

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

## **Approval Package for:**

### ***APPLICATION NUMBER:***

**21-272/S-005**

***Trade Name:*** Remodulin Injection 1.0, 2.5, 5.0, and 10 mg/ml.

***Generic Name:*** treprostinil sodium

***Sponsor:*** United Therapeutics Corporation

***Approval Date:*** March 20, 2006

***Indications:*** Remodulin is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise.

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**21-272/S-005**

## **CONTENTS**

<b>Reviews / Information Included in this NDA Review.</b>
-----------------------------------------------------------

<b>Approval Letter</b>	<b>X</b>
<b>Approvable Letter</b>	
<b>Labeling</b>	<b>X</b>
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Medical Review(s)</b>	<b>X</b>
<b>Chemistry Review(s)</b>	
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Other Review(s)</b>	<b>X</b>
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-272/S-005**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-272/S-005

United Therapeutics Corporation  
Attention: Dean Bunce  
P.O. Box 14186  
One Park Drive  
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your supplemental new drug application dated October 12, 2005, received October 13, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin Injection (treprostinil sodium) 1.0, 2.5, 5.0, and 10 mg/ml.

We acknowledge receipt of your submissions dated February 1, 7, 8, 21 and March 6, 2006.

This supplemental new drug application provides a final study report for Phase 4 commitments required as a condition of your May 21, 2002 Subpart H approval. Specifically, this supplement provides information to the labeling on the use of Remodulin Injection (treprostinil sodium) 1.0, 2.5, 5.0, and 10 mg/ml for the treatment of patients with pulmonary arterial hypertension (PAH) requiring transition from Flolan®.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-272/S-005.**" Approval of this submission by FDA is not required before the labeling is used.

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Mr. John David  
Regulatory Project Manager  
(301) 796-1059

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Agreed upon labeling text

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Norman Stockbridge  
3/20/2006 03:59:46 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-272/S-005**

**LABELING**

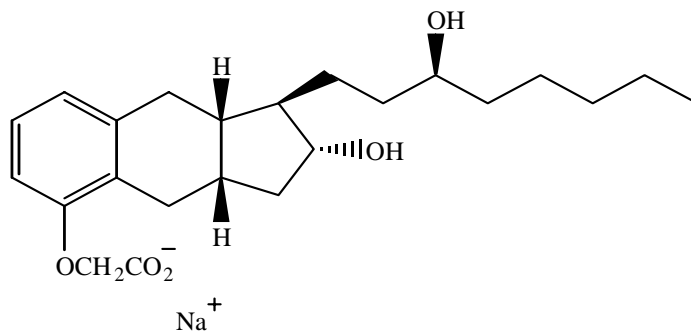
**PRODUCT INFORMATION****REMODULIN<sup>®</sup> (treprostinil sodium) Injection****DESCRIPTION**

Remodulin<sup>®</sup> (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil sodium is (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 monosodium salt. Treprostinil sodium has a molecular weight of 412.49 and a molecular formula of C<sub>23</sub>H<sub>33</sub>NaO<sub>5</sub>.

The structural formula of treprostinil sodium is:

**CLINICAL PHARMACOLOGY**

**General:** The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

**Pharmacokinetics**

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 22.5 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 mcg/L) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 22.5 ng/kg/min has not been studied.

Subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.

**Absorption:** Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2 mcg/L.

**Distribution:** The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Remodulin at *in vitro* concentrations ranging from 330-10,000 mcg/L was 91% bound to human plasma protein.



**Metabolism:** Remodulin is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of *in vitro* human hepatic cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether Remodulin induces these enzymes has not been studied.

**Excretion:** The elimination of Remodulin is biphasic, with a terminal half-life of approximately 4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

### Special Populations

**Hepatic Insufficiency:** In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, Remodulin at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a  $C_{max}$  that was increased 2-fold and 4-fold, respectively, and an  $AUC_{0-\infty}$  that was increased 3-fold and 5-fold, respectively, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

In patients with mild or moderate hepatic insufficiency, the initial dose of remodulin should be decreased to 0.625 ng/kg/min ideal body weight and should be increased cautiously. Remodulin has not been studied in patients with severe hepatic insufficiency.

**Renal Insufficiency:** No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

**Effect of Other Drugs on Remodulin:** *In vitro* studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

*In vivo* studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

### Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of Remodulin to placebo in a total of 470 patients with NYHA Class II-IV pulmonary arterial hypertension (PAH). PAH was primary in 58% of patients, associated with collagen vascular disease in 19%, and the result of congenital left to right shunts in 23%. The mean age was 45 (range 9 to 75 years). About 81% were female and 84% were Caucasian. Pulmonary hypertension had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with Remodulin may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Remodulin was administered as a subcutaneous infusion, described in DOSAGE AND ADMINISTRATION, and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses > 40 ng/kg/min. Background therapy, determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

## Hemodynamic Effects

As shown in Table 1, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

**Table 1: Hemodynamics During Chronic Administration of Remodulin in Patients with PAH in 12-Week Studies**

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)
CI (L/min/m <sup>2</sup> )	2.4 ± 0.88	2.2 ± 0.74	+0.12 ± 0.58*	-0.06 ± 0.55
PAPm (mmHg)	62 ± 17.6	60 ± 14.8	-2.3 ± 7.3*	+0.7 ± 8.5
RAPm (mmHg)	10 ± 5.7	10 ± 5.9	-0.5 ± 5.0*	+1.4 ± 4.8
PVRI (mmHg/L/min/m <sup>2</sup> )	26 ± 13	25 ± 13	-3.5 ± 8.2*	+1.2 ± 7.9
SVRI (mmHg/L/min/m <sup>2</sup> )	38 ± 15	39 ± 15	-3.5 ± 12*	-0.80 ± 12
SvO <sub>2</sub> (%)	62 ± 100	60 ± 11	+2.0 ± 10*	-1.4 ± 8.8
SAPm (mmHg)	90 ± 14	91 ± 14	-1.7 ± 12	-1.0 ± 13
HR (bpm)	82 ± 13	82 ± 15	-0.5 ± 11	-0.8 ± 11

\*Denotes statistically significant difference between Remodulin and placebo, p<0.05.

CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance indexed; RAPm = mean right atrial pressure; SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO<sub>2</sub> = mixed venous oxygen saturation; HR = heart rate.

## Clinical Effects

The effect of Remodulin on 6-minute walk, the primary end point of the 12-week studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters from a baseline of approximately 345 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Remodulin also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

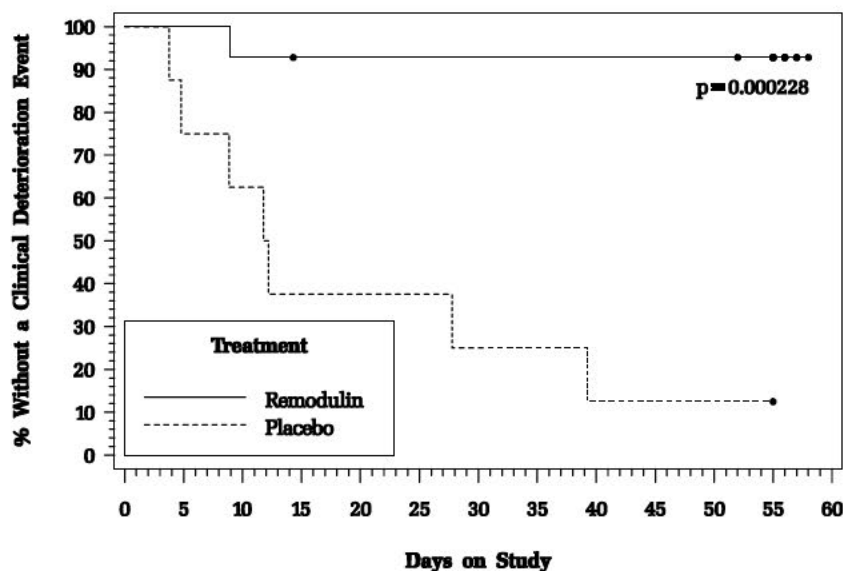
## Flolan-to-Remodulin Transition Study

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study, patients on stable doses of Flolan were randomly withdrawn from Flolan to placebo or Remodulin. Fourteen Remodulin and 8 placebo

patients completed the study. The primary endpoint of the study was the time to clinical deterioration, defined as either an increase in Flolan dose, hospitalization due to PAH, or death. No patients died during the study.

