089

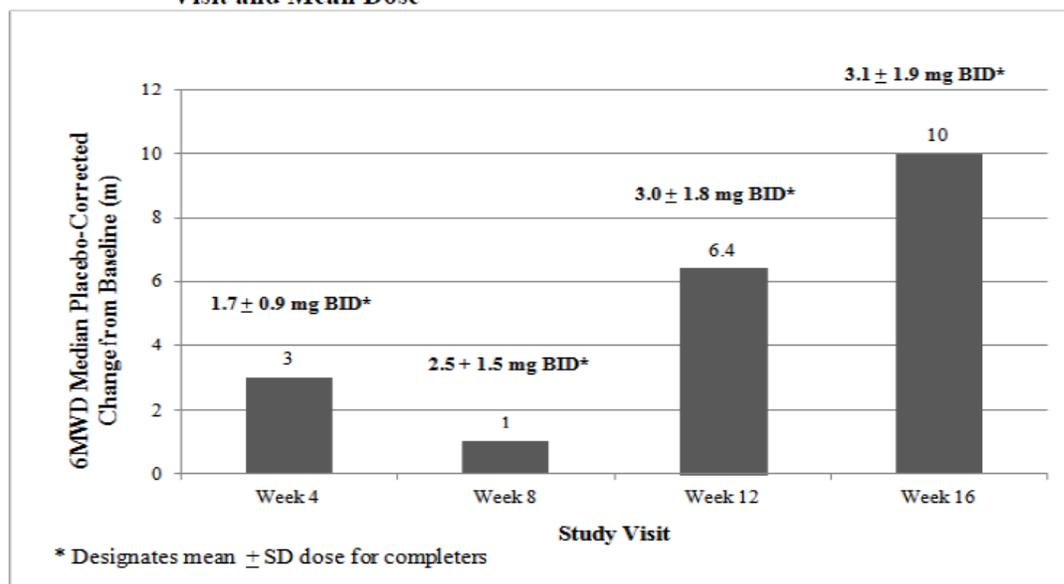
The treatment effect at each week was small and ranged from 1 m (week 8) and 10 m (week 16). The H-L estimates of treatment effect at all time points were not statistically significant using the pre-specified imputation methodology.

Drug Dose, Drug Concentration and Relationships

Formal dose analyses were not planned by the sponsor. Subjects were titrated to achieve a dose that resolved their signs and symptoms.

The mean doses for subjects receiving UT-15C by visit were 1.7, 2.5, 3.0 and 3.1 mg BID at Weeks 4, 8, 12, and 16 respectively. The figure below shows the Hodges-Lehman treatment effect by visit with mean dose for completers included.

Figure 11-10 Hodges-Lehman Estimate of Placebo-Corrected Treatment Effect by Visit and Mean Dose



Secondary efficacy endpoints

Clinical Worsening

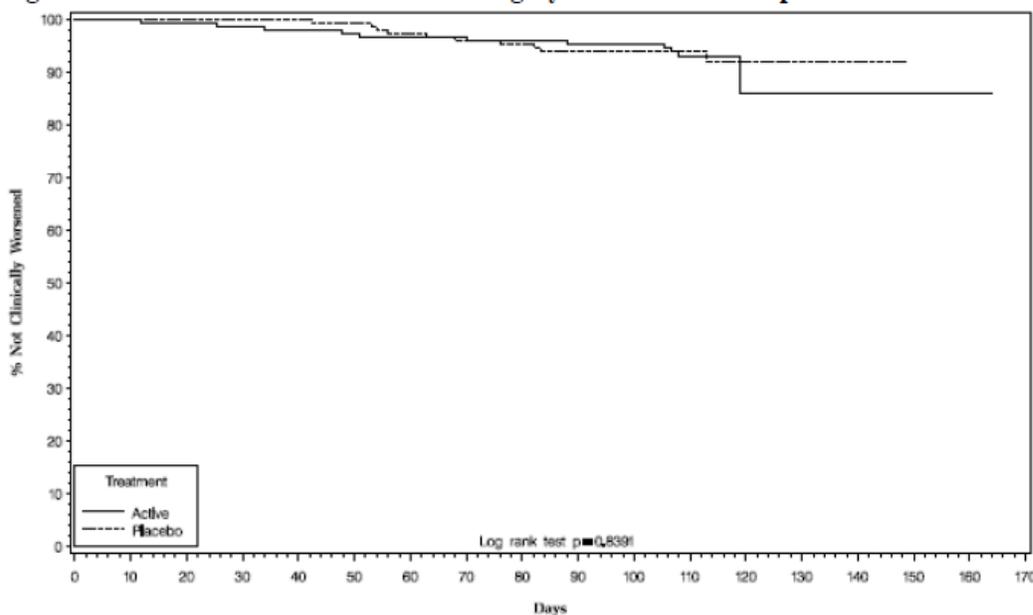
Time to clinical worsening was defined as the time from randomization to the first occurrence of death (except if resulting from accidental causes), transplantation, atrial septostomy or hospitalization due to right heart failure, a 20% or greater decrease in 6MWD from Baseline or were too ill to walk and had started a new PAH specific therapy (including either an ERA, a PDE5-I, or inhaled prostacyclin analogue) or if a parenteral prostacyclin had been added.

The results are shown in the table and Kaplan-Meier plot below.

Table 11-12 Summary of Clinical Worsening

Category	Clinical Worsening n (%)	
	UT-15C n = 157	Placebo n = 153
No Clinical Worsening	146 (93)	143 (93)
Clinical Worsening	11 (7)	10 (7)
Death	6 (4)	4 (3)
Transplantation	0 (0)	0 (0)
Atrial Septostomy	0 (0)	0 (0)
Right Heart Failure Hospitalization	4 (3)	2 (1)
Greater than or equal to 20% Decrease in 6MWD AND Inhaled/Oral PAH Medication Added	1 (<1)	3 (2)
Parenteral prostacyclin therapy for PAH Added	0 (0)	1 (<1)

Figure 11-8 Time to Clinical Worsening by Treatment Group



There is no evidence that UT-15C delays the time to clinical worsening in this 16-week study.

Borg Dyspnea Score

The Borg dyspnea score was assessed immediately following the walk test. Median scores remained similar (median score of 3.0) throughout the study in both treatment groups.

World Health Organization Functional Classification

WHO functional classification was assessed at baseline and during the week 4, 8, 12 and 16 visits. The majority of subjects were WHO functional class III at Baseline. There were no significant differences in WHO functional classification changes between treatment groups at Week 16.

Dyspnea-Fatigue Index

The dyspnea-fatigue index was assessed at baseline and weeks 4, 8, 12 and 16. Each of the three components of the dyspnea-fatigue index were rated on a scale 0 to 4, with 0 being the worst condition and 4 being the best condition for each component. The dyspnea-fatigue index is computed by summing the three component scores.

The table below shows the mean dyspnea-fatigue index scores at baseline and throughout the study.

Table 11-15 Mean Dyspnea-Fatigue Index Scores

Time Period	Mean Score	
	UT-15C n = 154*	Placebo n = 149**
Baseline	5.9	6.2
Week 4	6.2	6.1
Week 8	6.0	6.0
Week 12	6.0	6.0
Week 16	5.7	6.0

* Baseline dyspnea-fatigue index scores were not recorded for Subjects 114802, 126801, and 201801.

** Baseline dyspnea-fatigue index scores were not recorded for Subjects 126803, 126804, and 144801; Baseline dyspnea-fatigue index scores were recorded out of window for Subject 024803, and as a result, these Baseline dyspnea-fatigue index scores were not included in the analyses.

The mean score at baseline was somewhat worse for the placebo group (6.2) compared to the UT-15C group (5.9). Mean scores remained almost unchanged throughout the study for both treatment groups.

Symptoms of Pulmonary Arterial Hypertension

Symptoms of PAH including fatigue, dyspnea, edema, dizziness, syncope, chest pain and orthopnea were assessed at Baseline and at Weeks 4, 8, 12 and 16. The table below shows the change in PAH signs and symptoms scores at Week 16.

Table 11-16 Summary of PAH Symptoms at Week 16

Pulmonary Hypertension Signs and Symptoms	Treatment	
	Baseline (n) / Week 16 (n)	
	UT-15C n = 156*	Placebo n = 150**
Fatigue [#]		
None	14/16	16/31
Grade 1	63/68	65/54
Grade 2	70/52	64/48
Grade 3	9/20	5/17
Dyspnea [#]		
None	11/15	11/24
Grade 1	54/64	52/50
Grade 2	73/53	70/60
Grade 3	18/24	17/16
Edema		
None	82/94	87/98
Grade 1	49/30	50/37
Grade 2	15/18	12/5
Grade 3	10/14	2/11
Dizziness		
None	90/85	90/98
Grade 1	50/47	47/39
Grade 2	14/14	13/4
Grade 3	2/10	1/10
Syncope [#]		
None	147/141	146/135
Grade 1	8/4	3/5
Grade 2	0/1	0/0
Grade 3	1/10	1/10
Chest Pain		
None	113/118	102/109
Grade 1	31/22	40/20
Grade 2	10/5	7/13
Grade 3	2/11	2/9
Orthopnea [#]		
None	122/115	113/114
Grade 1	23/19	28/20
Grade 2	10/10	8/4
Grade 3	1/12	1/12

* Baseline PAH signs and symptoms were not recorded for Subject 126801.

