CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

MEDICAL REVIEW

Division of Cardio-Renal Drug Products
Medical Officer Review

NDA 21-272 (serial # not submitted)
Remodulin™ (treprostinil, UT-15) injection
Sponsor: United Therapeutics

Date of Submission: 14 March 2002

Reviewer: Abraham M. Karkowsky, M.D., Ph.D.

Date of Review: 14 March 2002

Background: This is an amended protocol. UT-15 was approved under 21 CFR 314 subpart H (314.500-560). Approval was conditioned on the submission of a protocol that demonstrates an interpretable clinical benefit for UT-15. The Division met with United Therapeutics and their consultants on 13 February 2002 during which the broad outline of a Flolan withdrawal study was explored. A protocol was received on 28 February 2002. Two major objections were raised and clarification of other issues was requested. The sponsor submitted a protocol on 13 march 2002. A meeting was held with the sponsor on 7 March 2002. This reviewer was invited but unable to attend that meeting. The reviewer's comments, however, were transmitted to those from the Agency who attended the meeting. Only cosmetic changes were recommended by the Agency. This reviewer, however, still has substantial reservations related to the protocol. These reservations are listed at the end of the study.

Protocol Review:

Study number P01:13.

Title of Study: A Multicenter, Randomized, Parallel, Placebo-Controlled Study of the Safety and Efficacy of Subcutaneous Remodulin™ Therapy After Transition From Flolan® in Patients With Pulmonary Arterial Hypertension:

Investigators and Sites: Not specified.

Formulations: 2.5, 5.0 and 10 mg/ml for continuous subcutaneous infusion or placebo.

Inclusion criteria: Subjects that are enrolled are:

- Between 18-75 years.
- If female incapable of childbearing.
- Have a diagnosis of pulmonary hypertension (either primary or secondary to systemic sclerosis syndrome).
- Class II or III status.
- Whose status was stable for at least 30 days.
- Have a baseline walk distance of > 250 meters.

- Receiving flolan at a dose of at least 20 ng/kg/min but less than 75 ng/kg/min.
- Received Flolan for at least 6 months and have been maintained on stable doses for at least 30 days.
- Unless contraindicated, be able to receive anticoagulants e.g. warfarin to achieve an INR of between 2.0 and 3.0 or heparin to produce an aPTT of between 1.3 to 1.5 x control.
- Able to manage a subcutaneous pump.
- Stability of corticosteroid doses.

Exclusion criteria: Subjects were excluded if:

- They are pregnant or nursing
- Had a new chronic therapy added for pulmonary hypertension or a stable medication changed within 30 days with the exception of anticoagulants.
- Received Remodulin or Bosentan (or other endothelial blocker) within 30 days.
- Have evidence of parenchymal lung disease. As indicated by:
    a) Total lung capacity < 60% predicted.
    b) [redacted]
    c) FEV/FVC ratio < 50%.
    d) If DLCO < 50% of that predicted, a high resolution CT must be performed to document diffuse interstitial fibrosis or alveolitis.
- HIV positive.
- Portal hypertension.
- Uncontrolled sleep apnea.
- Have a history of left sided heart disease including:
    a) aortic or mitral valve disease
    b) pericardial constriction or
    c) restrictive or congenital cardiomyopathy.
- Have evidence of current left-sided disease defined by:
    a) PCWP or left ventricular left-sided heart disease as defined by:
    b) LVEF < 40% by M(UGA or angiography or ECHO
    c) LV shortening of < 22% by ECHO
    d) Symptomatic coronary disease.
- Other disease (e.g. sickle cell disease) associated with pulmonary hypertension.
- Musculoskeletal disorder limiting ambulation.
- Uncontrolled hypertension (SBP > 160 or DBP > 100 mm Hg).
- Use of appetite suppressant within 3 months.
- Have chronic renal disease (Cr > 3.5 mg/dL).
- Recent investigational new drug or device.
- Have an atrial septostomy.
- Serious life-threatening disease.
- Unstable psychiatric status.
- Have anemia Hgb< 10 gm/dL

Primary end point:

The primary endpoint of the study is the time to clinical deterioration defined as the time from initiation of study drug to earliest incidence of clinical worsening of PAH symptoms requiring reinstitution of Flolan therapy or re-hospitalization or death. Any decision to re-institute Flolan should be supported by documented by objective criteria that the subject's status has deteriorated despite attempts to increase the dose of the study drug or placebo. The preferred assessment criteria consist of the following parameters: PAH clinical status, 6-minute walk distance, Borg dyspnea score, dyspnea evaluation scale, transcutaneous O_2 saturation, clinical signs and symptoms of PAH. If practical, the patient should be asked to perform light activity such as walking, to help in assessing whether clinical deterioration has occurred during the dose transition period.

The study investigator is responsible for determining whether the subject's status has deteriorated.

An independent adjudication process will be utilized to assess all deterioration events as well as all withdrawals. Those patients, not weaned from Flolan at the end of the 2-week period, would be considered a treatment failure. Patients who withdraw due to reason other than clinical deterioration will be censored. The time to clinical deterioration will be compared between treatment groups using a proportional hazard regression model, adjusting for Flolan dose.

Secondary end-points:

- Exercise capacity and Borg dyspnea score (assessed individually as well as through and index composed of both these components).
- Dyspnea fatigue index.
- Signs and Symptoms of PAH.
- Hospitalization for cardiovascular events or conditions.

The walks at each week of testing (at the end of the transition period and weeks 4 and 8) will be fitted as a function of the initial Flolan dose and distance walked at baseline. Standardized mid-ranks will be calculated. Subjects who experienced clinical deterioration will be assigned a standardized rank of zero, with the rank carried forward to the week 8 value. Standardized ranks of the resulting values will be calculated. Similar analysis will be performed for the Borg dyspnea scale. An arithmetic average of the mid-ranks will be calculated for the combination of the 6-minute walk and Borg dyspnea.

Changes in both measures will be assessed at Week 8 using a non-parametric analysis of covariance within the framework of the extended Cochran-Mantel Haenszel test.

Statistical analyses:

Two interim analyses are planned, limited to safety. An independent contractor will analyze the data for adverse events and deaths, with the analysis submitted to the DSMB.

A sample size of approximately 90 patients would provide 90% powered using a two-sided log rank test at a level of 0.05 to detect a 2.8 fold increase in the median tome to

clinical deterioration from a placebo median time of 4.6 weeks. In order to take in to account dropouts, the study size is increased to 100 subjects. The study will be continue until at least 50 clinical deterioration events have occurred.