During the study period, Remodulin effectively prevented clinical deterioration in patients transitioning from Flolan therapy compared to placebo (Figure 1). Thirteen of 14 patients in the Remodulin arm were able to transition from Flolan successfully, compared to only 1 of 8 patients in the placebo arm ( $p=0.0002$ ).

**Figure 1: Time to Clinical Deterioration for PAH Patients Transitioned from Flolan to Remodulin or Placebo in an 8-Week Study**



## INDICATIONS AND USAGE

Remodulin® is indicated as a continuous subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms (see **CLINICAL PHARMACOLOGY: Clinical Effects**) to diminish symptoms associated with exercise.

Remodulin is indicated to diminish the rate of clinical deterioration in patients requiring transition from Flolan®; the risks and benefits of each drug should be carefully considered prior to transition.

## CONTRAINDICATIONS

Remodulin is contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

## WARNINGS

Remodulin is indicated for subcutaneous or intravenous use only.

## PRECAUTIONS

### General

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Therapy with Remodulin may be used for prolonged periods, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered.

Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms (see **DOSAGE AND ADMINISTRATION**).

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

### **Information for Patients**

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy, Flolan<sup>®</sup> (epoprostenol sodium).

### **Drug Interactions**

Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications.

Remodulin has not been studied in conjunction with Flolan or Tracleer<sup>®</sup> (bosentan).

### **Effect of Other Drugs on Remodulin**

*In vivo* studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

### **Effect of Remodulin on Other Drugs**

*In vitro* studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

*In vivo* studies: Warfarin – Remodulin does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous Remodulin at an infusion rate of 10 ng/kg/min.

### **Hepatic and Renal Impairment**

Caution should be used in patients with hepatic or renal impairment (see **Special Populations**).

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical

trials, on a  $\text{ng}/\text{m}^2$  basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

### **Pregnancy**

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a  $\text{ng}/\text{m}^2$  basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a  $\text{ng}/\text{m}^2$  basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

### **Labor and delivery**

No treprostinil sodium treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

### **Nursing mothers**

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

### **Pediatric use**

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged  $\leq 16$  years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

### **Geriatric use**

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## **ADVERSE REACTIONS**

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported in postmarketing experience.

**Table 2. Percentages of subjects reporting subcutaneous infusion site adverse events**

	Reaction		Pain	
	Placebo	Remodulin	Placebo	Remodulin
Severe	1	38	2	39
Requiring narcotics*	NA**	NA**	1	32
Leading to discontinuation	0	3	0	7

\* based on prescriptions for narcotics, not actual use

\*\*medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

### Adverse Events During Chronic Dosing

Table 3 lists adverse events that occurred at a rate of at least 3% and were more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

**Table 3: Adverse Events in Controlled 12-Week Studies of Patients with PAH, Occurring with at Least 3% Incidence and More Common on Subcutaneous Remodulin than on Placebo.**

Adverse Event	Remodulin (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Dizziness	9	8
Edema	9	3
Pruritus	8	6
Hypotension	4	2

Reported adverse events (at least 3%) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

### **Adverse Events Attributable to the Drug Delivery System**

In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, or straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration.

There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38) treated for 12-weeks in an open-label study, 2 patients had either line infections or sepsis. Other events potentially related to the mode of infusion include arm swelling, paresthesias, hematoma and pain.

### **OVERDOSAGE**

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).

One pediatric patient was accidentally administered 7.5 mg of Remodulin via a central venous catheter. Symptoms included flushing, headache, nausea, vomiting, hypotension and seizure-like activity with loss of consciousness lasting several minutes. The patient subsequently recovered.

### **DOSAGE AND ADMINISTRATION**

Remodulin<sup>®</sup> is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL. Remodulin can be administered as supplied or diluted for intravenous infusion with Sterile Water for Injection or 0.9% Sodium Chloride Injection prior to administration.

#### **Initial Dose for Patients New to Prostacyclin Infusion Therapy**

Remodulin is administered by continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, the infusion rate should be reduced to 0.625 ng/kg/min.

#### **Dosage Adjustments**

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (see **PRECAUTIONS**).

## Administration

### Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be adjustable to approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of  $\pm 6\%$  or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

For subcutaneous infusion, Remodulin is **delivered without further dilution** at a calculated Subcutaneous Infusion Rate (mL/hr) based on a patient's Dose (ng/kg/min), Weight (kg), and the Vial Strength (mg/mL) of Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. The Subcutaneous Infusion rate is calculated using the following formula:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006^*}{\text{Remodulin Vial Strength (mg/mL)}}$$

\*Conversion factor of 0.00006 = 60 min/hour  $\times$  0.000001 mg/ng

Example calculations for *Subcutaneous Infusion* are as follows:

#### Example 1:

For a 60 kg person at the recommended initial dose of 1.25 ng/kg/min using the 1 mg/mL Remodulin Vial Strength, the infusion rate would be calculated as follows:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{1.25 \text{ ng/kg/min} \times 60 \text{ kg} \times 0.00006}{1 \text{ mg/mL}} = 0.005 \text{ mL/hr}$$

#### Example 2:

For a 65 kg person at a dose of 40 ng/kg/min using the 5 mg/mL Remodulin Vial Strength, the infusion rate would be calculated as follows:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{40 \text{ ng/kg/min} \times 65 \text{ kg} \times 0.00006}{5 \text{ mg/mL}} = 0.031 \text{ mL/hr}$$



***Intravenous Infusion***

**Remodulin must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection** and is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of  $\pm 6\%$  or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Diluted Remodulin has been shown to be stable at ambient temperature for up to 48 hours at concentrations as low as 0.004 mg/mL (4,000 ng/mL).

When using an appropriate infusion pump and reservoir, a predetermined intravenous infusion rate should first be selected to allow for a desired infusion period length of up to 48 hours between system changeovers. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL. With this selected Intravenous Infusion Rate (mL/hr) and the patient's Dose (ng/kg/min) and Weight (kg), the Diluted Intravenous Remodulin Concentration (mg/mL) can be calculated using the following formula:

$$\begin{array}{l} \text{Step 1} \\ \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{\begin{array}{l} \text{Dose} \\ \text{(ng/kg/min)} \end{array} \times \begin{array}{l} \text{Weight} \\ \text{(kg)} \end{array} \times 0.00006}{\begin{array}{l} \text{Intravenous Infusion Rate} \\ \text{(mL/hr)} \end{array}}$$

The Amount of Remodulin Injection needed to make the required Diluted Intravenous Remodulin Concentration for the given reservoir size can then be calculated using the following formula:

$$\begin{array}{l} \text{Step 2} \\ \text{Amount of} \\ \text{Remodulin} \\ \text{Injection} \\ \text{(mL)} \end{array} = \frac{\begin{array}{l} \text{Diluted Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array}}{\begin{array}{l} \text{Remodulin Vial} \\ \text{Strength} \\ \text{(mg/mL)} \end{array}} \times \begin{array}{l} \text{Total Volume of Diluted} \\ \text{Remodulin Solution in} \\ \text{Reservoir} \\ \text{(mL)} \end{array}$$

The calculated amount of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent (Sterile Water for Injection or 0.9% Sodium Chloride Injection) to achieve the desired total volume in the reservoir.