** Baseline PAH signs and symptoms were not recorded for Subjects 126804 and 144801; Baseline PAH signs and symptoms were recorded out of window for Subject 024803, and as a result, these results were not included in the analyses.

For fatigue, dyspnea, syncope and orthopnea, the n is 150. Subject 134802 did not have Baseline values for fatigue, dyspnea, syncope and orthopnea. Given there was no Baseline to Week 16 comparison, the subject's data was not analyzed for these particular symptoms.

There was no observed treatment effect on symptoms of PAH.

Serum N-terminal pro-BNP

The baseline serum NT pro-BNP concentrations were similar among treatment groups with a mean baseline value of 1324.80 pg/mL in the UT15C treatment group, and 1604.70 pg/mL in the placebo group. There was no significant difference between treatment groups for the change from Baseline to Week 16.

Quality of Life (CAMPHOR)

The CAMPHOR questionnaire was provided to subjects at Baseline and Week 16. The table below shows the results.

Table 11-18 Hodges-Lehmann Median Placebo-Corrected Change in CAMPHOR Scores from Baseline to Week 16

Section	Median Score		Hodges-Lehmann Estimate of Treatment Effect (95% CI)	P value
	UT-15C (n=102)	Placebo (n=85)		
Symptom	10.0	9.0	0.0 (-1.0, 1.0)	0.941
Energy	4.0	4.0	0.0 (0.0, 1.0)	0.780
Breathlessness	4.0	4.0	0.0 (-0.7, 0.0)	0.447
Mood	2.0	1.0	0.0 (0.0, 0.0)	0.685
Activity	10.0	10.0	0.0 (-1.0, 1.0)	0.693
Quality of Life*	9.0	5.0	1.0 (0.0, 2.0)	0.171
TOTAL CAMPHOR SCORE*	28.0	24.5	1.0 (-1.0, 4.0)	0.311

* n = 84

There is no evidence of a treatment effect regarding these characteristics.

In summary, there is no evidence that UT-15C improve the exercise tolerance of subjects with PAH who are taking concomitant PAH treatment.

Safety

Collection of adverse events

The protocol stated that:

Any event that is associated with the progression of a subject's PAH should NOT be recorded as an adverse event in the case report form as the most relevant symptoms of PAH will be evaluated and recorded as an efficacy endpoint and all other events will be captured as disease related events. Symptoms of PAH should only be recorded as an AE if the event is either serious, or is unusual with respect to intensity, frequency, duration, or there is a reasonable possibility that the event was caused by study drug.

Abdominal pain (Gastrointestinal disorders; ABDOMINAL PAIN)	Hemoptysis (Respiratory, thoracic & mediastinal disorders; HAEMOPTYSIS)
Anorexia (Metabolism and nutrition disorders; ANOREXIA)	Hypoxia (Respiratory, thoracic & mediastinal disorders; HYPOXIA)
Ascites (Gastrointestinal disorders; ASCITES)	Loss of consciousness (Nervous system disorders; LOSS OF CONSCIOUSNESS)
Cardiac arrhythmia (Cardiac disorders; ARRHYTHMIA)	Nausea (Gastrointestinal disorders; NAUSEA)
Cardiac arrest (Cardiac disorders; CARDIAC ARREST)	Edema (General disorders and administration site conditions; OEDEMA)
Heart failure (including exacerbation of) (Cardiac disorders; CARDIAC FAILURE)	Orthopnea (Cardiac disorders; ORTHOPNOEA)
Chest pain (General disorders and administration site conditions; CHEST PAIN)	Pallor (Vascular disorders; PALLOR)
Cardiovascular collapse (Vascular disorders; CIRCULATORY COLLAPSE)	Palpitations (Cardiac disorders; PALPITATIONS)
Cor pulmonale (Cardiac disorders; COR PULMONALE)	Cool extremities (General disorders and administration site conditions; PERIPHERAL COLDNESS)
Cough (Respiratory, thoracic & mediastinal disorders; COUGH)	Pulmonary arterial hypertension, exacerbation of (Vascular disorders; PULMONARY ARTERIAL HYPERTENSION)
Cyanosis (Cardiac disorders; CYANOSIS)	Sudden death (Cardiac disorders; SUDDEN DEATH)
Dizziness (Cardiac disorders; DIZZINESS)	Syncope (Cardiac disorders; SYNCOPE)
Dyspnea at rest (Respiratory, thoracic & mediastinal disorders; DYSPNOEA)	Vasovagal reaction (Nervous system disorders; SYNCOPE VASOVAGAL)
Dyspnea on exertion (Respiratory, thoracic & mediastinal disorders; DYSPNOEA EXERTIONAL)	Tachycardia (Cardiac disorders; TACHYCARDIA)
Paroxysmal nocturnal dyspnea (Cardiac disorders; DYSPNOEA PAROXYSMAL NOCTURNAL)	Vomiting (Gastrointestinal disorders; VOMITING)
Exercise intolerance (General disorders and administration site conditions; EXERCISE TOLERANCE DECREASED)	Weight loss (Investigations; WEIGHT DECREASED)
Fatigue (General disorders and administration site conditions; FATIGUE)	Weight gain (Investigations; WEIGHT INCREASED)

Part B: Expected events attributable to UT-15C Based on UT-15C and Remodulin Data (MedDRA system organ class and PREFERRED term, ver. 11.1)

When an adverse event may be attributed to the progression of pulmonary hypertension or UT-15C SR (e.g., listed in both Parts A and B) it must be recorded as an AE in the CRF if the event is either serious or unusual with respect to intensity, frequency, or duration, or there is a reasonable possibility that it may have been caused by study drug. Expected events attributable to UT-15C (e.g., listed in Part B only) must always be recorded as AEs in the CRF.

Abdominal pain (Gastrointestinal disorders; ABDOMINAL PAIN)	Insomnia (Psychiatric disorders; INSOMNIA)
Acute renal failure (Renal and urinary disorders; RENAL FAILURE ACUTE)	Leg pain (Musculoskeletal and connective tissue disorders; PAIN IN EXTREMITY)
Anemia (Blood and lymphatic system disorders; ANAEMIA)	Melena (Gastrointestinal disorders; MELAENA)
Anorexia (Metabolism and nutrition disorders; ANOREXIA)	Nausea (Gastrointestinal disorders; NAUSEA)
Backache (Musculoskeletal and connective tissue disorders; BACK PAIN)	Pain (General disorders and administration site conditions; PAIN)
Chest pain (General disorders and administration site conditions; CHEST PAIN)	Pallor (Vascular disorders; PALLOR)
Cor pulmonale (Cardiac disorders; COR PULMONALE)	Syncope (Cardiac disorders; SYNCOPE)
Diarrhea (Gastrointestinal disorders; DIARRHOEA)	Premature ventricular contractions (Cardiac disorders; VENTRICULAR EXTRASYSTOLES)
Dizziness (Cardiac disorders; DIZZINESS)	Pruritus (Skin and subcutaneous tissue disorders; PRURITUS)
Dyspnea (Respiratory, thoracic & mediastinal disorders; DYSPNOEA)	Pulmonary arterial hypertension, exacerbation of (Vascular disorders; PULMONARY ARTERIAL HYPERTENSION)
Edema (General disorders and administration site conditions; OEDEMA)	Rash (Skin and subcutaneous tissue disorders; RASH)
Epistaxis (Respiratory, thoracic & mediastinal disorders; EPISTAXIS)	Restlessness (Psychiatric disorders; RESTLESSNESS)
Fatigue (General disorders and administration site conditions; FATIGUE)	2nd degree heart block (Cardiac disorders; ATRIOVENTRICULAR BLOCK SECOND DEGREE)
Flushing (Vascular disorders; FLUSHING)	Spongiotic dermatitis (Skin and subcutaneous tissue disorders; DERMATITIS)
Gastrointestinal hemorrhage (Gastrointestinal disorders; GASTROINTESTINAL HAEMORRHAGE)	Sweating (Skin and subcutaneous tissue disorders; HYPERHIDROSIS)
Headache (Nervous system disorders; HEADACHE)	Thrombocytopenia (Blood and lymphatic system disorders; THROMBOCYTOPENIA)
Hearing loss (Ear and labyrinth disorders; DEAFNESS)	Vasodilatation (Vascular disorders; VASODILATATION)
Hypokalemia (Metabolism and nutrition disorders; HYPOKALAEMIA)	Vertigo (Ear and labyrinth disorders; VERTIGO)
Hypotension (Vascular disorders; HYPOTENSION)	Vomiting (Gastrointestinal disorders; VOMITING)
Hypoxemia (Respiratory, thoracic & mediastinal disorders; HYPOXIA)	Warmness / Feeling hot (General disorders and administration site conditions; FEELING HOT)
Jaw pain (Musculoskeletal and connective tissue disorders; PAIN IN JAW)	

It is unknown if this protocol requirement has an impact on the collection of adverse events.