Randomization: Subjects will be randomized in a 1: 1 ratio and stratified by the current dose of Flolan (> 35 ng/kg/min and ≤ 35 ng/kg/min). The block sizes will be variable.

Dosing: The dosing schedule for dose reduction of Flolan and the institution of UT-15/placebo is shown below. The transition period is defined by days and not by specific hours.

Table 1- Planned dose modifications for study P01:13

Day #	Flolan Dose	Study drug Dose		Day #	Flolan Dose	Study drug Dose
1	Unchanged	10% of initial Flolan Dose		8	5%	105% of initial Flolan Dose
2	85%	25% of initial Flolan Dose		9	5 %	110% of initial Flolan Dose
3	70%	40% of initial Flolan Dose		10	5%	110% of initial Flolan Dose + Additional 5-10% as needed
4	55%	55% of initial Flolan Dose		11	0%	Additional 5-10% as needed
5	40%	70% of initial Flolan Dose		12	0%	Additional 5-10% as needed
6	25%	85% of initial Flolan Dose		13	0%	Additional 5-10% as needed
7	15%	95% of initial Flolan Dose		14	0%	Additional 5-10% as needed

General guidelines to doses;

- The above dose should be followed as closely as possible.
- Increases in symptoms of PAH should be treated with increases in study drug first, even if it deviates from the above dosing recommendations.
- Should there be side effects suggesting an excessive effect, the dose of Flolan should be preferentially lowered.
- A study dose/placebo increase should occur at least one hour before a corresponding decrease in the Flolan dose.
- The subjects should not be discharged from the hospital until stable for at least 24 hours after the dose of Flolan is stopped.
- If the subject could not be withdrawn from Flolan by the end of day 14, the subject would be considered a treatment failure.
- No cardiac catheterizations should be conducted.
- Each subject is to be informed that infusion site pain is an expected outcome.

The dose could be down-titrated for the following reasons

- Any measured or observed changes in vital signs or clinical signs that suggest an excessive drug effect.
- Any adverse experience possibly related to Remodulin e.g. headache, nausea, restlessness and anxiety.
- Onset of significant pain at the infusion site.

Concomitant medications that were used prior to treatment are allowed.
The listing of procedures during the study is shown below:

Table 2- list of procedures during study P01:13

	Screening [a] Day –7 to 0	Baseline Day 0	Treatment Week 1 (day 1-14[b])	4 (day 28[c])	8 (day 56[c])
Informed consent; Inclusion/Exclusion criteria	X				
Medical History /PE/Vital Signs/12-lead ECG/Labs	X				X
PAH signs and symptoms		X	X----X[d]	X	X
Dyspnea-Fatigue Rating		X	X----X[d]	X	X
Exercise Capacity /Borg dyspnea scale [j,k]	X[e]	X	X----Xf	X	X
Randomization [g]					
Monitor [h]: ECG/Vital signs/ TcO_2					
Infusion of Remodulin			X----------	----------	----------→
Reduction of Flolan Dose [j]			X----------→		
Other Medications/Adverse Events			X_---------	----------	----------→

a. May be performed up to one week prior to randomization b. May be less than 1-week if all procedures completed
c. Patient will return ± 7 day seven even if prematurely discontinued. d. As needed for patient stability and prior to discharge
e. A practice walk test should may be performed up to 6 weeks before randomization
f. During the transition from Flolan to UT-15/placebo the walk/Borg test may be performed periodically and as soon as possible for premature termination
g. After all baseline eligibility is determined h. Continuous monitoring during dosing and transition period
i. Drug may be adjusted as outpatient transition period j. See text and table 1 k Data should be collected immediately prior to early discontinuation.

Termination of study: The study can be terminated for the following reasons:

- The principal investigator or IRB elects to discontinue the study.
- FDA regulations are not observed.
- The protocol is violated.
- The data are of poor quality.
- Changes in personnel or facilities adversely effect performance of the study.

Comments: This protocol is improved but not optimal. At the end there are likely several interpretations aside from a benefit for UT-15 for the treatment of pulmonary hypertension.

- There is little if any data to define how Flolan should be down-titrated except in the context of excessive hemodynamic effect. The current labeling for Flolan indicates that during clinical exposure there was a slow up-titration of Flolan at a rate of 2-3 ng/kg/min every 3 weeks during stable treatment. It would seem that the rate of down titration should be the reverse mirror image of the up-titration scheme. The proposed protocol, however, proposes a much more rapid decrease in Flolan doses. For example, a subject on 35 ng/kg/min of Flolan at baseline would down titrated 5.2 ng/kg/min on the first day, an additional 5.2 ng/kg/min on the second day and additional amounts on subsequent days and not 2-3 ng/kg/min over 2-3 weeks. The down titration phase for Flolan might precipitate a withdrawal response. Consequently, any inference from this study if outcome events occurred during the flolan withdrawal could be interpreted as UT-15 mitigation of the effects of Flolan withdrawal as opposed to a beneficial effect of UT-15 on pulmonary hypertension.

  With respect to the switch-over from Flolan to UT-15, the sponsor in the original NDA submitted a preliminary description of Study P01:11 in which three subjects

were transitioned from Flolan to UT-15. Also submitted by the sponsor was an abstract[1] in which 8 subjects were transitioned from, Flolan to UT-15 (I believe that the experience with the three subjects of study P01:11 are included in this abstract). The details are insufficiently described and the number of subjects too few to accept as known how to transition subjects off of Flolan to UT-15.

Although there are provisions for additional decreases in the dose of Flolan if the hemodynamic effects are excessive because of the concurrent addition of UT-15, there are no provisions for decreasing the rate of down-titration if Flolan withdrawal appears to destabilize a subject. Nor is there the possibility to temporarily increasing Flolan until subject's status stabilizes because of the rapid down-titration.

Those subjects who destabilize are likely in the placebo control group if the UT-15 acts to mitigate the withdrawal effects of Flolan. For example both Flolan and UT-15 are peripheral vasodilators (not just pulmonary vascular vasodilators). If the withdrawal of Flolan results in rebound peripheral hypertension, a second drug which vasodilates would apparently be interpreted as a useful drug for pulmonary hypertension but only serves to mitigate the peripheral effects of Flolan withdrawal. Given an inadequate database for defining the dynamic time course of Flolan withdrawal any deterioration during this portion of the study may not be easily interpreted as demonstrating a benefit for UT-15 during short-term withdrawal.