Example calculations for *Intravenous Infusion* are as follows:

**Example 3:**

For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 mL/hr and a reservoir of 50 mL, the Diluted Intravenous Remodulin Solution Concentration would be calculated as follows:

$$\begin{array}{l} \text{Step 1} \\ \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{5 \text{ ng/kg/min} \quad \times \quad 60 \text{ kg} \quad \times \quad 0.00006}{1 \text{ mL/hr}} = 0.018 \text{ mg/mL} \\ \text{(18,000 ng/mL)}$$

The Amount of Remodulin Injection (using 1 mg/mL Vial Strength) needed for a total Diluted Remodulin Concentration of 0.018 mg/mL and a total volume of 50 mL would be calculated as follows:

$$\begin{array}{l} \text{Step 2} \\ \text{Amount of} \\ \text{Remodulin Injection} \\ \text{(mL)} \end{array} = \frac{0.018 \text{ mg/mL}}{1 \text{ mg/mL}} \times 50 \text{ mL} = 0.9 \text{ mL}$$

The Diluted Intravenous Remodulin Concentration for the person in Example 3 would thus be prepared by adding 0.9 mL of 1 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 mL in the reservoir. The pump flow rate for this example would be set at 1 mL/hr.

**Example 4:**

For a 75 kg person at a dose of 30 ng/kg/min, with a predetermined intravenous infusion rate of 2 mL/hr, and a reservoir of 100 mL, the Diluted Intravenous Remodulin Solution Concentration would be calculated as follows:

$$\begin{array}{l} \text{Step 1} \\ \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{30 \text{ ng/kg/min} \quad \times \quad 75 \text{ kg} \quad \times \quad 0.00006}{2 \text{ mL/hr}} = 0.0675 \text{ mg/mL} \\ \text{(67,500 ng/mL)}$$

The Amount of Remodulin Injection (using 2.5 mg/mL Vial Strength) needed for a total Diluted Remodulin Concentration of 0.0675 mg/mL and a total volume of 100 mL would be calculated as follows:

$$\begin{array}{l} \text{Step 2} \\ \text{Amount of} \\ \text{Remodulin Injection} \\ \text{(mL)} \end{array} = \frac{0.0675 \text{ mg/mL}}{2.5 \text{ mg/mL}} \times 100 \text{ mL} = 2.7 \text{ mL}$$

The Diluted Intravenous Remodulin Concentration for the person in Example 4 would thus be prepared by adding 2.7 mL of 2.5 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 100 mL in the reservoir. The pump flow rate for this example would be set at 2 mL/hr.

#### **In patients requiring transition from Flolan:**

Transition from Flolan to Remodulin is accomplished by initiating the infusion of Remodulin and increasing it, while simultaneously reducing the dose of intravenous Flolan. The transition to Remodulin should take place in a hospital with constant observation of response (e.g., walk distance and signs and symptoms of disease progression). During the transition, Remodulin is initiated at a recommended dose of 10% of the current Flolan dose, and then escalated as the Flolan dose is decreased (see Table 4 for recommended dose titrations).

Patients are individually titrated to a dose that allows transition from Flolan therapy to Remodulin while balancing prostacyclin-limiting adverse events. Increases in the patient's symptoms of PAH should be first treated with increases in the dose of Remodulin. Side effects normally associated with prostacyclin and prostacyclin analogs are to be first treated by decreasing the dose of Flolan.

**Table 4: Recommended Transition Dose Changes**

<b>Step</b>	<b>Flolan Dose</b>	<b>Remodulin Dose</b>
1	Unchanged	10% Starting Flolan Dose
2	80% Starting Flolan Dose	30% Starting Flolan Dose
3	60% Starting Flolan Dose	50% Starting Flolan Dose
4	40% Starting Flolan Dose	70% Starting Flolan Dose
5	20% Starting Flolan Dose	90% Starting Flolan Dose
6	5% Starting Flolan Dose	110% Starting Flolan Dose
7	0	110% Starting Flolan Dose + additional 5-10% increments as needed

#### **HOW SUPPLIED**

Remodulin® is supplied in 20 mL multi-use vials at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinil sodium equivalent to 1 mg/mL, 2.5 mg/mL, 5 mg/mL, or 10 mg/mL treprostinil. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F). Store at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. Diluted Remodulin Solution can be administered up to 48 hours at 37°C when diluted to concentrations as low as 0.004 mg/mL in Sterile Water for Injection or 0.9% Sodium Chloride Injection. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

20-mL vial containing treprostinil sodium equivalent to 1 mg treprostinil per mL, carton of 1 (NDC 66302-101-01).

20-mL vial containing treprostinil sodium equivalent to 2.5 mg treprostinil per mL, carton of 1 (NDC 66302-102-01).

20-mL vial containing treprostinil sodium equivalent to 5 mg treprostinil per mL, carton of 1 (NDC 66302-105-01).

20-mL vial containing treprostinil sodium equivalent to 10 mg treprostinil per mL, carton of 1 (NDC 66302-110-01).

US Patent No. 5,153,222 (Use Patent)

United Therapeutics Corp.  
Research Triangle Park, NC 27709

©Copyright 2006 United Therapeutics Corp. All rights reserved.

REMODULIN manufactured by:

Baxter Pharmaceutical Solutions LLC  
Bloomington, IN 47403

For United Therapeutics Corp.  
Research Triangle Park, NC 27709

**Rx only**

March 2006

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Norman Stockbridge  
3/20/2006 03:59:46 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-272/S-005**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type 21-272  
Submission Number S005  
Submission Code SE 7

Letter Date Oct. 11, 2005  
Stamp Date Oct. 13, 2005  
PDUFA Goal Date April 13, 2006

Reviewer Name Abraham M. Karkowsky  
Review Completion Date February 9, 2006

Established Name Treprostinil  
(Proposed) Trade Name Remodulin  
Therapeutic Class Pulmonary arterial vasodilator  
Applicant United Therapeutics

Priority Designation "P"

Formulation Subcutaneous infusion  
Dosing Regimen: Gradual increase in infusion rate  
Indication: Pulmonary arterial hypertension  
Intended Population: Patients with PAH

<b>TABLE OF CONTENT</b>	<b>TABLE OF TABLES.....</b>	<b>4</b>
<b>TABLE OF FIGURES .....</b>		<b>4</b>
<b>1 EXECUTIVE SUMMARY .....</b>		<b>5</b>
1.1 RECOMMENDATION ON REGULATORY ACTION .....		5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS .....		5
1.2.1 Risk Management Activity .....		5
1.2.2 Required Phase 4 Commitments .....		5
1.2.3 Other Phase 4 Requests I .....		5
1.3 SUMMARY OF CLINICAL FINDINGS.....		5
1.3.1 Brief Overview of Clinical Program .....		5
1.3.2 Efficacy .....		5
1.3.3 Safety .....		5
1.3.4 Dosing Regimen and Administration .....		6
1.3.5 Drug-Drug Interactions .....		6
1.3.6 Special Populations .....		6
<b>2 INTRODUCTION AND BACKGROUND .....</b>		<b>6</b>
2.1 PRODUCT INFORMATION .....		6
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS .....		6
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES.....		6
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS .....		6
2.5 PRESUBMISSION REGULATORY ACTIVITY .....		7
2.6 OTHER RELEVANT BACKGROUND INFORMATION .....		7
<b>3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....</b>		<b>7</b>
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) .....		7
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY .....		7
<b>4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY .....</b>		<b>7</b>
4.1 SOURCES OF CLINICAL DATA.....		7
4.2 TABLES OF CLINICAL STUDIES .....		7
4.3 REVIEW STRATEGY .....		7
4.4 DATA QUALITY AND INTEGRITY .....		7
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES .....		7
4.6 FINANCIAL DISCLOSURES .....		7
<b>5 CLINICAL PHARMACOLOGY.....</b>		<b>8</b>
5.1 PHARMACOKINETICS.....		8
5.2 PHARMACODYNAMICS .....		8
5.3 EXPOSURE-RESPONSE RELATIONSHIPS .....		8
<b>6 INTEGRATED REVIEW OF EFFICACY.....</b>		<b>8</b>
6.1 INDICATION.....		8
6.1.1 Methods .....		8
6.1.2 General Discussion of Endpoints .....		8
6.1.3 Study Design.....		8
6.1.4 Efficacy Findings .....		9
6.1.5 Clinical Microbiology .....		9
6.1.6 Efficacy Conclusions .....		9
<b>7 INTEGRATED REVIEW OF SAFETY .....</b>		<b>9</b>
7.1 METHODS AND FINDINGS.....		9
7.1.1 Deaths .....		9
7.1.2 Other Serious Adverse Events .....		10