Extent of exposure

Study drug was administered over 16 weeks during the course of this study. Dosing was initiated at a dose of 0.25 mg twice daily. At the discretion of the investigator, doses could be increased in 0.25 mg increments every three days during the first four weeks of the study and then either 0.25 or 0.5 mg increments after Week 4 as tolerated. When

the dose 0.125 mg was available, it was used for dose titration if 0.25 mg dose increments were not tolerated. Maximum allowed dose was 16 mg twice daily.

The mean dose is shown below by study visit and treatment group.

Table 12-1 Mean Study Drug Dose at Each Scheduled Visit

Study Visit (n = UT-15C / Placebo)	Study Drug Dose Achieved Mean Dose ± SD (mg BID)	
	UT-15C	Placebo
Week 4 (n = 152/152)	1.7 ± 0.9	2.3 ± 1.1
Week 8 (n = 145/151)	2.5 ± 1.5	3.9 ± 2.1
Week 12 (n = 141/143)	3.0 ± 1.8	5.7 ± 3.2
Week 16 (n = 134/140)	3.1 ± 1.9	6.1 ± 3.6

The mean dose was lower in the UT-15C group compared to placebo at all visits, suggesting a lack of tolerance for UT-15C.

Serious safety

Deaths

There were 6 reported deaths in the UT-15C group compared to 4 in the placebo group. The following table lists all ten reported deaths

Protocol: TDE-PH-308 dpressley(Deaths) 01NOV11 15:36

Table 14.3.2.1
Listing of Deaths

Subject	Random- ization	First Dose	Last Dose	Reason for Stopping Study Drug	D/C	Reason for Study Discontinuation	Date of Death	Day of Death	Cause of Death:
Treatment: Active									
059802	11JAN11	11JAN11	01APR11	Adverse Event	28APR11	Other	29APR11	109	Other: "Adverse Event"
134807	16MAR11	16MAR11	28JUN11	Adverse Event	01JUL11	Death	01JUL11	108	Other: "Sepsis Due To Lower Respiratory Tract Infection"
201806	17DEC10	17DEC10	10JAN11	Clinical Deterioration	11JAN11	Death	11JAN11	26	Other: "Severe Lung Infection, Respiratory Failure"
201814	03MAR11	03MAR11	23MAY11	Adverse Event	30MAY11	Death	30MAY11	89	Other: "Massive Haemoptysis"
202801	28OCT10	28OCT10	01DEC10	Death	01DEC10	Death	01DEC10	35	Other: "Sudden Death Under Unknown Reason"
202806	11NOV10	11NOV10	23NOV10	Death	23NOV10	Death	23NOV10	13	Progression of disease under study
Treatment: Placebo									
046802	18JUN10	18JUN10	19AUG10	Adverse Event	20AUG10	Death	20AUG10	64	Other: "Adverse Event: Dehydration"
111803	11NOV10	11NOV10	06JAN11	Death	06JAN11	Death	06JAN11	57	Other: "Cardio-Pulmonary Arrest"
114803	04JUN10	05JUN10	19AUG10	Death	19AUG10	Death	19AUG10	77	Other: "Pneumonia, A Complication Of Her T5 Crush Fracture"
200834	21FEB11	21FEB11	15APR11	Death	16APR11	Death	16APR11	55	Other: "Death Of Unknown Cause"

Narratives for each death from the UT-15C group are below..

Subject 059802

This was a 75-year-old, 92.3-kg, white female with a history of rheumatoid arthritis. Concomitant medications included nystatin, atenolol, spironolactone, furosemide, and oxygen.

Subject started 0.25 mg dose, reported headache, tongue swelling and thrush at 1 week, 1 week, and 1 month after starting study, respectively. Dose was decreased at time subject reported thrush.

Approximately 3 months after starting the study, the subject was admitted to the hospital with a diagnosis of **gastroenteritis and dehydration**. It was also reported that patient had **fallen** on that same day. The subject was withdrawn from study drug and **placed in hospice**. The patient's daughter, who was also her primary care provider, called the investigator and reported that the patient died on 29 Apr 2011. Information regarding an autopsy was not provided. The investigator made numerous attempts to contact the patient's daughter to gather more information regarding the death, but there was no response to voicemails and letter requests. Further information was not expected.

Subject 134807

This was a 66-year-old, 54.3 kg, white female with a medical history that included systemic sclerosis and lower respiratory tract infection. Concomitant medications included bosentan, warfarin, simvastatin, dosulepin, tramadol, gabapentin, ferrous sulfate, nifedipine, paracetamol, Oramorph (morphine sulfate), omeprazole, bendroflumethiazide, Seretice accuhaler (seretide), lisinopril, MIMS artificial tears (hyetellose), temazepam, lacri-lube, Viscol tears (carbomer).

On [REDACTED] (b) (6), the patient initiated blinded study drug (trepstinil/diethanolamine) at an unspecified dose. About 3 months after starting study drug (total daily dose of 11.5 mg) the subject was discontinued and was **hospitalized for vomiting, dizziness**, and 2 episodes of **collapse** without loss of consciousness. Upon presentation, the patient was hypotensive (85/55 mmHg) and tachycardic (110 bpm). The impression was the patient was intravascularly depleted because of **vomiting and hyperkalemia** secondary to pre-renal failure. She was treated with intravenous fluids and her potassium was corrected. The patient **deteriorated rapidly with drowsiness, hypotension and poor urine output**. She was admitted to the intensive treatment unit, ventilated and treated for presumed sepsis. Blood cultures were positive for *staphylococcus aureus* with an unclear source. The subject initially responded but then experienced a sudden cardiac arrest. Resuscitation was unsuccessful. Post mortem was not performed. The cause of death was certified as sepsis due to lower respiratory tract infection (patchy consolidation on chest x-ray), severe pulmonary hypertension and systemic sclerosis.

Subject 201806

This subject was a 57-year-old, 45-kg, Asian female with a medical history that was significant for hypertension and cough. Concomitant medications included sildenafil, amlodipine, digoxin, furosemide, potassium chloride, cetirizine and Fraxiparine (nadroparin calcium). Approximately 22 days after initiating study drug, the patient reported **fever, productive cough and worsening dyspnea**. The symptoms became worse and she was admitted for pulmonary infection. The patient was intubated and

ventilated. The patient subsequently died from **respiratory failure because of severe pulmonary infection**. The death certificate stated cause of death was respiratory failure, pulmonary hypertension and severe pulmonary infection. No autopsy was carried out.

Subject 201814

This subject was a 19-year-old, 43-kg. Concomitant medications included sildenafil, digoxin, furosemide, spironolactone and potassium chloride. The subject was receiving 4 mg total daily dose. Approximately 68 days after initiation of study drug, the patient reported **hemoptysis** and was hospitalized. All oral medications were stopped on admission. Study drug was restarted at a dose of 1.5 mg twice a day. The subject died about 3 weeks after hospitalization of massive hemoptysis. No autopsy was performed.

Subject 202801

This was a 31-year-old, 49.5-kg, Asian female with an unremarkable medical history except PAH. Concomitant medications included sildenafil and warfarin. The dose of UT-15C was increased to 2 mg daily. Approximately 5 weeks after starting drug, the subject suddenly felt **chest pain and dyspnea**. Death occurred despite immediate artificial respiration and external chest compressions. No autopsy was performed.

Subject 202806

This was a 37-year-old, 43-kg, Asian female with a medical history that included significant for systemic lupus erythematosus. Concomitant medications included furosemide, spironolactone, digoxin, warfarin, azathioprine and prednisone. Maximum total daily dose of study drug was 1 mg. Approximately 12 days after initiating study drug, the patient developed a fever and went to a local clinic. The patient was treated with bupleurum (a Chinese medicine) and oral amoxicillin. The patient's temperature returned to normal. Later that day, the patient suddenly experienced **dyspnea and chest discomfort**. She did not respond to oxygen, **lost consciousness** and died. An autopsy was not performed.

Most likely, these deaths are the result of the underlying disease.

Serious adverse events

The following table shows all serious adverse events reported by more than one subject in the UT-15C group.