Should a subject decompensate during the process of the switch over from Flolan to UT-15control, the interpretation would therefore, be ambiguous. One potential inference is that UT-15 is an equivalent Flolan and is therefore, an active drug. The second interpretation is that UT-15 mitigated a rebound effect of the Flolan discontinuation and in itself is not active in the treatment of pulmonary hypertension.

This reviewer would suggest that a much longer time frame be used for down-titration. In response to this concern the sponsor modified the crossover time to up to 10 days from as short as < 2 days. Furthermore, this reviewer would allow up-titration of Flolan if acutely, the subject did not appear to tolerate the rapid down-titration. The sponsor, in the revised protocol, however, leaves no room for up-titration of Flolan. In fact any increase in Flolan dose would be counted as a deterioration end point. This reviewer would use the full two-week period for optimal down titration of Flolan as well as optimization of UT-15.

The interpretation of this study as demonstrating efficacy would be markedly dependent on the outcome during this down-titration portion of the study. If nearly all events were a consequence of the Flolan down-titration the study could be interpreted as mitigating the withdrawal effects of Flolan. If the events occurred later in the study the interpretation would be less ambiguous.

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[1] Vachiery JL, Hill N, Zwicke D, Barst R, Blackburn S, Naeije R International Society for Heart and Lung Transplantation 22nd Annual Meeting and Scientific Session

- Should the predominance of events occur during the Flolan withdrawal phase, an alternate interpretation of the outcome is that the UT-15 modifies hemodynamics and is useful for short term but not necessarily longer-term benefit. Since the purpose of UT-15 use is for chronic treatment, the importance of demonstrating a short-term benefit is unclear. For CHF, predominantly of left-sided origin, drugs are often classified for short term or chronic use. The anticipation is that drugs beneficial during the short term may not reflect long-term benefit to the patient. If all events occur during the Flolan withdrawal an argument can be made that all benefit is of hemodynamic/short term type.

- The study results can be compromised by the consequence of site pain and the attendant unblinding.

During the initial clinical studies (P01:04 and P01:05), subjects were started on a dose of UT-15 at an infusion rate of 1.25 ng/kg/min for the initial week then slowly up-titrated at subsequent weeks. Even with this conservative protocol, infusion site pain was nearly universal among those treated with UT-15. Pain or infusion site reaction listed as "severe" in intensity were each 39% (there could be overlap) and according to the sponsor lead to discontinuation in approximately 9% of those treated with UT-15. Using fairly aggressive dosing regimens would likely increase the rate of discontinuations in subjects. Should the dropout rate be too high due to infusion site pain the study may not be interpretable. In the two cases during the initial NDA where subjects were inadvertently started on fairly high doses of UT-15, both were hospitalized for intolerable pain. The dose of one of these two subjects was approximately 8.3 ng/kg/min. The dose at which the other subject was switched over is unclear. These doses would be achieved by approximately day 2 (presuming an initial Flolan of 35 ng/kg/min).

Because of the occurrence of severe infusion site pain, there is the potential for informative censoring of subjects who discontinue. The protocol plans to censor any subjects who discontinue for reason other than worsening disease. Those who discontinue would likely not be allowed to remain untreated but would be re-started on Flolan. The question is how can one differentiate those that decided to discontinue because of intolerance to pain when compared to worsening or a non-improvement in pulmonary hypertensive status?

In order to separate out the discontinuations for adverse events from those due to worsening status, as much data as possible would be collected on subjects at the time of discontinuation. The results would then be submitted to a blinded adjudication committee. Although this proposal is a marked improvement over the specifics in the initial protocol, the data submitted to the adjudication committee is filtered through the treating physician who may be entirely unblinded. The adjudicated resluts would therefore, not be entirely objective.

This reviewer had suggested that a true intent-to treat study be performed, that Flolan not be restarted at the time of the discontinuation but only be re-started once symptoms of pulmonary hypertension supervene. The event would then be considered as an end-point. It appears to this reviewer that if it is ethical to discontinue subjects to placebo until symptoms reoccur it is equally ethical to discontinue the treatment till symptoms re-occur.

It appears counter-intuitive that the exact same outcome i.e. terminating trial and restarting Flolan in one situation is treated as an outcome and in the other as a non-event.

- It would be up to the sponsor to limit the number of subjects who discontinue. If none or few subjects discontinued, the study would be taken at its face value. If, however, many subjects discontinue, predominantly in the UT-15 group, the adequacy of the results based on censoring and imputation would not be convincing. The planned dosing regimen, in this context appears to be overly aggressive with high doses of UT-15 achieved over short period of times. Infusion site pain with discontinuation is likely to be equal to or greater than observed in P01:04 and P01:05.

- The primary endpoint of the study is the time to clinical deterioration defined as the time from initiation of study drug to earliest incidence of clinical worsening of PAH symptoms requiring reinstitution of Flolan therapy or re-hospitalization or death. Whereas death, assuming adequate follow-up, is objective, the other end points are subjective. The outcomes could be markedly altered by the degree of unblinding. It is likely that given the perceived benefit of UT-15, classification of events would be altered. The end-point of re-institution of Flolan would be aggresively pursued only in those without pain (placebo).

  The sponsor makes some effort to mitigate some of the consequence of unblinding. An adjudication process is to be performed by a committee blinded, to both treatment and the presence of infusion site pain. This analysis diminishes to a certain extent the degree of subjectivity in the outcomes. The problem, however, is the data, which is supplied to the adjudication committee is largely subjective and supplied by an unblinded (because of pain) observer.

  With respect to cause specific hospitalization as an end-point, any hospitalization, aside from elective procedures or acute trauma, should be considered as an outcome. If those enrolled are relatively stable for 30 days prior to enrollment any hospitalization should be considered as worsening of disease.

- The adjudication committee's charge is not defined. One way of defining a true discontinuation for adverse event versus deterioration, given the potential of unblinding and the subject nature of the endpoints, is to affirmatively require proof that those who discontinued for adverse events were not symptomatically worse. That is, absent adequate and convincing data the presupposition by the adjudication committee should be conservative and assume the subject deteriorated.