7.1.3 Dropouts and Other Significant Adverse Events .....	10
7.1.4 Other Search Strategies .....	10
7.1.5 Common Adverse Events.....	10
7.1.6 Less Common Adverse Events .....	11
7.1.7 Laboratory Findings .....	11
7.1.8 Vital Signs.....	12
7.1.9 Electrocardiograms (ECGs) .....	12
7.1.10 Immunogenicity .....	13
7.1.11 Human Carcinogenicity .....	13
7.1.12 Special Safety Studies .....	13
7.1.13 Withdrawal Phenomena and/or Abuse Potential.....	13
7.1.14 Human Reproduction and Pregnancy Data .....	13
7.1.15 Assessment of Effect on Growth.....	13
7.1.16 Overdose Experience .....	13
7.1.17 Postmarketing Experience.....	14
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS.....	14
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety .....	14
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety .....	14
7.2.3 Adequacy of Overall Clinical Experience.....	15
7.2.4 Adequacy of Special Animal and/or In Vitro Testing.....	15
7.2.5 Adequacy of Routine Clinical Testing.....	15
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup .....	15
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.....	16
7.2.8 Assessment of Quality and Completeness of Data.....	16
7.2.9 Additional Submissions, Including Safety Update.....	16
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS .....	16
7.4 GENERAL METHODOLOGY .....	16
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence .....	16
7.4.2 Explorations for Predictive Factors.....	16
7.4.3 Causality Determination .....	17
<b>8 ADDITIONAL CLINICAL ISSUES.....</b>	<b>17</b>
8.1 DOSING REGIMEN AND ADMINISTRATION.....	17
8.2 DRUG-DRUG INTERACTIONS.....	17
8.3 SPECIAL POPULATIONS .....	17
8.4 PEDIATRICS.....	17
8.5 ADVISORY COMMITTEE MEETING.....	17
8.6 LITERATURE REVIEW .....	17
8.7 POSTMARKETING RISK MANAGEMENT PLAN.....	17
8.8 OTHER RELEVANT MATERIALS.....	17
<b>9 OVERALL ASSESSMENT.....</b>	<b>17</b>
9.1 CONCLUSIONS.....	18
9.2 RECOMMENDATION ON REGULATORY ACTION .....	18
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS .....	18
9.3.1 RISK MANAGEMENT ACTIVITY .....	18
9.3.2 Required Phase 4 Commitments .....	18
9.3.3 Other Phase 4 Requests.....	18
9.4 LABELING REVIEW .....	18
9.5 COMMENTS TO APPLICANT .....	18
<b>10 APPENDICES .....</b>	<b>19</b>
10.1 REVIEW OF INDIVIDUAL STUDY REPORTS.....	19

10.2 LINE-BY-LINE LABELING REVIEW .....	19
NDA 21-272 (SERIAL # 005) .....	20
BACKGROUND: .....	20
PROTOCOL REVIEW: .....	20
STUDY NUMBER P01:13.....	20
Dates of study: .....	20
TITLE OF STUDY: .....	20
Inclusion criteria: .....	23
Exclusion criteria: .....	23
Primary end point:.....	24
Secondary end-points:.....	25
Statistical analyses: .....	25
Result .....	29
Time to clinical worsening:.....	32
SAFETY:.....	46
Deaths .....	46
Dropouts.....	46
Serious adverse events .....	46

## Table of Tables

Table 1 Demographics.....	14
Table 2.Flolan down-titration and Remodulin/Placebo upward titration scheme.....	22
Table 3 Planned dose modifications for study P01:13 .....	27
Table 4 List of procedures.....	28
Table 5 Investigators Sites and number of subjects.....	29
Table 6 Demographics.....	31
Table 7: Six-minute walk distance. ....	33
Table 8 six-minute walk distance, worst distance imputed by ranks.....	34
Table 9 Borg dyspnea scale.....	34
Table 10 Dyspnea-fatigue index.....	34
Table 11 PAH symptoms for placebo at baseline and for Remodulin at baseline and week 8.....	35
Table 12 Adverse events listed as “severe” in intensity .....	48
Table 13 Overall adverse events.....	48

## Table of Figures

Figure 1 Patient disposition .....	30
Figure 2 Protocol (original and amended) and Flolan decrease in dose for Placebo and Remodulin.....	32
Figure 3 Time to deterioration.....	33

# 1 Executive Summary

## 1.1 Recommendation on Regulatory Action

Based on the results of the interim analysis of the single submitted study and based on a series of robustness assessments, I believe that there adequate information that Remodulin has some activity in patients with pulmonary arterial hypertension. The labeling, however, should be extremely cautious in its recommendations that patients who are currently well controlled on Flolan can be switched to Remodulin.

## 1.2 Recommendation on Postmarketing Actions

Not applicable

### 1.2.1 Risk Management Activity

There should be no encouragement to switch from Flolan to Remodulin.

### 1.2.2 Required Phase 4 Commitments

Not applicable.

### 1.2.3 Other Phase 4 Requests I

Not applicable.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Remodulin was approved under subpart H with a commitment to perform a study convincing of benefit. The original application demonstrated minimal effect on walk distance but did demonstrate a *post-hoc* defined benefit on a composite of dyspnea and walk distance. The current study reflects the result of the sponsor's commitment to define the clinical benefit of Remodulin.

### 1.3.2 Efficacy

This submission contains the results of an interim analysis of a study that would support continued marketing of Remodulin. The study randomized subjects treated currently with fixed doses of Remodulin to either placebo or Remodulin. The primary metric of the study was the time to decompensation; defined as the time to death, hospitalization (aside from the initial hospitalization for weaning from Flolan) or reinstitution of Flolan. The sponsor believes that the results at the interim analysis support the efficacy of this drug.

### 1.3.3 Safety

The safety of Remodulin was derived from previous safety data bases. The only observation pertinent to safety was two subjects one in the clinical study and one in the safety update who had pancreatitis. The subject who developed pancreatitis and sepsis is not further described. The subject who developed pancreatitis in the safety update remained on Remodulin therapy albeit at approximately 70% of the initial dose. The association of pancreatitis with Remodulin therapy is, therefore, unclear.

### 1.3.4 Dosing Regimen and Administration

A dosing regimen is possible among those who have to discontinue Flolan. There however, should be no encouragement to switch subjects to Remodulin from Flolan, since the efficacy of Remodulin relative to Flolan is unclear. This study is not adequate to support persistence of benefit among those switching from Flolan to Remodulin.

### 1.3.5 Drug-Drug Interactions

None studied.