Table 12-8 Summary of Serious Adverse Events Occurring in More Than One Subject Receiving UT-15C

Adverse Event	Treatment n (%)	
	UT-15C n = 157	Placebo n = 153
Any event	23 (15%)	23 (15%)
Right ventricular failure	5 (3%)	2 (1%)
Dyspnea	4 (3%)	2 (1%)
Lower respiratory tract infection	3 (2%)	0 (0%)
Pulmonary hypertension	2 (1%)	4 (3%)
Fluid overload	2 (1%)	1 (<1%)
Pyrexia	2 (1%)	1 (<1%)
Back pain	2 (1%)	0 (0%)
Fall	2 (1%)	0 (0%)

The reports of serious adverse events were similar for both treatment groups. Most were symptoms suggestive of PAH including right ventricular failure and dyspnea.

Discontinuations for adverse events

There were 23 subjects (15%) who were discontinued from UT-15C because of an adverse event compared to 11 subjects (7%) in the placebo group. This difference between drug groups was statistically significant.

Table 12-9 Summary of Adverse Events Resulting in Permanent Study Drug Discontinuation in More Than One UT-15C Subject

Adverse Event	Treatment n (%)	
	UT-15C n = 157	Placebo n = 153
Any event*	23 (15%)	11 (7%)
Headache*	9 (6%)	0 (0%)
Nausea	5 (3%)	0 (0%)
Diarrhea	3 (2%)	0 (0%)
Vomiting	3 (2%)	0 (0%)
Pulmonary hypertension	2 (1%)	2 (1%)
Right ventricular failure	2 (1%)	1 (<1%)
Chest pain	2 (1%)	0 (0%)
Dyspnea	2 (1%)	0 (0%)
Lower respiratory tract infection	2 (1%)	0 (0%)
Muscle spasms	2 (1%)	0 (0%)
Pain in extremity	2 (1%)	0 (0%)
Pain in jaw	2 (1%)	0 (0%)

*p < 0.05

Some of the events that were reported by more subjects in the UT-15C group included headache, nausea, diarrhea, and vomiting.

All reported adverse events

The table below shows the adverse events reported by at least 3% of subjects in the UT-15C group and reported by more subjects in this group compared to placebo.

Table 12-5 Summary of Adverse Events Occurring in at least 3% of Subjects Receiving UT-15C and More Frequently Than in Placebo Patients

Adverse Event	Treatment n (%)	
	UT-15C n = 157	Placebo n = 153
Any Event*	157 (100%)	136 (89%)
Headache*	112 (71%)	61 (40%)
Diarrhea*	87 (55%)	38 (25%)
Nausea*	73 (46%)	34 (22%)
Flushing*	55 (35%)	16 (10%)
Pain in jaw*	39 (25%)	10 (7%)
Vomiting*	33 (21%)	16 (10%)
Dizziness*	30 (19%)	15 (10%)
Pain in extremity*	27 (17%)	11 (7%)
Dyspnea*	25 (16%)	10 (7%)
Fatigue	23 (15%)	16 (10%)
Myalgia	18 (11%)	10 (7%)
Upper respiratory tract infection	17 (11%)	13 (8%)
Edema peripheral	17 (11%)	10 (7%)
Abdominal pain	12 (8%)	11 (7%)

Adverse Event	Treatment n (%)	
	UT-15C n = 157	Placebo n = 153
Arthralgia	12 (8%)	9 (6%)
Abdominal pain upper	12 (8%)	7 (5%)
Back pain	12 (8%)	6 (4%)
Muscle spasms	12 (8%)	5 (3%)
Decreased appetite	12 (8%)	4 (3%)
Dyspepsia	11 (7%)	8 (5%)
Nasal congestion*	10 (6%)	0 (0%)
Abdominal discomfort	7 (4%)	3 (2%)
Gastroesophageal reflux disease	7 (4%)	1 (<1%)
Frequent bowel movements*	7 (4%)	0 (0%)
Sinusitis	6 (4%)	5 (3%)
Fluid overload	6 (4%)	4 (3%)
Chest discomfort	6 (4%)	3 (2%)
Right ventricular failure	6 (4%)	2 (1%)
Hypolemia	6 (4%)	3 (2%)
Constipation	5 (3%)	3 (2%)
Lower respiratory tract infection	5 (3%)	3 (2%)
Brain natriuretic peptide increased	5 (3%)	2 (1%)
Malaise	5 (3%)	2 (1%)
Depression	5 (3%)	1 (<1%)
Edema	5 (3%)	1 (<1%)
Rash	5 (3%)	0 (0%)
Sinus congestion	5 (3%)	0 (0%)
Flatulence	4 (3%)	3 (2%)
Presyncope	4 (3%)	3 (2%)
Gastroenteritis viral	4 (3%)	2 (1%)
Chills	4 (3%)	1 (<1%)
Musculoskeletal pain	4 (3%)	1 (<1%)
Neck pain	4 (3%)	1 (<1%)
Anemia	4 (3%)	0 (0%)

* p < 0.05

There were substantially more reports of headache, diarrhea, nausea, flushing, jaw pain, vomiting, dizziness, pain in extremity, dyspnea, nasal congestion, and frequent bowel movements by the UT-15C subjects compared to placebo subjects. Other events reported by more UT-15C subjects include fatigue, myalgia, URI, peripheral edema, back pain, muscle spasms, and decreased appetite.

Clinical laboratory

Laboratory evaluations of hematology, chemistry, urinalysis and NT pro-BNP were collected at Baseline, Week 8 and Week 16 to assess the effect of UT-15C on individual laboratory parameters. Laboratory analyses were conducted (b) (4)

Hematology

There were decreases from baseline at week 16 in the UT-15C group for several of the hematology parameters. These changes are shown in the table below.

Mean change from baseline at week 16

	UT-15C N=123	Placebo N=133
RBC count 10 ¹² /L	-0.01	0.02
Hemoglobin g/dL	-0.27	0.02
Hematocrit %	-0.1	0.5
WBC 10 ⁹ /L	-0.38	-0.06

Table 14.3.4.2

There is a small but consistent decrease from baseline for these parameters in the UT-15C group compared to placebo.

A list of reported adverse events pertaining to hematology by each treatment groups is shown below.

Table 14.3.1.2
 Summary of Adverse Events By Body System

Preferred Term:	Treatment	
	Active	Placebo
** Any Body System **:		
** Any Event **	157/157 (100) [1179]	136/153 (89) [705]
<u>Blood and lymphatic system disorders:</u>		
Anaemia	4/157 (3) [4]	0
Hypocoagulable state	1/157 (<1) [1]	0
Iron deficiency anaemia	0	1/153 (<1) [1]
Leukocytosis	1/157 (<1) [1]	0
Thrombocytopenia	1/157 (<1) [1]	1/153 (<1) [1]
Haemorrhagic diathesis	1/157 (<1) [1]	0

Although the number of reports are small, there were more reports of anemia in the UT-15C group (3%) compared to none in placebo (one placebo report was for iron deficiency anemia).

Chemistry parameters

There were no obvious trends in changes in the mean values from baseline at endpoint for the chemistry parameters (table 14.3.4.4). Regarding shift tables, there were more subjects in the UT-15C with an ALT value that went from normal at baseline to high at week 16 (8%) compared to placebo (4%). This was also seen in the AST values: 9% for UT-15C compared to 5% for placebo.

There were shifts from normal at baseline to high at week 16 in the UT-15C group compared to placebo for creatinine (10% vs. 8%) and BUN (9% vs. 5%).

There was 1 report of abnormal hepatic function in the UT-15C group compared to no reports in the placebo group although placebo had one report of transaminase increased.

The table below lists the subjects with reports of abnormal laboratory values, UT-15C only.

Table 12-10 Adverse Events Related to Laboratory Parameters in the UT-15C Group

Adverse Event (Preferred Term)	Subject Number
Hypokalemia	041806, 103802, 154801*, 200814, 200824, 200839
Brain natriuretic peptide increased	006805, 008803, 036802, 060801, 077801*
Anemia	040802, 041812*, 067802, 114806
Blood alkaline phosphatase increased	033805*, 137801
Proteinuria	201805*, 201812*
Hyperkalemia	117802
International normalized ratio increased	134807
Thrombocytopenia	201811
Azotemia	046801
Blood bicarbonate decreased	072801
Blood calcium increased	036801
Blood creatinine increased	067802
Hematuria	036801
Hepatic function abnormality	200824
Hyperglycemia	159802*
Hypoglycemia	159802*.*
Iron deficiency	114806
Leukocytosis	006803
Liver function test abnormal	114802
Protein urine present	033802*

* Possibly or reasonably attributable to study drug

* Serious adverse event

Hypokalemia was the most often reported adverse event (6 subjects, one serious).

Vital signs

At each study visit, vital signs (systemic blood pressure, heart rate, respiration rate, and weight) were assessed.

Mean change from baseline at week 16

	UT-15C	Placebo
Weight kg	-0.14	0.20
Pulse bpm	1.9	2.3
SBP mmHg	-1.7	-4.7
DBP mmHg	-2.7	-1.8

Table 14.3.7

The changes from baseline appear to be minor for both groups. While SBP dropped more for the placebo group, DBP change was larger for UT-15C

Abnormal vital sign changes reported as adverse events in the UT-15C group are shown below.