- The overall safety of the study should be predicated on overall event rates that are lethal or potentially lethal. The sponsor purposefully does not include a Flolan group. The inherent assumption is that those stable on Flolan would unlikely deteriorate during this modest duration study. The charge to the DSMB is that the study should be discontinued based not on placebo versus UT-15 outcome but based on the outcome of the imputed Flolan group.

- The need for re-instituting Flolan once off treatment seems a reasonable surrogate for worsening of status. But the definition of "re-institution" needs some further discussion. This reviewer does not accept short-term increase in Flolan during the down-titration phase as indicating deterioration.

- The amended protocol limits inclusion to those on Flolan whose underlying disease is either primary pulmonary hypertension or for scleroderma spectrum of disease, which corresponds to the approved labeling of Flolan. Subjects whose pulmonary hypertension is due to congenital left-right shunting are now excluded. This reviewer concurs.

- Blinding may be compromised at the point when a subject crosses over at the end of 8-weeks. There is no provision for re-titration or reinstitution of the original Flolan dose. Therefore, only placebo (vehicle) subjects will be re-titrated. The integrity of the data needs to be protected by this stage.

- Subjects with known left sided failure are to be excluded. There is no affirmative need to document the absence of left-sided cardiac disease. This reviewer would require affirmative proof that no left-sided disease exists prior to entry.

- An informed consent should prominently display the risk of stopping Flolan. In particular, there is some risk that should symptoms re-occur restarting Flolan may not salvage the subject if their status worsens and this might lead to death or hospitalization.

- The study limits the age range to < 18. During clinical studies children as young as 9 years old were enrolled. Is there any reason for limiting the age?

- The sponsor should collect data on the need for and adequacy of pain medication.

- No CRFs were submitted.

- There are several walk tests to be performed during the flolan withdrawal phase of the study. It is unclear how these data would be used. Please clarify.

- The sponsor should clarify if those who discontinue due to site pain will be replaced.

Conclusions:

- The study should be improved by allowing for intermittent up-titration of Flolan. Should two increases of drug/placebo doses not stabilize the subject a reversion of the last down-titration of Flolan should be allowed.

- The protocol should allow the full 2-weeks to optimize the down titration of Flolan. Not 8 days for down titration and six days for the optimization of either dose regimen.

- The definition for hospitalization should include any non-elective hospitalization

- The DSMB should be informed that the assumption is that there would be no or few events should the subject remain on Flolan. Safety should therefore be predicated on overall deaths, serious or irreversible events

- There is no stipulation that the DSMB can stop the study. Presumably this is implied in the mandate of the DSMB.

- If too many subjects discontinue due to site pain, the study is likely to be un-interpretable even with imputed values. The current dosing instructions for UT-15 may be aggressive and may predispose to dropouts due to infusion pain.

- There are components of the end-points that are subjective. The information transmitted to the adjudication committee is likely to be colored by some knowledge as to treatment. Therefore, a small effect may not be convincing for efficacy.

- An effect driven by early dropouts in the placebo group could be interpreted as a mitigating effect of UT-15 on withdrawal.

- Alternatively, an effect driven by early dropouts could be interpreted as a benefit limited to short term therapy.

- The informed consent should prominently display the potential risk of death and the inability to easily salvage subjects upon cessation of Flolan. The current

- Blinding at the end of the 8-week period will be compromised since only those who were treated with placebo will require re-titration. The data needs to be locked in prior to unblinding or all patients should be restarted on their initial dose of Flolan.

- The CRFs should be submitted.

- The sponsor should capture need for pain medication. In addition to clarifying the down-side of UT-15 treatment, this parameter would be important in defining the adequacy of blinding.

- The adjudication committee's charge is not defined. This reviewer would require that affirmative information must be supplied that the subject did not discontinue due to worsening disease. The presumption would be that all those who discontinue did so

due to worsening of disease unless adequate data is there to be convincing that the status did not deteriorate.

- The sponsor should define which forms of hospitalization would not be considered as an event.

- The sponsor should collect data on the need for and adequacy of pain medication.

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/s/

Abraham Karkowsky
4/18/02 01:20:27 PM
MEDICAL OFFICER

Division of Cardio-Renal Drug Products
Medical Officer Review

NDA 21-272
Remodulin ™ (treprostinol sodium) Injection
Reviewer: Abraham M. Karkowsky, M.D., Ph.D.

Date: July 13, 2001

This document amends a statement in the review dated June 19, 2001. In that document this reviewer stated that no protocol was supplied for those Flolan patients transitioned to UT-15 (protocol P01:11). The sponsor (United Therapeutics) correctly pointed out that a protocol, amendments and CRFs were supplied with the original NDA. The conclusions of the June 19, 2001 document are not changed by this information.

Division of Cardio-Renal Drug Products
Medical Officer Review

NDA 21-272
Remodulin ™ (treprostinol sodium) Injection

This review covers the submissions dated 12 April 2001 and 15 May 2001. This review incorporates Dr. Lawrence, the FDA statistician's review for the April 12 submission. United Therapeutics submitted these two submissions in response to a meeting on 11 April 2001. At that meeting United Therapeutics proposed to analyze the combination of six-minute walk and the Borg-dyspnea score by combining these metrics into a single value. The rationale for combining these two parameters is they are the least likely (but not totally) devoid of bias due to unblinding by the nearly universal presence of infusion site pain limited to those treated with UT-15. Placebo-treated subjects rarely had infusion site pain.

United Therapeutics also submits additional data on the use of narcotic pain medication among those in treated long-term with UT-15.

Lastly, the sponsor submits information on a total of eight patients who were transitioned to UT-15 after adverse events while receiving Flolan infusions.

1) Additional analyses combining six-minute walk and Borg-dyspnea Index

The sponsor's analysis was <u>not</u> pre-specified and only considered after the results of the study were available. The overall process of defining a metric was to combine normalized (to a scale of 0-1) rankings of six minute walk and normalized (to a scale of 0-1) ranking of the Borg-dyspnea scale. The resultant values were summed and then the subjects were then re-ranked with the ranks normalized (on a scale of 0-1). The sponsor graphs the % of patients in each group who achieve at least a given rank versus the rank scale that spanned the range of 0 to 1.