### 1.3.6 Special Populations

There was no study specific to the usual special populations. Two patients, both with porto-pulmonary hypertension were enrolled. One patient received Remodulin and the other placebo. Both patients successfully completed 8 weeks of therapy. Neither Flolan nor Remodulin are not approved for the use in porto-pulmonary hypertension.

## 2 Introduction and Background

### **2.1 Product Information**

Remodulin is currently approved, under subpart H for the symptomatic treatment of pulmonary arterial hypertension. The drug may be administered either as a subcutaneous or intravenous constant infusion.

### **2.2 Currently Available Treatment for Indications**

Several classes of drugs are currently approved for this Indication  
1- Intravenous Flolan; inhaled Iloprost; oral sildenafil citrate, and oral bosentan

### **2.3 Availability of Proposed Active Ingredient in the United States**

Remodulin is currently available for both subcutaneous and intravenous use. The interim analysis of the current study was submitted in support of their Subpart H commitment.

### **2.4 Important Issues With Pharmacologically Related Products**

Flolan requires administration as a constant infusion via an indwelling line. The indwelling catheter has the potential for acting as a nidus of infection and subsequent sepsis. Failure of the pump could lead to rapid cessation of drug delivery and rapid decompensation. The major side effects include jaw and other joint pains.

Bosentan is an endothelin inhibitor. It is a potent teratogen and has produced life-threatening hepatotoxicity.

Iloprost is a prostacyclin administered by inhalation. The treatment must be performed approximately every three hours during waking hours and the persistence of effect throughout the interdosing period is unclear. The frequency of administration and the constant need for having the nebulizer available is cumbersome.

Revatio (a PDE-V) inhibitor is relatively safe and orally administered. The drug has a persistence of benefit of walk distance for at least 4 hours post administration. There is no outcome data demonstrating a benefit on long-term outcomes.

## **2.5 Presubmission Regulatory Activity**

Remodulin was originally approved under 21 CFR 314 subpart H (314.500-560) on April 11, 2002. This protocol was submitted as part of that approval process on 25 February 2002.

## **2.6 Other Relevant Background Information**

# **3 Significant Findings from Other Review Disciplines**

None

## **3.1 CMC (and Product Microbiology, if Applicable)**

None.

## **3.2 Animal Pharmacology/Toxicology**

None submitted

# **4 Data Sources, Review Strategy, and Data Integrity**

The current application consists of the interim analysis of study P01:013. Because Remodulin is a difficult drug to blind, this reviewer went through each of the CRFs for the 22 enrolled patients and asked for a reanalysis of those patients on active therapy whose course seems to have been treated differently than placebo. Dr. John Lawrence performed the sensitivity analyses.

## **4.1 Sources of Clinical Data**

The source of clinical data was the one placebo or Remodulin withdrawal study form Flolan.

## **4.2 Tables of Clinical Studies**

The only submitted study was study P01:13.

## **4.3 Review Strategy**

Each of the CRFs in the study was analyzed. The subjects who received active treatment that appeared to be treated different than placebo patients were analyzed via a sensitivity analysis.

## **4.4 Data Quality and Integrity**

DSI audit report dated 9 November 2005 reviewed two clinical study sites. The two sites contributed 16 of the 22 enrolled patients. One study site (Dr. Schilz) was issued a two item Form 483. One item referred to a single subject did not have the required pulmonary function tests performed within the 12-month period prior to enrolling. The second item indicated that a subject was enrolled with a Flolan dose of 9 ng/kg/min (the protocol stipulated 10 ng/kg/min). This patient had that enrollment criterion waived prior to enrollment.

This reviewer does not consider the two items above as sufficiently serious to bring into question the integrity of the study.

## **4.5 Compliance with Good Clinical Practices**

The study was performed under good clinical practice.

## **4.6 Financial Disclosures**

The sponsor submits form 3454.

(b) (6)

(b) (6) A DSI report indicated no Form 483 was issued to this investigator.

## 5 Clinical Pharmacology

### 5.1 Pharmacokinetics

None submitted. The current labeling for Remodulin adequately defines the pharmacokinetics.

### 5.2 Pharmacodynamics

Not studied here.

### 5.3 Exposure-Response Relationships

None performed for this submission.

## 6 Integrated Review of Efficacy

Remodulin was originally approved under subpart H by demonstrating a symptomatic benefit in a post-hoc composite endpoint of walk distance and Borg-dyspnea. The current study was describe a defined benefit of Remodulin. To this purpose, a study was conducted among subjects on constant infusions of Flolan with withdrawal of Flolan and randomization to either placebo or Remodulin. The primary metric of the study was time to first decompensation defined as time to clinical worsening of status sufficient to require reinstitution of Flolan, rehospitalization or death.

The current submission reflects an interim analysis of study P01:13. Of the proposed thirty six enrolled patients the current submission consists of 22 patients (14 Remodulin and 8 placebo).

### 6.1 Indication

The sponsor proposes to alter current labeling by the inclusion of instructions for switch-over from Flolan to Remodulin. Although the study contains a regimen for the switch-over, the underlying data do not allow an assessment as to whether such a switch-over is of benefit. Switchover to Remdoulin from Flolan should be limited to those who are patently intolerant to Flolan.

#### 6.1.1 Methods

#### 6.1.2 General Discussion of Endpoints

The primary endpoint is the time to deterioration. Deterioration was defined as the need to increase Flolan dose once titration began, hospitalization (other than for down-titraton) or death. All other metrics of benefit such as six minute walk were strongly influenced by the deterioration time. Those who deteriorated were assigned worst rank for the secondary endpoint.

The differences in these endpoints comparing Remodulin to placebo patients, depends on the imputation of worst rank to placebo patients who restarted Flolan. The analysis of the secondary endpoints between placebo and Remodulin add little to the overall interpretation of the study.

#### 6.1.3 Study Design

The study was designed as a randomized withdrawal study. Patients on active treatment (Flolan) were randomized to either Remodulin or placebo. The time to deterioration was the primary metric. In addition,

protocol stipulated as secondary measurements, the ability to tolerate withdrawal from Flolan (e.g., 6-minute walk distance, Borg dyspnea scale, Dyspnea fatigue index and signs of PAH).

#### 6.1.4 Efficacy Findings

This was an interim analysis. Based on the sponsor's analysis and the series of robustness analyses performed by Dr. John Lawrence, FDA statistician, the results are suggestive that Remodulin has some benefit in patients with pulmonary arterial hypertension.

#### 6.1.5 Clinical Microbiology

None.

#### 6.1.6 Efficacy Conclusions

The interim analysis for study P:01:13 although significant at the pre-stated Pocock boundary, is very much dependent on a few events. The interpretation of the results is further complicated by the difficulty in blinding the treatment in this study. Although there was a DEAC (Data Events Adjudication Committee), the committee was largely left with *fait accompli* if the investigator restarted the subject on or increased the dose of Flolan.

The small number of subjects enrolled does not allow for comfort based on the randomization process that the two treatment groups were matched. In addition, the protocol was altered from an initial 1: 1 randomization to a 2: 1 Remodulin: Placebo randomization. Those who were enrolled later on were disproportionately enrolled into active treatment. It is also not convincing that those enrolled early were equivalent to those who were later enrollees.

There were some subjects who I have difficulty with their adjudication. I have asked Dr. John Lawrence perform a sensitivity analysis to see if the small number of patients who appear to be handled differently than the placebo patient alter the conclusion. This robustness or sensitivity analyses, although lessening the observed significance, the results still demonstrate a difference between placebo and Remodulin.

Lastly, the prevention of decompensation in patients who were aggressively down-titrated from Flolan may reflect the effects of Remodulin, not entirely for its effect on the disease process, but in preventing any withdrawal effects from Flolan. However, the ability of those randomized to Remodulin to persist relatively stable for the duration of the study argues against a benefit limited to the prevention of a withdrawal effect from Flolan.