Table 12-11 Adverse Events Related to Vital Signs in the UT-15C Group

Adverse Event (Preferred Term)	Subject Number
Palpitations	006805*, 075802#, 112808, 114806*, 161802*, 202815
Pyrexia	018805*, 103802#, 161803#, 200833, 201808, 202806*
Atrial fibrillation	055801, 103802#, 126801*
Tachycardia	036802, 134808*, 201805
Orthostatic hypotension	021801*, 133806
Sinus tachycardia	006803, 036802
Arrhythmia	126801
Atrial flutter	067802
Body temperature†	036801*
Cardiac flutter	006803*
Heart rate irregular	067803*
Hypotension	006803
Ventricular extrasystoles	077801*
Weight decreased	133806
Weight increased	134801*

* Possibly or reasonably attributable to study drug

Serious adverse event

† Reported term: temperature fluctuation

These adverse events were similar for both treatment groups.

12-lead ECG

Twelve-lead ECGs were recorded after five minutes of rest in the semi-recumbent position at baseline prior to starting study drug and at the end of the Treatment Phase at Week 16. ECG parameters collected included heart rate, PR interval, QT interval, QRS duration and any clinically significant abnormalities. There were no obvious differences between treatment groups in ECG parameters (Table 14.3.6).

Appendix 6

Study Number: TDE-DU-201 (Safety review)

Title: DISTOL-1: Digital Ischemic Lesions in Scleroderma Treated with Oral Trepstinil Diethanolamine: A randomized, doubleblind, placebo-controlled, multicenter study

Indication: Digital Ulcers

Brief study description

This was a randomized, double-blind, placebo-controlled, multicenter study of trepstinil diethanolamine in adult patients with SSc and presence of at least one digital ulcer that met protocol defined qualifications for an active digital ulcer at Baseline. Subjects were randomly allocated 1:1 to receive either active drug or placebo and stratified by number of active ulcers at Baseline (less than or equal to two ulcers and greater than two ulcers). Initially prohibited, the protocol was amended [Amendment 2] to allow background phosphodiesterase inhibitor therapy, provided treatment had been started at least six months prior to Baseline assessments (except for intermittent treatment of male erectile dysfunction) and the stratification was modified to include background phosphodiesterase use. The Treatment Phase consisted of a 20-week period.

A total of 148 subjects were enrolled, with 147 subjects (71 active and 76 placebo) receiving study medication.

Twenty-four subjects (thirteen active and eleven placebo) discontinued the study prematurely.

There were no deaths reported during this study.

A total of twenty-seven serious adverse events were reported by thirteen subjects: nine UT-15C subjects reported 22 events and four placebo subjects reported five events. The table below shows all reported adverse events.

Table 14.3.2.1
 Summary of Serious Adverse Events

System Organ Class/ Preferred Term	UT-15C SR (N=71)		Placebo (N=76)		Total (N=147)	
	Subjects	Events	Subjects	Events	Subjects	Events
All System Organ Classes	9 (13%)	22	4 (5%)	5	13 (9%)	27
Infections and infestations	2 (3%)	2	2 (3%)	2	4 (3%)	4
Pneumonia	1 (1%)	1	1 (1%)	1	2 (1%)	2
Cellulitis	0	0	1 (1%)	1	1 (<1%)	1
Gastroenteritis	1 (1%)	1	0	0	1 (<1%)	1
Respiratory, thoracic and mediastinal disorders	3 (4%)	6	1 (1%)	1	4 (3%)	7
Pneumothorax	2 (3%)	4	0	0	2 (1%)	4
Dyspnoea	1 (1%)	1	0	0	1 (<1%)	1
Hypoxia	1 (1%)	1	0	0	1 (<1%)	1
Pulmonary embolism	0	0	1 (1%)	1	1 (<1%)	1
Gastrointestinal disorders	2 (3%)	6	1 (1%)	1	3 (2%)	7
Vomiting	1 (1%)	1	1 (1%)	1	2 (1%)	2
Constipation	1 (1%)	1	0	0	1 (<1%)	1
Erosive oesophagitis	1 (1%)	1	0	0	1 (<1%)	1
Gastric ulcer haemorrhage	1 (1%)	1	0	0	1 (<1%)	1
Gastrointestinal haemorrhage	1 (1%)	1	0	0	1 (<1%)	1
Nausea	1 (1%)	1	0	0	1 (<1%)	1
Blood and lymphatic system disorders	1 (1%)	1	0	0	1 (<1%)	1
Anaemia	1 (1%)	1	0	0	1 (<1%)	1
Cardiac disorders	1 (1%)	1	0	0	1 (<1%)	1
Tachyarrhythmia	1 (1%)	1	0	0	1 (<1%)	1
General disorders and administration site conditions	1 (1%)	1	0	0	1 (<1%)	1
Device dislocation	1 (1%)	1	0	0	1 (<1%)	1
Hepatobiliary disorders	1 (1%)	1	0	0	1 (<1%)	1
Cholecystitis acute	1 (1%)	1	0	0	1 (<1%)	1
Metabolism and nutrition disorders	1 (1%)	1	0	0	1 (<1%)	1
Hypokalaemia	1 (1%)	1	0	0	1 (<1%)	1
Musculoskeletal and connective tissue disorders	0	0	1 (1%)	1	1 (<1%)	1
Scleroderma	0	0	1 (1%)	1	1 (<1%)	1
Nervous system disorders	1 (1%)	1	0	0	1 (<1%)	1
Syncope	1 (1%)	1	0	0	1 (<1%)	1
Skin and subcutaneous tissue disorders	1 (1%)	1	0	0	1 (<1%)	1
Skin ulcer	1 (1%)	1	0	0	1 (<1%)	1
Vascular disorders	1 (1%)	1	0	0	1 (<1%)	1
Hypotension	1 (1%)	1	0	0	1 (<1%)	1

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There were nine subjects (13%) randomized to UT-15C who reported a total of 22 serious adverse events. There was only one event (pneumothorax) that was reported by at least 2 subjects. On the other hand, there were four subjects (5%) randomized to placebo who reported a total of 5 events. No event was reported by more than one placebo subject.

Permanent discontinuations for adverse events

Table 14.3.2.2
 Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug

System Organ Class/ Preferred Term	UT-15C SR (N=71)		Placebo (N=76)		Total (N=147)	
	Subjects	Events	Subjects	Events	Subjects	Events
All System Organ Classes	11 (15%)	20	8 (11%)	12	19 (13%)	32
Gastrointestinal disorders	6 (8%)	9	3 (4%)	5	9 (6%)	14
Diarrhoea	4 (6%)	4	1 (1%)	1	5 (3%)	5
Nausea	3 (4%)	3	0	0	3 (2%)	3
Abdominal discomfort	1 (1%)	1	0	0	1 (<1%)	1
Abdominal distension	0	0	1 (1%)	1	1 (<1%)	1
Abdominal pain	0	0	1 (1%)	1	1 (<1%)	1
Change of bowel habit	1 (1%)	1	0	0	1 (<1%)	1
Flatulence	0	0	1 (1%)	1	1 (<1%)	1
Vomiting	0	0	1 (1%)	1	1 (<1%)	1
Musculoskeletal and connective tissue disorders	2 (3%)	3	1 (1%)	1	3 (2%)	4
Arthralgia	1 (1%)	1	0	0	1 (<1%)	1
Back pain	0	0	1 (1%)	1	1 (<1%)	1
Myalgia	1 (1%)	1	0	0	1 (<1%)	1
Pain in jaw	1 (1%)	1	0	0	1 (<1%)	1
Respiratory, thoracic and mediastinal disorders	2 (3%)	3	1 (1%)	1	3 (2%)	4
Dyspnoea	1 (1%)	1	0	0	1 (<1%)	1
Hypoxia	1 (1%)	1	0	0	1 (<1%)	1
Pneumothorax	1 (1%)	1	0	0	1 (<1%)	1
Pulmonary arterial hypertension	0	0	1 (1%)	1	1 (<1%)	1
General disorders and administration site conditions	1 (1%)	1	1 (1%)	1	2 (1%)	2
Asthenia	0	0	1 (1%)	1	1 (<1%)	1
Fatigue	1 (1%)	1	0	0	1 (<1%)	1
Nervous system disorders	2 (3%)	3	0	0	2 (1%)	3
Headache	2 (3%)	2	0	0	2 (1%)	2
Syncope	1 (1%)	1	0	0	1 (<1%)	1
Skin and subcutaneous tissue disorders	1 (1%)	1	1 (1%)	1	2 (1%)	2
Rash	0	0	1 (1%)	1	1 (<1%)	1
Skin ulcer	1 (1%)	1	0	0	1 (<1%)	1
Cardiac disorders	0	0	1 (1%)	1	1 (<1%)	1
Palpitations	0	0	1 (1%)	1	1 (<1%)	1
Metabolism and nutrition disorders	0	0	1 (1%)	1	1 (<1%)	1
Decreased appetite	0	0	1 (1%)	1	1 (<1%)	1
Vascular disorders	0	0	1 (1%)	1	1 (<1%)	1
Peripheral ischaemia	0	0	1 (1%)	1	1 (<1%)	1

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There were 11 subjects (15%) randomized to UT-15C who discontinued because of an adverse event. Events reported by more than 1 subject include diarrhea, nausea, and headache. There were 8 subjects (11%) randomized to placebo who discontinued because of an adverse event. There were no events reported by more than one subject.

