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:

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