The sponsor treats dropouts in different ways. Two extremes of these analyses are shown below. The first analysis (Figure 1) treated those who died, were transplanted, discontinued due to worsening of disease or who were too ill to perform the assessment as worse outcomes. All others who discontinued had last observations carried forward. Since there were far more discontinuations in among those treated with UT-15 than among those treated with placebo, additional analyses that assigned worse rank to subjects who discontinued based on criteria such as death or transplantation during the 100 days since randomization even after discontinuation due to adverse events. Other analyses also treated those who received flolan during the first month or those who received flolan during the 100 day span of the study as worst case scenarios. The analysis shown as Figure 2 treats all subjects who discontinued as worst outcomes independent of the reason for discontinuation and is the most conservative of the analyses performed by the sponsor. [Comment: The most conservative analysis would treat he UT-15 as worst outcome and censor placebo patients.]

Based on these two analyses, there was a difference among those treated by placebo and those treated with UT-15. The interpretation of these curves however is obscure. Perhaps the only interpretation is that approximately 57-60% of those treated with UT-15 did better than the median (rank of 0.5) than the 43-40% of those treated with placebo. Describing this benefit in words is not easy and would require de-convoluting the ranks. In essence all that can be said is that there is little benefit in walk distance (< 10 meters) and some benefit in Borg-dyspnea measurements.

This interpretation adds little to the information currently available.

The very small p-values associated with this analysis is hardly surprising. As Dr. Lawrence notes in his review

" [W]hen the p-value from one variable is very small and this variable is combined with a second variable, it should not be surprising that the p-value from the sum of the two variables is small".

One last point, the Borg-dyspnea measurement is not entirely devoid of the problem of unblinding. The methodology that was employed by the sponsor was however, about a s good as it gets. There was a designated individual who not involved in the subject's care elicited this metric. Unblinding, however, may have occurred at the level of the subject-investigator. The investigator likely knew the subject's treatment based on the presence or absence of infusion site pain.

Again combining the six-minute walk with the Borg index does not really add much to what we know about the individual components.

Figure Addendum- 1 Combined Rank analysis with patients who discontinued due to death, transplantation, worsening of status or unable to exercise at week 12 treated as worst outcomes

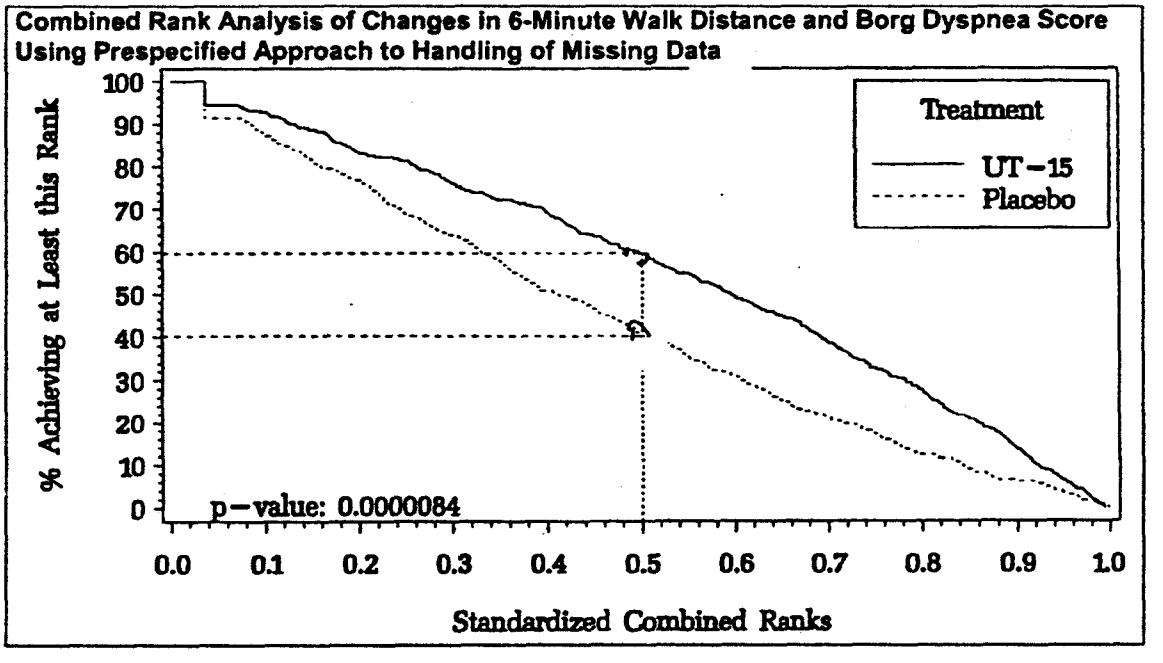
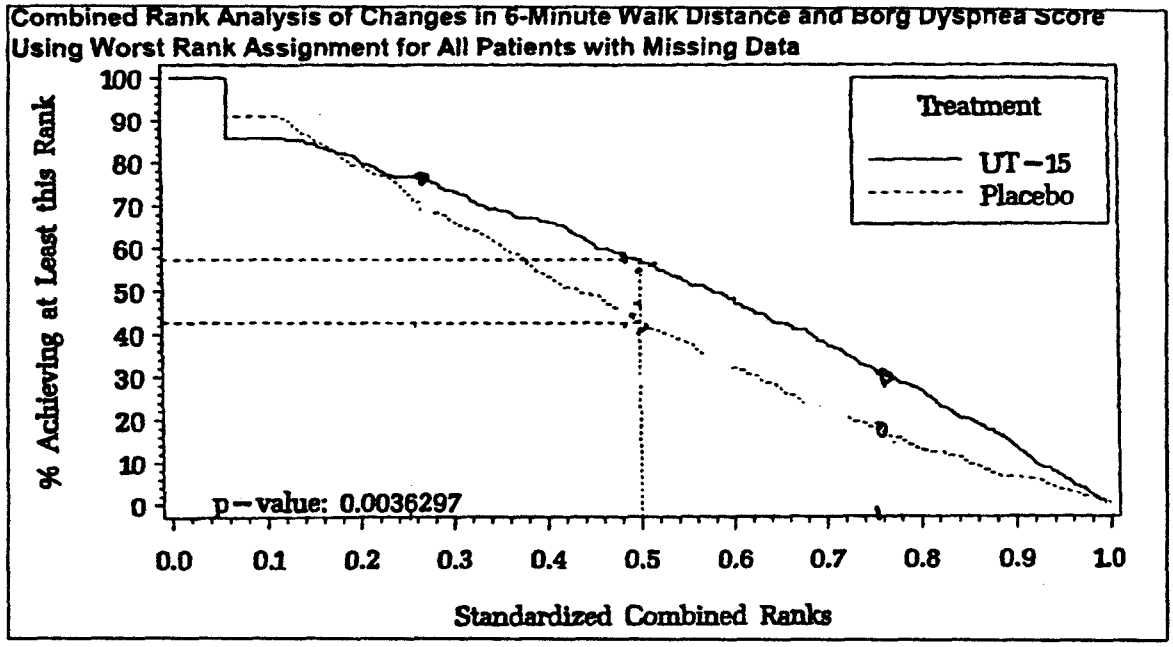


Figure Addendum- 2. All dropouts treated as worst outcomes



2) Use of Narcotics.