## 7 Integrated Review of Safety

### 7.1 Methods and Findings

The database is relatively modest compared to the original database and adds little either in the observation of adverse events or in defining the frequency of such events.

#### 7.1.1 Deaths

There were no deaths during the study. One subject, however died 15 days after completing the study from sepsis and pancreatitis.

## 7.1.2 Other Serious Adverse Events

Aside from events suggesting worsening of underlying disease processes (e.g., worsening of PAH, panserositis), there were two episodes of syncope. There was one episode of pancreatitis and two episodes of catheter related sepsis (both in the Remodulin group).

## 7.1.3 Dropouts and Other Significant Adverse Events

Aside from worsening of baseline disease, only one additional subject (Remodulin) discontinued due to site pain.

### 7.1.3.1 Overall profile of dropouts

Not applicable.

### 7.1.3.2 Adverse events associated with dropouts

See above.

### 7.1.3.3 Other significant adverse events

Site pain was observed predominantly in the Remodulin-treated group. 11/14 subjects treated with Remodulin reported site-pain of “moderate” to “severe” in intensity. Only one placebo patient reported such site pain.

## 7.1.4 Other Search Strategies

None.

## 7.1.5 Common Adverse Events

Current labeling is the source for this information.

### 7.1.5.1 Eliciting adverse events data in the development program

This is a modest database compared to the assessment covered by labeling. This database adds little information concerning adverse events compared to current labeling.

### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Not applicable.

### 7.1.5.3 Incidence of common adverse events

Please refer to current labeling.

### 7.1.5.4 Common adverse event tables

Please refer to current labeling.



#### 7.1.5.5 Identifying common and drug-related adverse events

Not applicable.

#### 7.1.5.6 Additional analyses and explorations

Not done.

#### 7.1.6 Less Common Adverse Events

Not applicable.

#### 7.1.7 Laboratory Findings

The database is too small and confounded by the down-titration of Flolan. There is little information to be gleaned from this study.

##### 7.1.7.1 Overview of laboratory testing in the development program

##### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable

##### 7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable

##### *7.1.7.3.1 Analyses focused on measures of central tendency*

Not applicable

##### *7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Not applicable.

##### *7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities*

None.

##### 7.1.7.4 Additional analyses and explorations

None.

##### 7.1.7.5 Special assessments

None.

## 7.1.8 Vital Signs

### 7.1.8.1 Overview of vital signs testing in the development program

The small database, the differences in duration of exposure as well as the confounding effects of Flolan withdrawal makes an assessment of the effect of Remodulin on vital signs difficult to interpret.

### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable

### 7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable

#### 7.1.8.3.1 *Analyses focused on measures of central tendencies*

Not applicable

#### 7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Not applicable

#### 7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

Not applicable

### 7.1.8.4 Additional analyses and explorations

None

## 7.1.9 Electrocardiograms (ECGs)

The small and asymmetric database does not allow a useful description of ECG effects of Remodulin.

### 7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The study adds little to the knowledge base of the effects of Remodulin on ECG effects.

### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

### 7.1.9.3 Standard analyses and explorations of ECG data

Not done.

#### 7.1.9.3.1 *Analyses focused on measures of central tendency*

Not done.

*7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Not done.

*7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities*

Not done.

7.1.9.4 Additional analyses and explorations

Not relevant.

7.1.10 Immunogenicity

Not relevant.

7.1.11 Human Carcinogenicity

As per current labeling.

7.1.12 Special Safety Studies

Not done.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No data on Remodulin withdrawal.

7.1.14 Human Reproduction and Pregnancy Data

As per current labeling.

7.1.15 Assessment of Effect on Growth

Not done.

7.1.16 Overdose Experience

In the safety update, one subject (REM\_00075\_2004) sustained an intravenous overdose of treprostinil. The subject, a 12 year old Caucasian female, had her intravenous access accidentally flushed with undiluted drug. The estimated dose was approximately 7.5 mg. Symptoms included flushing, headache, nausea, vomiting, seizure-like activity, with subsequent unconsciousness lasting approximately 5 minutes. She recovered.

### 7.1.17 Postmarketing Experience

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety database derived from this study adds little.

#### 7.2.1.1 Study type and design/patient enumeration

The study was a randomized withdrawal study from an active drug (Flolan) to either Remodulin or placebo. The metrics of interest relate to the time to decompensation.

#### 7.2.1.2 Demographics

The demographics of those enrolled into the study (P01:13) are shown below:

Demographics:

**Table 1 Demographics**

Parameter	Remodulin	Placebo
Age (years $\pm$ SD)	47 $\pm$ 12	43 $\pm$ 12
Gender male/female	2/12	1/7
Race (Caucasian/Black/Asian/Hispanic)	10/3/0/1	5/1/1/1
Etiology of PAH PPH/Scleroderma/ Congenital Shunt/ porto-pulmonary hypertension	10/2/1/1	6/1/0/1
WHO functional Class (I/II/III)	0/9/5	1/3/4
Flolan Dose at Randomization (Mean $\pm$ SEM) ng/min	22.3 $\pm$ 3	30 $\pm$ 6
Duration on Flolan (years) (Mean $\pm$ SD)	3.2 $\pm$ 2.6	3.4 $\pm$ 2.7
Anticoagulants	9 (64%)	7 (88%)
Vasodilators	4 (29%)	2 (25%)
Digoxin	8 (57%)	5 (63%)
Diuretics	10 (71%)	6 (75%)

#### 7.2.1.3 Extent of exposure (dose/duration)

The median duration of exposure for placebo was approximately 12 days, for Remodulin only one subject did not complete the 8 weeks of treatment.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

None.

#### 7.2.2.1 Other studies

None.

### 7.2.2.2 Postmarketing experience

Since the original approval of Remodulin, the sponsor has submitted three quarterly reports and five periodic update reports. The sponsor submits, as part of this supplemental application, the fifth of these reports. Since marketing of Remodulin began, there have been (b) (4) subjects exposed to Remodulin that reflects approximately 1500 patient-years of exposure. There are approximately (b) (4) patients worldwide currently receiving treatment with Remodulin. During the most recent 6 month PSUR, covering 22 November 2004 through 21 May 2005, 26 case reports were submitted to the sponsor. Of these 11 reports were submitted as expedited reports. The vast majority of the reports reflect either site-related adverse events (including erythema, pain and possible cellulitis), disease progression related symptoms (shortness of breath etc) or joint pain (e.g., jaw pain). There were two subjects with gastrointestinal symptoms. Both subjects recovered. Other notable events were:

One subject (REM\_00093\_2005) developed pancreatitis. She was a 69 year old female of African ancestry who developed idiopathic pancreatitis and was hospitalized. Concomitant medications included bosentan, digoxin, ranitidine, atorvastatin, warfarin, furosemide, verapamil, trazodone, lithium and O<sub>2</sub>. The patient's dose of Remodulin was decreased from 18.6 ng/kg/min to 13 ng/kg/min. Upon cessation of symptoms the dose was not further weaned.

One subject (REM\_00076\_2005) developed transient blindness while receiving inhaled treprostinil. An embolic event was ruled out. The blindness resolved but the sequelae consisted of blurred vision in one eye. An ophthalmologist diagnosed venous stasis as a consequence of the subject's underlying pulmonary hypertension as the etiology of the event.

One subject (REM\_00075\_2004) sustained an intravenous overdose of treprostinil. The subject, a 12 year old Caucasian female, had her intravenous access accidentally flushed with undiluted drug. The estimated dose was approximately 7.5 mg. Symptoms included flushing, headache, nausea, vomiting, seizure-like activity, with subsequent unconsciousness lasting approximately 5 minutes. She eventually recovered.

### 7.2.2.3 Literature

No information on randomized studies.