Appendix 7

Phase I studies, terminated studies, PK studies, studies in indications other than PAH			
Study number/title	number of subjects/dose	Number of deaths/serious adverse events	comments
TDE-PH-101 Open-label, dose escalation, pharmacokinetic and safety study with UT-15C oral solution	24/ 0.05, 0.125, 0.25, or 0.5 mg every 2 hours x 4 doses	0/0	none
TDE-PH-102 Open-label, two period cross-over, pharmacokinetic and safety study with single doses of UT-15C administered as SR tablets and capsules in the fasted and fed states (8-hour formulations)	28/1 mg two separate doses separated by a washout period	0/0	none
TDE-PH-103 Open-label, two period, cross-over, pharmacokinetic and safety study with single doses of UT-15C SR administered as three tablet prototypes (12-hour formulations) in the fasted and fed states	30/1 mg Three separate doses separated by washout periods	0/0	none
TDE-PH-104	36/ 1 mg BID – 3 mg	0/0	There were 6 subjects

Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Pharmacokinetics and Safety of a Sustained Release Tablet of UT-15C (treprostinil diethanolamine) Administered in Fixed and Escalating Doses in Healthy Volunteers	BID 13 days		who required dose reduction because of adverse events which included flushing, headache, vomiting, nausea, abdominal pain, pain in jaw.
TDE-PH-105 Open-label, randomized, three period, three sequence, cross-over study to evaluate the effect of bosentan on steady state UT-15C SR pharmacokinetics	24/1 mg 4.5 days of dosing with and without bosentan	0/0	Subject 001011, who withdrew consent and was discharged on dosing Day 4, experienced moderate nausea and vomiting during Period 1 while receiving UT-15C and Tracleer® in combination. These events were reported approximately 6 and 50 hours, respectively, following first dosing.
TDE-PH-106 Open-label, randomized, three period, three sequence, cross-over study to evaluate the effect of sildenafil on steady state UT-15C SR pharmacokinetics	18/ 1 mg 4.5 days of dosing with and without sildenafil	0/0	The three most frequently reported events in the UT-15C SR alone, Revatio alone and the combination of UT-15C SR and Revatio treatment groups, were headache (12%, 22%, 39%), pain in extremity (18%, 6%, 22%) and nausea (6%, 0%, 17%). More of these events were reported with the combination.
TDE-PH-107 Open-label, mass balance, metabolite profiling and safety study of [14C],[3H]UT-15C (treprostinil diethanolamine)	8/ 0.5 mg One dose	0/0	none
TDE-PH-108 Open-label, cross-over study to evaluate the bioavailability of a	20/ 1 mg Two separate doses as 2, 0.5 mg	0/0	none

1 mg dose of UT-15C SR administered as a single 1 mg tablet or two 0.5 mg tablets	tablets or 1, 1 mg		
TDE-PH-109 Open-label, randomized, single sequence, cross-over study to evaluate the effect of repeated rifampin dosing on a single dose of UT-15C SR	20/ 1 mg Two separate doses separated by a washout	0/0	there were no clinically important safety findings associated with administration of a UT-15C SR 1 mg dose following repeated administration of rifampin, when compared to administration of a single UT-15C SR 1 mg dose alone (in the absence of rifampin).
TDE-PH-110 Open-label, randomized, two-period, two-sequence, cross-over study to evaluate the effect of repeated gemfibrozil or fluconazole dosing on the pharmacokinetics of a single dose of UT-15C SR	40/1 mg Two cohorts each receiving two separate doses separated by a washout	0/0	Repeated oral doses of gemfibrozil (600 mg twice daily) increased the plasma treprostinil C _{max} by 96% and AUC values (AUC _{0-∞} , AUC _{0-48h} , and AUC _{0-t}) of a single 1 mg oral dose of UT-15C SR by 92%, 116%, and 117%, respectively. The frequency and event rate of adverse events increased during the administration of UT-15C SR plus gemfibrozil, with events reported in 35% of subjects (20 events) versus 25% of subjects (12 events) receiving UT-15C SR alone.
TDE-PH-111 Open-label, cross-over study to evaluate the bioavailability of a 1 mg dose of UT-15C SR administered as a single 1 mg tablet or four 0.25 mg tablets	24/1 mg Two separate doses as four 0.25 mg tablets or one 1 mg, separated by a washout	0/0	none
TDE-PH-112 Open-label, single-dose, pharmacokinetic and safety study in	30/ 1 mg One dose in four cohorts	0/0	Mean treprostinil clearance values decreased markedly with the severity of hepatic impairment resulting in a

three cohorts of subjects with various degrees of hepatic impairment and one cohort of healthy volunteers			marked increase in exposure levels of treprostinil
TDE-PH-113 Open-label, two-sequence, crossover study to evaluate the bioavailability of a 1 mg dose of UT- 15C as compared to a 2.5 mg dose of UT-15C SR	28/ 1 mg and 2.5 mg Two separate Doses separated by a washout	0/0	One subject reported hypotension requiring intravenous fluids after receiving 2.5 mg.
TDE-PH-114 Open-label, two-sequence, crossover study to evaluate the absolute bioavailability of a 1 mg dose of UT- 15C SR as compared to an IVinfusion of treprostinil sodium	24/1 mg and 0.2 mg Remodulin Two separate doses separated by a washout	0/0	none
TDE-PH-115 Open-label, randomized, single dose, four-period, cross-over pharmacokinetic and safety study evaluating the effect of different meal compositions on treprostinil pharmacokinetics	32/ 1 mg Four separate doses separated by washouts	0/0	none
TDE-PH-116 Open-label, single sequence, crossover study to evaluate the effect of repeated esomeprazole dosing on the pharmacokinetics of a single dose of UT-15C SR	30/1 mg Two separate doses separated by a washout	0/0	none

TDE-PH-120 Open label, single-dose, pharmacokinetic, safety and tolerability study in healthy volunteers and patients with ESRD (Two-period, two-way cross-over for those subjects with ESRD)	16/1 mg ESRD – two separate doses separated by a washout; healthy volunteers –one dose	0/0	none
TDE-PH-121 Open-label, two sequence, crossover study to evaluate the comparative bioavailability of a 1 mg dose of UT-15C SR manufactured by two independent facilities	64/1 mg Two separate doses separated by a washout	0/0	2 subjects discontinued because of a.) decreased WBC and b.) chest discomfort.
TDE-PH-122 Open-label study to evaluate the comparative pharmacokinetics of a 0.5, 1 and 2.5 mg dose of UT-15C SR	36/ 0.5, 1, and 2.5 mg Three separate doses separated by washouts	0/1 withdrawal for serious esophagitis, 1 withdrawal for headache	none
TDE-PH-123 Open-label, two-sequence, crossover study to evaluate the comparative bioavailability of a 1 mg dose of UT-15C administered as a single UT-15C SR tablet or as a UT-15C oral solution	24/ 1 mg and 0.25 mg q2 hrs x 4 doses Two doses separated by a washout	0/0	none
TDE-DU-101 (under IND (b) (4)) Open-label, two-part, PK study in two cohorts of patients with systemic sclerosis.	28/1-4 mg BID Up to 8 weeks	0/0	none

<p>TDE-PH-201 Open-label, multicenter, four- cohort study in subjects with PAH</p>	<p>8/ 1 or 2 mg single dose 1 day</p>	<p>0/0</p>	<p>study was terminated early because “the single dose design and small sample size, it is difficult to identify or interpret any trends in the data set and support any conclusions regarding the hemodynamic effects caused by a single dose of UT-15C in PAH patients who are at least partially responsive to acute vasodilator testing. Furthermore, dose response was not assessed due to enrollment issues resulting in early study termination.</p>
<p>TDE-PH-306 Open-label pharmacokinetic,study</p>	<p>74/0.25-1 mg BID starting dose with dose increasing over time 1 day (substudy of TDE-PH- 304)</p>	<p>0/0</p>	<p>none</p>

Appendix 8

The studies below are ongoing and except for TDE-PH-304 are not reported on in this application.