The sponsor submits several analyses as to the use of narcotics (of all types) among those who were treated with UT-15 and had infusion-site pain. The sponsor notes that 27% of those enrolled were treated with opiates during the two pivotal studies P01: 04 and P01: 05. Of these patients 19% were treated with either class II narcotics (that includes codeine, oxycodone, methadone, meperidine or fentanyl) or Class III narcotics (that include codeine mixtures, dihydrocodeine or hydrocodone).

Among those who were enrolled into study P01: 06, 135/631 (21%) of the subjects were treated with narcotics. Those who entered P01: 06 were those who enrolled into previous studies and completed these studies on UT-15 (i.e. did not dropout or die and therefore tolerated the UT-15 infusion) or placebo patients who completed crossed over to UT-15. In addition, there were 208 subjects who were enrolled into this open-label extension who were naïve to either infusion.

During study P01:06 , subjects who were prescribed narcotics were not asked whether the pain medication was necessary on an on-going basis and whether the pain was still present. These prescriptions were left for the patient to fill use on a PRN basis.

In order to ascertain some measurement of the need for narcotics, 535 of the 545 subjects still on treatment were contacted as to whether they were using narcotics the day prior to contact. Of those contacted 45 (8%) were taking some form of opiate.

[Comment: The on-going need for narcotics such be interpreted in the context that the duration of inquiry was short (1 day), the population who were questioned were those who did not discontinue due to site pain and did not include those whose pain was sufficiently severe to require NSAIDS.]

3) Cross-over subjects from Flolan to UT-15

No protocol was submitted. The data that was reviewed consists of 12 pages of study summary.

As of May 1, 2001, eight subjects (6 males and 2 females) age range 29-54 with pulmonary hypertension were transitioned from intravenous flolan to subcutaneous UT-15. Some specifics are shown below.

Table addendum-1 specifics among those switched from Flolan to UT-15

Patient #	Reason for Flolan D/C	Time on Flolan (months)	Dose of Flolan	UT-15 dose after transition (ng/kg/min)	Time of Transition	Time on UT-15 (months)
1102001	Recurrent paradoxical emboli	5	3.5	3	24	15
1121001	Central line infection	29	26	15	50	5
1121002	Jaw/leg pain Line infection	36	75	65	120	3
1129001	Line infection-septicemia	26	22.5	23.3	42	2
1129002	Line infection-epidermal necrosis	33	40	36.6	54	2
1153001	Line infection	21	15	7	36	9
1153002	Severe Headache, jaw pain and diarrhea	30	13	10	22	6
1153003	Line infection-septicemia	19	18	16	22	6

The sponsor notes no increase in pulmonary hypertension symptoms during the transition period. The sponsor also notes that adverse events were those of prostacyclin excess and/or infusion site discomfort. In addition, one patient # 1102001 had a cerebrovascular accident during the transition period from Flolan o UT-15. Seven of the eight subjects are reported by the sponsor to be still alive and doing well. One subject is reported as having worsening symptoms while on Flolan that continued after transition to UT-15.

Comment: There was no randomization process to determine whether those transitioned actually benefited from Flolan (i.e. worsening of symptoms upon decrease of dose of flolan). No efficacy conclusions can be derived from this data.

Abraham Karkowsky, M.D. Ph.D. /S/

Cc: HFD-110 A Karkowsky
N Stockbridge
D Throckmorton
E Fromm

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/s/

Abraham Karkowsky
6/19/01 03:04:29 PM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Clinical Review

NDA: 21-272

Sponsor: United Therapeutics Corp.

Submission: (16 October 2000) Request for marketing approval for UT-15 (uniprost, remodulin), for the treatment of pulmonary arterial hypertension.

Review date: March 9, 2001

Reviewers: A. Karkowsky, M.D., Ph.D., HFD-110

/S/

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

/S/

D.C. Throckmorton, M.D., HFD-110

/S/

Summary: UT-15 was the subject of a development program for pulmonary hypertension in a population somewhat broader than that for which epoprostenol (Flolan) is approved. UT-15 has some potential advantages over Flolan in that UT-15 is administered by subcutaneous infusion, rather than a central line. UT-15 did not meet its primary end point in the pivotal portion of its development program, probably because its effects on exercise tolerance are smaller than expected. UT-15 doses rise progressively with time of exposure; the explanation for this is not known. The use of UT-15 is limited by tolerance to pain and local reaction at the site of infusion. There are no other safety issues, but UT-15 probably lacks Flolan's apparent benefits on mortality.

Distribution: NDA 21-272

HFD-110/Project Manager

HFD-110/Karkowsky

HFD-110/Stockbridge

HFD-110/Throckmorton

Table of contents

List of tables

List of figures

1 Materials utilized in the review

1.1 Materials from NDA/ IND

No reference was made to the IND during the course of this review.

Materials from the NDA that were utilized for this review are listed in the table below.

Submission	Description
16 October 2000	Original NDA submission
03 November 2000	Clinical amendment
16 November 2000	Clinical amendment
05 January 2001	Clinical amendment
11 January 2001	Clinical amendment
15 February 2001	120-day safety update

In addition to the documents, the electronic data supplied by the sponsor were used in this review.

1.2 Related reviews or consults

Not applicable.

1.3 Other resources

Not applicable.

APPEARS THIS WAY
ON ORIGINAL

2 Background

2.1 Indication

The proposed indication for UT-15 is for the treatment of primary or secondary pulmonary hypertension:

[redacted]

2.2 Information from pharmacologically related agents

UT-15 bears some structural similarity to Flolan (epoprostinol). The two also share an apparent mechanism of action.

2.3 Administrative history

This development program was managed under IND [redacted] (opened 15 April 1991). The application was inactive from 1992 to 1997. The Division last met with the sponsor in 20 February 1998 for end-of-phase-II discussions of the design of pivotal studies[1]. There was a pre-NDA meeting 15 November 1999. Since filing the NDA, the Division met with the sponsor 8 December 2000 to discuss possibly taking UT-15 before the Cardio-Renal Advisory Committee and 25 January 2001 to discuss clinical review issues.