## 7.2.3 Adequacy of Overall Clinical Experience

The drug is presently approved under subpart H.

## 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

## 7.2.5 Adequacy of Routine Clinical Testing

Adequate.

## 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new studies were submitted.

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The drug is currently marketed. The sponsor suggests modification of the adverse events section by including various rashes not limited to those at the site of infusion.

### 7.2.8 Assessment of Quality and Completeness of Data

The potential for unblinding makes the small study of limited utility.

### 7.2.9 Additional Submissions, Including Safety Update

The sponsor submits the fifth safety update.

## ***7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions***

## ***7.4 General Methodology***

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not relevant.

#### 7.4.1.1 Pooled data vs. individual study data

Not relevant.

#### 7.4.1.2 Combining data

Not relevant.

### 7.4.2 Explorations for Predictive Factors

Not relevant.

#### 7.4.2.1 Explorations for dose dependency for adverse findings

Not done.

#### 7.4.2.2 Explorations for time dependency for adverse findings

Not done.

#### 7.4.2.3 Explorations for drug-demographic interactions

Not done.

#### 7.4.2.4 Explorations for drug-disease interactions

Not done.

#### 7.4.2.5 Explorations for drug-drug interactions

Not done.

#### 7.4.3 Causality Determination

Not done.

### 8 Additional Clinical Issues

#### **8.1 Dosing Regimen and Administration**

The current study allows some information as to how to transition subjects from Flolan to Remodulin. The information that is lacking is whether such a decision is a good one. The transitional dosing should, therefore, be limited only to those subjects who are so intolerant of Flolan infusion, that they would, in the course of treatment discontinue Flolan's use. For this population transition to Remodulin may be a reasonable alternative.

#### **8.2 Drug-Drug Interactions**

None derived from this study.

#### **8.3 Special Populations**

One patient with porto-pulmonary hypertension was treated with Remodulin and tolerated treatment.

#### **8.4 Pediatrics**

Previous waiver was granted.

#### **8.5 Advisory Committee Meeting**

None.

#### **8.6 Literature Review**

#### **8.7 Postmarketing Risk Management Plan**

None.

#### **8.8 Other Relevant Materials**

None.

### 9 Overall Assessment

The interim analysis is sufficient to demonstrate that Remodulin has some effect in patient with pulmonary hypertension. There should be no encouragement to switch subjects from Flolan to Remodulin.

## **9.1 Conclusions**

The study is useful in satisfying the Phase IV commitment of Remodulin. The recommendation for use of Remodulin instead of Flolan should only be made for subjects so intolerant to Flolan that they would consider discontinuing Flolan's use.

## **9.2 Recommendation on Regulatory Action**

The study is adequate to approve with limited labeling.

## **9.3 Recommendation on Postmarketing Actions**

None.

### **9.3.1 Risk Management Activity**

None.

### **9.3.2 Required Phase 4 Commitments**

The study is an interim analysis of the phase 4 commitment for this drug.

### **9.3.3 Other Phase 4 Requests**

## **9.4 Labeling Review**

My comments reflect changes assuming that others accept the current database as sufficient to fulfill the phase 4 commitment.

## **9.5 Comments to Applicant**



## **10 Appendices**

### ***10.1 Review of Individual Study Reports***

See below.

### ***10.2 Line-by-Line Labeling Review***

Follows study summary.

## ***NDA 21-272 (serial # 005)***

Remodulin™ (treprostinil, REMODULIN) injection

Sponsor: United Therapeutics

### ***Background:***

Remodulin 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 Remodulin. The Division met with United Therapeutics and their consultants on 13 February 2002 with the broad outline of a Flolan withdrawal proposed. A protocol was received on 28 February 2002. Two major objections were raised and additional clarification of other issues requested. A submission dated 13 March 2002 was the sponsor's attempt to address the reservations lodged about the original protocol, by the submission of this amended protocol. This study is largely the results of that submission.

### ***Protocol Review:***

### ***Study number P01:13.***

Dates of study:

- Original protocol: April 1, 2002.
- Amendment #1: September 27, 2002.
- Amendment #2: February 13, 2003.
- Amendment #3: April 25, 2003.
- Amendment #4: November 7, 2003.
- Amendment #5: September 9, 2004.
- Amendment #6: July 18, 2005.
- First patient randomized: October 28, 2005.
- Most recent analysis plan: June 22, 2005.
- Interim look: July 29, 2005.

### ***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:

Nature of Amendments:

Amendment #1-

- Eliminated the requirement for performing a DLCO with < 50% of predicted which would require a high resolution CT to document interstitial fibrosis.
- Added the requirement that all scleroderma patients require PFTs performed within the prior 6 months.
- Redefined serious adverse events, to exclude elective treatment for a pre-existing condition, however, prolongation of such elective hospitalization due to complications are considered as serious adverse events.
- Required following of all adverse events until the events resolved or are no longer clinically significant.
- Changed to the MedRA classification for adverse events.
- Walk tests are not blinded now.
- In Appendix G described the Dyspnea scale to be performed at a comparable level of activity.
- Added instructions to patients as to the performance of the Dyspnea Evaluation Scale.

Amendment #2:

- Decreased the minimum allowable Flolan dose from 20 ng/kg/min to 15 ng/kg/min.
- Added a BNP assessment.

Amendment #3

- Decreased the size of the study from 100 patients with a 1:1 randomization scheme to 26 Remodulin and 13 placebo patients.
- Removed the stratification based on Flolan dose.
- Altered the assumptions underlying the power calculations. The original assumptions were a 90% power to detect a 50% relative reduction in the time to deterioration. The placebo rate was assumed to be 80% at 8 weeks with a 2-sided alpha of 0.05.  
To  
A power of 90% to detect a reduction in the time to clinical deterioration from a PBO rate of 90% at weeks to a rate of 30% on patients treated with Remodulin with a 2-sided alpha of 0.05.
- Added an interim analysis after 21 patients completed the study. The primary metric will be assessed by the O'Brien-Fleming boundary. The alpha-spending function corresponds to a level of alpha of 0.0045 and a final alpha of 0.0485 for the completed study.
- Changed the number of interim looks from two to one. The interim look, to be performed by an independent contractor was originally limited to adverse events and death. The recommendations for continuation of the study are to be transmitted to the DSMB. This look, however, was changed to an assessment of efficacy.

- Increased the available population to include those whose pulmonary hypertension was a consequence of congenial systemic to pulmonary shunts or human immunodeficiency virus.

## Amendment #4

- Decreased the required Flolan dose at baseline from 15- to 10-ng/kg/min.
- Allowed recruitment of patients whose etiology of pulmonary hypertension was due to porto-pulmonary disease. The exclusion criteria was still in effect for those with more severe degrees of liver failure (based on Child-Pugh classification B or C)

## Amendment # 5

- Decreased the time on Flolan before randomization from 6 to 3 months
- Decreased the time on stable Flolan dose from 30 to 15 days
- Altered the weaning from Flolan

Table 2.Flolan down-titration and Remodulin/Placebo upward titration scheme

Dose Transition Period Day	Flolan Dose	Study Drug Dose
1	Unchanged	10% Starting Flolan Dose
2	85% Starting Flolan Dose	25% Starting Flolan Dose
3	70% Starting Flolan Dose	40% Starting Flolan Dose
4	55% Starting Flolan Dose	55% Starting Flolan Dose
5	40% Starting Flolan Dose	70% Starting Flolan Dose
6	25% Starting Flolan Dose	85% Starting Flolan Dose
7	15% Starting Flolan Dose	95% Starting Flolan Dose
8	5% Starting Flolan Dose	105% Starting Flolan Dose
9	5% Starting Flolan Dose	110% Starting Flolan Dose
10	5% Starting Flolan Dose	110% Starting Flolan Dose + additional 5-10% as needed
11	0	Additional 5-10% as needed
12*	0	Additional 5-10% as needed
13*	0	Additional 5-10% as needed
14*	0	Additional 5-10% as needed

\*As needed. Patients must remain hospitalized at least 24 hours after Flolan dose has been discontinued.