Table 1-2 Overview of Ongoing Studies with UT-15C

Protocol Number	Study Description	Sample Size / Number Enrolled	Dose of Treprostinil	Duration of Dosing
TDE-DU-202 (under IND#103,070)	Open-label extension study (patients formerly in study TDE-DU-201)	115 / 115	0.25 mg BID starting dose with dose increasing over time	Long term; study discontinued (data analysis ongoing)
TDE-PH-202	Open-label, randomized, dose response study – exercise hemodynamics	50 / 27	Three dosing cohorts: 0.25 mg BID; Titrate to 1.25 mg BID; Individual maximum tolerated dose	12 weeks
TDE-PH-203	Open-label study of UT-15C added to patients stabilized on inhaled treprostinil	50 / 1	0.25 mg BID starting dose with dose increasing over time	24 weeks with continuing open-label access
TDE-PH-304	Open-label extension study (patients formerly in studies TDE-PH-301, 302, 308, and 202)	900 / 824	0.25 mg BID starting dose with dose increasing over time	Continuing open-label access
TDE-PH-307	Biomarker substudy	33 / 33	0.25-1 mg BID starting dose with dose increasing over time	12 weeks (substudy of TDE-PH-302)

Appendix 9

Title of the Study:

An Evaluation of Cardiopulmonary Hemodynamics in Subjects with Pulmonary Arterial Hypertension (A substudy of TDE-PH-301 and TDE-PH-302). Substudy 305

Objectives:

The objective of this study was to assess the effect of chronic dosing with oral UT-15C SR on specific cardiopulmonary hemodynamic parameters (i.e., heart rate [HR], cardiac output [CO], diastolic pulmonary arterial pressure [PAPd], systolic pulmonary arterial pressure [PAPs], mean pulmonary capillary wedge pressure [PCWPM], mean right arterial pressure [RAPm], diastolic systemic arterial pressure [SAPd], systolic systemic arterial pressure [SAPs], systemic arterial oxygen saturation [SaO₂], mixed venous oxygen saturation [SvO₂], and calculated parameters) as assessed by right heart catheterization (RHC) in subjects with pulmonary arterial hypertension (PAH).

Methodology:

This multicenter hemodynamics substudy was associated with the conduct of protocols TDE-PH-301⁷ and TDE-PH-302⁸.

Cardiopulmonary hemodynamic assessments were conducted at Baseline (prior to initiation of study drug) and during the Week 16 or Week 12 clinic visits for TDE-PH-301 and TDE-PH-302, respectively.

If a subject had undergone a RHC within 30 days prior to Baseline for either TDE-PH-301 or TDE-PH-302, and had not undergone any concurrent medication changes for the treatment of their pulmonary hypertension

⁷ A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Combination with an Endothelin Receptor Antagonist and/or a Phosphodiesterase-5 Inhibitor in Subjects with Pulmonary Arterial Hypertension

⁸ A 12-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects with Pulmonary Arterial Hypertension

within those 30 days, then the results from that RHC may have be substituted for the baseline RHC for this substudy. Changes to the dose or frequency of digoxin, diuretics, calcium channel blockers, nitroglycerin preparations, or oxygen would have required a subject to be re-catheterized to be eligible to participate in this substudy.

Number of Subjects

Sixty subjects were enrolled from protocols TDE-PH-301 (n= 40) or TDE-PH-302 (n=20) and completed the baseline RHC prior to receiving study drug. Forty-five subjects (32 subjects [80%] from TDE-PH-301 and 13 subjects [65%] from TDE-PH-302) were included in the hemodynamic analysis.

Efficacy parameters

The study was not powered to support statistical evaluation of the efficacy parameters.

Hemodynamic parameters included: HR, CO, PAPd, PAPs, PCWp, RAPm, SAPd, SAPs, SaO₂, and SvO₂.

Derived parameters included: cardiac index (CI), mean pulmonary arterial pressure (PAPm), pulmonary vascular resistance (PVR), pulmonary vascular resistance index (PVRI), mean systemic arterial pressure (SAPm), systemic vascular resistance (SVR), and systemic vascular resistance index (SVRI).

Results

Forty-five subjects (32 subjects [80%] from TDE-PH-301 and 13 subjects [65%] from TDE-PH-302) completed drug and study in window and were included in the hemodynamic analysis.

Thermodilution and the Fick method were used to determine CO at both RHC procedures in 80% and 16% of subjects, respectively. One subject included and one subject not included in the hemodynamic analysis (2 subjects; 4%) had CO values determined by alternating methods (e.g., 011108 by thermodilution at Baseline and Fick at End of Study and 005202 by Fick at Baseline and thermodilution at End of Study, respectively).

Demographics

The table below shows the baseline demographics of the 45 subjects.

Table 11-1 Summary of Baseline Demographic Information of Subjects in the Hemodynamic Analysis: Pooled and by Individual Studies (TDE-PH-301 or TDE-PH-302)

Characteristic	UT-15C SR	Placebo
	Pooled: n = 22 TDE-PH-301: n = 13 TDE-PH-302: n = 9	Pooled: n = 23 TDE-PH-301: n = 19 TDE-PH-302: n = 4
Age in years: mean (range)	52.7 (37 – 69) 54.2 (37 – 69) 50.6 (43 – 63)	51.7 (33 – 70) 52.7 (33 – 70) 47.3 (36 – 57)
Sex: m/f (n)	9/13 4/9 5/4	3/20 2/17 1/3
Race: n (%)		
White	18 (82%) 10 (77%) 8 (89%)	20 (87%) 16 (84%) 4 (100%)
Black/African American	2 (9%) 1 (8%) 1 (11%)	2 (9%) 2 (11%) 0
Asian	1 (5%) 1 (8%) 0	1 (4%) 1 (5%) 0
American Indian/Alaska Native	1 (5%) 1 (8%) 0	0 0 0
PAH Etiology: n (%)		
IPAH/HPAH	14 (64%) 7 (54%) 7 (78%)	17 (74%) 13 (68%) 4 (100%)
CVD	7 (32%) 5 (38%) 2 (22%)	5 (22%) 5 (26%) 0
Repaired CHD	1 (5%) 1 (8%) 0	1 (4%) 1 (5%) 0
Background PAH Therapy: n (%)		
ERA	4 (18%) 4 (31%) 0	4 (17%) 4 (21%) 0
PDE5-I	2 (9%) 2 (15%) 0	6 (26%) 6 (32%) 0
Both	7 (32%) 7 (54%) 0	9 (39%) 9 (47%) 0
None	9 (41%) 0 9 (100%)	4 (17%) 0 4 (100%)
Baseline WHO Functional Class: II/III/IV (n)	5/17/0 3/10/0 2/7/0	3/16/4 3/13/3 0/3/1

Characteristic	UT-15C SR	Placebo
	Pooled: n = 22 TDE-PH-301: n = 13 TDE-PH-302: n = 9	Pooled: n = 23 TDE-PH-301: n = 19 TDE-PH-302: n = 4
Baseline 6MWD: mean ± SD (m)	331.6 ± 80.8 336.8 ± 75.2 324.0 ± 92.4	333.1 ± 83.4 330.9 ± 79.3 343.5 ± 114.4

The mean age was 52.2 years (range 33 to 70 years), 84% of subjects were white, and 73% female. The majority (69%) subjects were diagnosed with idiopathic or heritable PAH and the rest had a diagnosis of PAH related to collagen vascular disease (27%) or had PAH related to a repaired congenital heart defect (4%). Regarding background PAH treatment, 18% were receiving an ERA alone, 18% were receiving a PDE5-I alone, 36% were receiving both an ERA and PDE5-I, and 29% were not receiving any background treatment at Baseline. Subjects were predominantly WHO functional class III (73%) and the mean baseline 6MWD was 332 m.

Hemodynamic parameters

The tables below show the results for the hemodynamic values by study and treatment as well as pooled. Sample size varied for the different parameters.