UT-15 is not approved for marketing in any country.

2.4 Proposed labeling

Labeling is reviewed fully in section 7 (page 33).

2.5 Other background information

Not applicable.

[1] *Tolerance was discussed at that time.*

3 Microbiology, pharmacology, chemistry, biopharmaceutics, and inspections

3.1 Microbiology

In the microbiology review, dated10.24.00, Dr. Langille concluded that the NDA was approvable pending resolution of five specific deficiencies noted on page 17 of his review, for which additional information was requested from the sponsor.

3.2 Chemistry

In the review of Chemistry, Manufacturing, and Controls, dated 8.27.00, Dr. Advani concluded that the NDA was approvable pending information on five specific deficiencies, listed on page 3 of his review, for which additional information is being sought.

3.3 Pharmacology

In the review of Pharmacology and Toxicology, Dr. Joseph commented on several critical aspects of UT-15 pharmacology and toxicology, summarized below and discussed in greater detail in his review. He concluded that 'there are no approvability issues for UT-15 based on the non-clinical toxicity-testing program.'

3.3.1 Pharmacokinetics and metabolism

UT-15 was cleared rapidly in all animal species following administration, with a terminal T1/2 of 20 minutes. Radioactively-labeled UT-15 accumulated in tissues, with the longest T1/2 being fat (478 hours). The feces were the major route of elimination for UT-15 in rats, with 14% of dose excreted in urine and 82% in feces. In contrast, in humans found that the primary route of excretion for the radioactive label (measuring intact drug and metabolites) was urine (79%) and not feces (13%).

Microsomal preparations from human liver showed no significant inhibition of the activities of any of the P450 isozymes (CYP 1A2, 2C9, 2C19, 2D6, 2E1, 3A).

The route(s) of metabolism for UT-15 has not been well-characterized in man. Metabolites identified are the products of oxidation and glucuronidation. The activity of these metabolites has not been determined. See the review, Figure 9, page 32, for proposed metabolic pathway.

In vitro, UT-15 was found to be heavily protein bound in human plasma (91%).

Per the reviewer, UT-15 produced dose-dependent decreases in PR and QRS intervals with no effect on QTc.

3.3.2 Pharmacodynamic effects

In animal models and/or *in vitro*, UT-15 has at least three relevant pharmacodynamic effects: inhibition of platelet activation, vasorelaxation, and inhibition of smooth muscle cell proliferation.

- The inhibition of platelet activation occurs at a IC50 of 13.5 ng/ml for the free UT-15. Since UT-15 is heavily protein-bound (at least in man), this concentration of free UT-15 is appreciably higher than the concentrations anticipated in the clinical setting.
- UT-15 causes vasorelaxation in a dose-dependent fashion and lowers pulmonary arterial pressure in animals. First, UT-15 causes vasorelaxation in a dose-dependent manner on *ex vivo* muscle strips. In animals, doses of as little as 0.4 µg/kg/min in anesthetized rats, administered IV lowered mean arterial pressure. This dose-dependent effect of IV UT-15 was seen in rabbits, cats and dogs as well. The effect of subcutaneous UT-15 was

examined in rats, where a dose-dependent reduction in BP was seen (see table 4 in Pharm/Tox review). Interestingly, oral doses of UT-15 also lowered blood pressure in rats and dogs.

Regarding changes in central hemodynamics following UT-15, IV doses caused reductions in mean pulmonary artery pressure and pulmonary vascular resistance in hypoxic cats and anesthetized dogs. However, systemic vascular resistance also fell, and the pharmacologist suggested that 'there might be little or no selectivity of UT-15 for the pulmonary or peripheral circulation in the normotensive anesthetized dog.' In this same model, UT-15 had a negative inotropic effect at doses of 1 and 3 μg/kg/min IV, although cardiac output rose at doses ≥0.3 μg/kg/min (presumably as a result of vasodilation).

- UT-15 has an anti-proliferative effect on smooth muscle cells in culture. This effect is related to the production of cAMP by cells exposed to UT-15. It isn't know if this effect is seen in animals exposed to UT-15.

3.3.3 Toxicology/ carcinogenicity

In the chronic toxicology studies, reaction site lesions were the most prominent toxicity. The incidence and severity of these lesions were dose-related, which included erythema, inflammation, and the formation of nodules and/or thickening of the skin. Histologically, these nodules contained edema, hemorrhage, cellulitis and/or fibrosis. Increases in spleen and heart weight were also seen in high-dose male and female rats. Laboratory abnormalities seen at high-doses included reversible increases in white blood cell count (male and female rats) and increased total bilirubin (males rats). At lethal doses in dogs, death resulted from intestinal intussusception and/or rectal prolapse. Histologically, hemorrhage and necrosis of the ileum and rectum were noted.

Carcinogenicity studies were not performed. There was no evidence of mutagenicity or clastogenicity in the standard assays (see the Pharmacology/Toxicology review for details). There was no dose-dependent effect on reproductive parameters or on fetal malformations. In rats, maternal toxicity was see at high doses (450 and 900 ng/kg/min).

3.3.4 Tolerance

The reviewer concluded that tolerance was not demonstrated in the studies submitted, although 'tachyphylaxis' was observed in anesthetized animals. In one dog study (summarized on pages 22-24 of the Pharm/Tox review) continuous infusion of UT-15 predicted a ...'close relationship between plasma concentration and the onset of hemodynamic effect'. During continuous infusion for 5 hours, however, the measured decreases in total peripheral resistance (TPR) were maintained, but the decreases in pulmonary vascular resistance (PVR) returned towards baseline. This rise in PVR occurred despite steady-state serum concentrations, suggesting tachyphylaxis for the drug effects on PVR.

3.4 Biopharmacology/ Pharmacokinetics

The Biopharmacology/ Pharmacokinetics reviewers concentrated on two large issues related to the clinical pharmacology of UT-15. The first was PK/PD modeling for the following: the concentration of UT-15, the change in hemodynamics (mean pulmonary artery pressure, PAPm), and the six minute walk distance. The second issue addressed in the review was the possible development of hemodynamic tolerance. See the final Biopharmacology/ Pharmacokinetics review for their final assessment regarding the approvability of UT-15.