Table 11-2 Summary of Hemodynamic Analysis: Pooled and by Individual Studies (TDE-PH-301 or TDE-PH-302)

Parameter	Hemodynamic Values (Mean ± SD)			
	Pooled			
	TDE-PH-301		TDE-PH-302	
	UT-15C SR n = 22*		Placebo n = 23**	
	Baseline	End of Study	Baseline	End of Study
HR (beats/min)	69.86 ± 10.83	73.91 ± 10.03	79.87 ± 11.41	81.04 ± 12.69
	66.77 ± 9.47	71.08 ± 10.58	80.11 ± 11.40	80.16 ± 10.96
	74.33 ± 11.64	78.00 ± 8.02	78.75 ± 13.15	85.25 ± 20.76
RAPm (mmHg)	9.23 ± 4.64	10.09 ± 4.77	8.77 ± 3.28	10.96 ± 4.37
	8.23 ± 4.38	10.23 ± 4.92	8.67 ± 3.57	10.72 ± 4.66
	10.67 ± 4.87	9.89 ± 4.83	9.25 ± 1.71	12.00 ± 2.94
CI [L/(min/m ²)]	2.48 ± 0.65	2.47 ± 0.68	2.37 ± 0.64	2.44 ± 0.66
	2.53 ± 0.64	2.39 ± 0.57	2.42 ± 0.65	2.52 ± 0.70
	2.40 ± 0.69	2.58 ± 0.84	2.06 ± 0.59	2.11 ± 0.29
PAPm (mmHg)	44.64 ± 10.89	44.27 ± 12.57	49.73 ± 11.81	53.27 ± 14.02
	42.39 ± 12.82	44.08 ± 15.05	48.17 ± 12.23	52.33 ± 15.38
	47.89 ± 6.70	44.56 ± 8.65	56.75 ± 6.85	57.50 ± 2.38
PVRI [mmHg/(L/min/m ²)]	14.64 ± 5.27	13.72 ± 6.16	18.81 ± 12.60	19.34 ± 9.05
	14.37 ± 5.83	14.26 ± 5.88	18.17 ± 12.69	18.74 ± 9.37
	15.02 ± 4.75	12.98 ± 6.87	29.60 ± N/A	24.70 ± 0.56
SAPm (mmHg)	87.64 ± 14.29	88.64 ± 15.60	84.32 ± 11.41	87.83 ± 15.53
	87.23 ± 16.62	89.39 ± 19.50	82.94 ± 11.89	88.32 ± 13.65
	88.22 ± 11.01	87.56 ± 8.10	90.50 ± 6.95	85.50 ± 25.33
SVRI [mmHg/(L/min/m ²)]	33.92 ± 11.86	34.81 ± 12.78	35.16 ± 14.89	34.36 ± 12.64
	33.69 ± 13.51	35.59 ± 12.80	33.77 ± 14.48	33.90 ± 11.98
	34.25 ± 9.75	33.69 ± 13.44	42.98 ± 17.93	36.30 ± 17.25
SaO ₂ (%)	93.14 ± 8.14	92.77 ± 8.30	93.78 ± 3.30	92.78 ± 6.66
	92.58 ± 10.56	91.46 ± 10.53	93.79 ± 3.34	92.42 ± 7.08
	93.89 ± 3.33	94.67 ± 2.74	93.75 ± 3.59	94.50 ± 4.44
SvO ₂ (%)	64.19 ± 10.64	63.67 ± 11.48	64.55 ± 10.52	66.40 ± 12.53
	65.33 ± 13.34	61.83 ± 13.55	64.00 ± 10.44	64.50 ± 10.87
	62.67 ± 5.79	66.11 ± 8.09	66.75 ± 12.18	74.00 ± 17.51
PCWPM (mmHg)	9.68 ± 3.54	11.16 ± 3.63	9.47 ± 4.16	9.70 ± 3.13
	8.36 ± 3.38	10.91 ± 3.56	9.35 ± 4.36	9.61 ± 3.18
	11.50 ± 3.07	11.50 ± 3.93	10.50 ± 2.12	10.50 ± 3.54

* Maximum sample size reported. Due to missing CRF data, sample size was variable across hemodynamic parameters. UT-15C SR at Baseline and End of Study: Pooled, n = 19 – 22; TDE-PH-301, n = 11 – 13; and TDE-PH-302, n = 8 – 9.

** Placebo at Baseline: Pooled, n = 18 – 23; TDE-PH-301, n = 16 – 19; and TDE-PH-302, n = 1 – 4. Placebo at End of Study: Pooled, n = 20 – 23; TDE-PH-301, n = 16 – 19; and TDE-PH-302, n = 2 – 4.

Change from baseline for the hemodynamic parameters for studies 301 and 302 combined.

Table 11-3 Summary of Change From Baseline in Hemodynamic Parameters: Pooled and by Individual Studies (TDE-PH-301 or TDE-PH-302)

Parameter	Hemodynamic Values (Mean ± SD)	
	Pooled	
	UT-15C SR n = 22*	Placebo n = 23**
HR (beats/min)	4.05 ± 9.89	1.17 ± 11.39
	4.31 ± 10.44	0.05 ± 10.03
	3.67 ± 9.63	6.50 ± 17.41
RAPm (mmHg)	0.86 ± 4.94	2.18 ± 4.31
	2.00 ± 5.23	2.06 ± 4.54
	-0.78 ± 4.24	2.75 ± 3.50
CI [L/(min/m ²)]	-0.01 ± 0.68	0.09 ± 0.73
	-0.15 ± 0.67	0.10 ± 0.79
	0.18 ± 0.68	0.03 ± 0.28
PAPm (mmHg)	-0.36 ± 7.38	3.55 ± 9.79
	1.69 ± 6.76	4.17 ± 10.55
	-3.33 ± 7.58	0.75 ± 5.32
PVRI [mmHg/(L/min/m ²)]	-0.92 ± 4.59	-0.07 ± 10.50
	-0.11 ± 5.02	0.19 ± 10.77
	-2.04 ± 3.97	-4.52 ± N/A
SAPm (mmHg)	1.00 ± 12.28	2.36 ± 13.04
	2.15 ± 10.91	4.00 ± 10.61
	-0.67 ± 14.56	-5.00 ± 21.53
SVRI [mmHg/(L/min/m ²)]	0.90 ± 10.51	-0.76 ± 14.1
	1.91 ± 10.55	-0.55 ± 15.36
	-0.56 ± 10.91	-1.91 ± 0.35
SaO ₂ (%)	-0.38 ± 3.89	-1.00 ± 7.01
	-1.25 ± 4.33	-1.37 ± 7.64
	0.78 ± 3.07	0.75 ± 2.36
SvO ₂ (%)	-0.52 ± 8.75	1.85 ± 10.36
	-3.50 ± 9.75	0.50 ± 9.65
	3.44 ± 5.46	7.25 ± 12.87
PCWp (mmHg)	1.47 ± 3.60	0.11 ± 3.81
	2.55 ± 3.78	0.12 ± 4.03
	0.00 ± 2.93	0.00 ± 1.41

* Maximum sample size reported. Due to missing CRF data, sample size was variable across hemodynamic parameters. UT-15C SR: Pooled, n = 19 – 22; TDE-PH-301, n = 11 – 13; and TDE-PH-302, n = 8 – 9.

** Placebo: Pooled, n = 18 – 23; TDE-PH-301, n = 16 – 19; and TDE-PH-302, n = 1 – 4

Compared to placebo, subjects randomized to UT-15C showed an increase in heart rate by about 3 bpm, a small rise in RAP, a slight decline in CI, a larger decline in PAP and PVRI. The effect on these parameters seems to be negligible.

In summary, this study does not demonstrate an effect of UT-15C on hemodynamic parameters.

Safety evaluations are found in the individual studies TDE-PH-301 and TDE-PH-302.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYANN GORDON
10/03/2012

JOHN P LAWRENCE
10/03/2012

HSIEN MING J HUNG
10/03/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 <p style="text-align: right;">Indication:</p> Pivotal Study #2 <p style="text-align: right;">Indication:</p>				TDE-PH-302. Study title: "A 12-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects with Pulmonary Arterial Hypertension". The indication is for treatment of PAH (WHO Group I) to improve exercise capacity.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	This will be a central issue of the review process. This was discussed at length with the sponsor at many time points, over many years. They did not conduct a separate TQT for this product, but have presented an array of arguments to justify their not conducting a TQT study. In our preNDA discussions, we committed to not doing RTF over this issue, given the arguments presented

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					by the sponsor. Furthermore, we stated that this might be addressable in labeling.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	This is an NME.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			1612 patients have been exposed to test drug, 1009 for at least 6 months, and 824 for at least 1 year.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	This is a chronically-administered drug.
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	We didn't require any special studies.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric testing will be waived since this an orphan drug.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			Sponsor claims that there is no known abuse potential for study drug as it has no structural or pharmacological relation to any drug with known abuse

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					issues. Moreover, they found no evidence of abuse in their clinical studies of test drug.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No additional CRF's were requested by the Division.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			In multiple places in NDA, sponsor states that all studies were conducted within guidelines of GCP and ICH.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

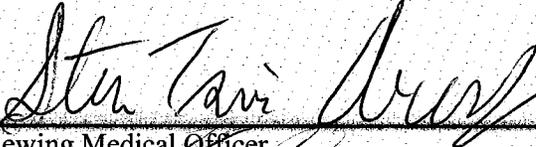
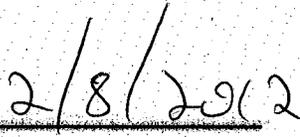
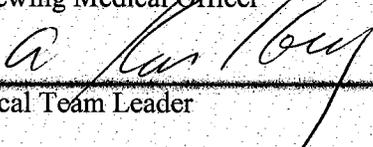
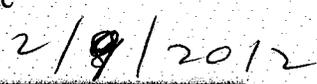
If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No issues need to be forwarded to the applicant in the 74-day letter.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	
_____ Reviewing Medical Officer	_____ Date
	
_____ Clinical Team Leader	_____ Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVEN T ARANOFF
02/09/2012