3.4.1 Metabolism

The absorption of UT-15 following SC administration is approximately 100%. UT-15 is metabolized in the liver with <4% excreted unchanged in the urine. Five metabolites (of unknown activity) are formed, although the metabolic pathways used have not been identified. As discussed in the Pharmacology and Toxicology review, oxidation and glucuronidation is responsible for several of the metabolites.

3.4.2 Pharmacokinetics

The pharmacokinetics of UT-15 are linear over a dose range of 2.5 to 15 ng/kg/min. The drug follows a 2-compartment body model, with a half-life of 2-4 hours in man. This half-life was not affected by gender, race or obesity. The presence of hepatic impairment significantly increased both the Cmax and the $AUC_{0\text{-}inf}$. Of note, no evaluation of the pharmacokinetics of UT-15 in severe hepatic impairment was performed. Similarly, the effect of renal insufficiency on the pharmacokinetics of UT-15 has not been characterized. This is relevant as 78% of a given dose is excreted in the urine, largely as metabolites, and we lack information about their possible activity.

3.4.3 Concentration-effect relationship of UT-15 to pulmonary hemodynamics and clinical outcomes

Drs. Gobburu and Nguyen concluded that there was a concentration-effect relationship of UT-15 on mean pulmonary artery pressure (PAPm) and other hemodynamic measures and that the slope of the relationship was shallow, suggesting a small effect of UT-15 on hemodynamics over the dose range utilized in the clinical trials. They were also able to conclude that there was a relationship between changes in PAPm and changes in the six-minute walk distance. Again, the slope of the relationship was shallow, suggesting a small effect of UT-15 over the range of doses used in the clinical trials. One explanation for these findings (unproven) is that the free concentrations of UT-15 achieved in the trials were on the low end of the concentration-response curve when compared with the EC_{50} derived from *in vitro* experiments.

3.4.4 Tolerance

The reviewer's have made no written statements with regard to the development of clinical tolerance when this documents was created. In discussions with Drs. Nguyen and Gobburu, they pointed out the difficulty in assessing the development of tolerance in the available clinical data. With regard to central hemodynamic measurements (*e.g.*, PAPm, cardiac output), no study included more than two measures of these values. This seemingly precludes evaluation of tolerance for these parameters.

3.5 Division of Scientific Investigation

The overall evaluation of the inspection reports, performed by Jorge C. Rios, M.D., found that this study was performed well, informed consent was obtained in all cases, only minor protocol violations were noted. Overall, the data were classified as acceptable

4 Description of clinical data sources

4.1 Primary source data

4.1.1 Study type and design

The information in this review includes the results of the two pivotal trials P01:04 and P01:05 as well as 10 smaller studies (P01:01; P01:02; P01:03; P01:02; P01:07; P01: 08; P01:09 and P01:10 P01:11, P02:01, P03:01 and P76:01). The 10 smaller studies enrolled a total of 145 patients that were either normals, patients with pulmonary hypertension, patients with CHF or patients with peripheral vascular disease. The specifics of the studies are summarized in Table 1.

Table 1. Short-term, non-pivotal studies of UT-15

	Type	Demo-graphics	Subjects[2]	Design, duration
P01:01	Acute, dose-range-finding study of iv UT-15 compared to intravenous, (iv) Flolan® in patients with severe Primary Pulmonary Hypertension [PPH]	12-57y; 11F / 4M	15/15	1) Flolan®: dose-ranging to a maximally-tolerated dose (MTD); 2) 90-minute Flolan® washout segment; 3) UT-15 dose-ranging to a MTD; 4) a 90-minute UT-15 maintenance segment (at the MTD); and 5) a 120-minute UT-15 washout segment
P01:02	Acute, dose-range-finding study of a fixed iv dose and subcutaneous (sc) UT-15 doses up to the MTD patients with severe PPH	22-71y; 20F / 5M	30/25	1) 75-minute intravenous infusion of 10 ng/kg/min UT-15; 2) 150-minute washout.; 3) 150-minute subcutaneous UT-15 infusion; 4)150-minute washout.
P01:03	Multicenter, double-blind, randomized (2:1, Active: Placebo), parallel, placebo-controlled 8-week trial in NYHA III/IV PPH	12 - 73 y 21 F/5 M	Total 24/26 Treatment 16/17 UT-15 8/9 Placebo	8 weeks Subcutaneous infusion 2.5 - 50 ng/kg/min
P01:07	Bioavailability of UT-15 in Healthy Volunteers	18 - 49 y; 7F / 8M	15/15	Acute, IV versus sc infusion 15 ng/kg/min for 150 min
P01:08	Effects of Acetaminophen on the Pharmacokinetics of UT-15 in Healthy Volunteers	18-47 y; 17F / 12M	29/29	Acute SC infusion 2 doses of 15 ng/kg/min each
P01:09	Chronic (28 day) Dose-Escalation study of the pharmacokinetics of UT-15 in Healthy Volunteers	23-49 y; 8F / 6M	14/14	Chronic SC infusion Four 7 day infusions at 2.5, 5, 10, and 15 ng/kg/min
P01:10	Mass Balance, Urinary Metabolite Profiling, And Safety Study of [^{14}C] UT-15 in Healthy Volunteers	23-45y; 6M	6/6	Acute SC infusion 15 ng/kg/min for 8 hr (72.5 to 95.7 µCi)
P01:11	Patients transitioning from Flolan® to UT-15	29-54y 3F	—/3	UT-15 administered SC
P02:01	Patients with porto-pulmonary hypertension	25-59 y 3F/6M 1B/8W	12/9	Acute subcutaneous infusion at a rate of ng/kg/min for 150 min.
P03:01	Patients peripheral vascular disease	56-78 3F/5M 1B/8W	8/8	Intravenous dose escalating phase to tolerance . followed by a 120 minute infusion
PP76:01	Patients with CHF class III-IV	Mean age 47 7B/5W	12/12	Dose escalating study every 15 minutes followed by 90 minute fixed infusion

Of these patients, 64 normals were exposed to UT-15 in biopharmaceutical or mass balance studies. The results are included in the biopharm review. The patients who enrolled into the other studies either had pulmonary hypertension, CHF or peripheral vascular disease as their underlying medical problem. None of these studies was sufficiently well designed or sufficiently large to add information with respect to efficacy, dose response or safety of UT-15. Long term safety is derived from study P01:06. This

[2] *Planned/actual*