With

Dose Transition Period Day	Flolan Dose	Study Drug Dose
1	Unchanged	10% Starting Flolan Dose
2	80% Starting Flolan Dose	30% Starting Flolan Dose
3	60% Starting Flolan Dose	50% Starting Flolan Dose
4	40% Starting Flolan Dose	70% Starting Flolan Dose
5	20% Starting Flolan Dose	90% Starting Flolan Dose
6	5% Starting Flolan Dose	110% Starting Flolan Dose
7	0	110% Starting Flolan Dose + additional 5-10% as needed
8*	0	Additional 5-10% as needed
9*	0	Additional 5-10% as needed
10*	0	Additional 5-10% as needed
11*	0	Additional 5-10% as needed
12*	0	Additional 5-10% as needed
13*	0	Additional 5-10% as needed
14*	0	Additional 5-10% as needed

\*As needed. Patients must remain hospitalized at least 24 hours after Flolan dose has been discontinued.

### Inclusion criteria:

Subjects that are enrolled are or have:

- Between 18-75 years.
- If female, is incapable of childbearing.
- Have a diagnosis of pulmonary hypertension, either primary disease or secondary to systemic sclerosis syndrome; congenital shunts, HIV or porto-pulmonary hypertension were added via amendments #3 and #4.
- Stable in cardiac status for at least 30 days.
- Able to walk distance of > 250 meters at baseline.
- Receiving Flolan at a dose of at least 20 ng/kg/min (changed to 10 ng/kg/min) but less than 75 ng/kg/min.
- Received Flolan for at least 6 (changed to 3) months and have been maintained on stable doses for at least 30 (changed to 15) 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.

### 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 other prostacyclin other than Flolan) 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) If TLC between 60-70% a high resolution CT must document interstitial fibrosis or alveolitis.
  - 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 (altered to just require PFTs within previous 6 months).
- HIV positive (allowed by amendment).
- Portal hypertension (porto-pulmonary hypertension with hepatic disease Child-Pugh grade A allowed).  
Portal hypertension excluded:
  - if AST or ALT > 3 x ULN.
  - Recent (within 3 months) esophageal varices.

- Lack of improvement in NYHA class of a least one functional class since beginning of Flolan.
- INR > 1.5 or contraindication to warfarin anticoagulation.
- History of encephalopathy.
- 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 end diastolic pressure > 15 mm Hg.
  - b) LVEF < 40% by MUGA 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, 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<sub>2</sub> 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. 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.

#### Preserving blinding:

The individual responsible to assess whether deterioration has occurred is to be kept as blinded as possible to treatment. The subject is told to anticipate site pain. The therapeutic team is to designate an individual not responsible for defining a deteriorated patient to deal with issues of subcutaneous site pain.

#### Randomization:

Patients will be randomized 2:1 between Remodulin and placebo (The initial randomization of 1:1, placebo: Remodulin, was changed by amendment #3). The randomization will be administered centrally with a permuted block randomization. The block size is to be variable. The original randomization and stratification was abandoned based on Amendment #3.

#### Statistical analyses:

The statistical plan including the nature of and timing of interim analyses were markedly changed by amendments #3. As of the last amendment, one interim analysis was

planned after 21 subjects completed the 8 week time point or were designated as having achieved an endpoint. The primary endpoint was tested using a Pocock boundary. This alpha-spending function corresponds to an interim nominal alpha level of approximately 0.0324 and a nominal alpha level of approximately 0.0324 for the final test of efficacy.

The primary endpoint, time to clinical deterioration, defined as the time from initiation of study drug to first occurrence of clinical worsening of PAH symptoms that required reinstitution of Flolan, rehospitalization or resulted in death. A DEAC committee will be constituted to assess those who apparently deteriorated.

Patients who withdraw for other reasons other than deterioration are to be censored.

For the secondary endpoints (6-minute walk test, the Borg Dyspnea Score):

- Standardized mid-ranks of walk distances will be calculated as follows.
- An ordinary least square regression will be fit to the protocol-observed parameter (e.g., walk distance, Borg dyspnea) at the end of the dose transition period, week 4 and week 8 as a function of initial Flolan dose and distance walked at baseline.
- Standardized mid-ranks of the standardized residuals from this regression will be calculated.
- Patients who clinically deteriorate will be assigned the standardized mid-ranks of “0”. Other dropouts will have the mid-rank imputed as a LOCF.
- Standardized mid-ranks for the resulting values will be calculated.

The combination of Borg and dyspnea scale will be calculated by taking the mid-ranks for walk distance and Borg scale and calculating a mid-rank average of the mid-ranks of the two parameters. Standardized mid-ranks of the resulting means will be calculated. A Cochran-Mantel-Haenszel mean score statistic will be calculated comparing the standardized mid-ranks between the treatment groups, adjusting for the stratification groupings (these stratifications were subsequently dropped) that were used at randomization.

Dyspnea fatigue index:

This parameter will be compared between treatments using the Wilcoxon rank-sum test. Deterioration will be assigned the lowest value, censored values for those who discontinue for reasons other than deterioration.

Symptoms and signs of PAH:

Their change in status from baseline will be descriptive.

CV hospitalization:

The number of patients requiring hospitalization for CV conditions or events will be compared between the two treatment groups.



### Dosing:

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

**Table 3 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	0%	Additional 5-10% as needed
2	80%	30% of initial Flolan Dose	9	0 %	Additional 5-10% as needed
3	60%	50% of initial Flolan Dose	10	0%	Additional 5-10% as needed
4	40%	70% of initial Flolan Dose	11	0%	Additional 5-10% as needed
5	20%	90% of initial Flolan Dose	12	0%	Additional 5-10% as needed
6	5%	110% of initial Flolan Dose	13	0%	Additional 5-10% as needed
7	0%	110% of initial Flolan Dose Additional 5-10% as needed	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.
- Subjective symptoms associated with prostacyclins should be treated by a decrease in Flolan dose, even if it means deviating from the dose schedule.
- A study dose/placebo increase should occur at least one hour before a corresponding decrease in the Flolan dose.
- Any need to increase the dose of Flolan would be considered as reinstitution of Flolan.
- 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.
- Need for inotropic support the patient is considered a treatment failure.

[Comment: there was no algorithm to allow for a more gradual decrease in the Flolan dose.]

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 to be performed during the study is shown below:

**Table 4 List of procedures**

	Screening <sup>a</sup> Day –7 to 0	Baseline Day 0	Treatment Week		
			1 (day 1-14 <sup>b</sup> )	4 (day 28 <sup>c</sup> )	8 (day 56 <sup>c</sup> )
Informed consent; inclusion/exclusion criteria	X				
Medical history /PE/vital signs/12-lead ECG/labs	X				X
PAH signs and symptoms		X	X---X <sup>d</sup>	X	X
Dyspnea-fatigue rating		X	X---X <sup>d</sup>	X	X
Exercise capacity /Borg dyspnea scale <sup>i, k</sup>	X <sup>e</sup>	X	X---X <sup>f</sup>	X	X
Randomization <sup>g</sup>					
Monitor <sup>h</sup> : ECG/vital signs/ TcO <sub>2</sub>					
Infusion of Remodulin			X----- -	----- ---	-----→
Reduction of Flolan dose <sup>j</sup>			X----- →		
Other medications/adverse events			X-----	----- --	-----→
<p>a. May be performed up to one week prior to randomization.      b. May be less than 1-week if all procedures completed.</p> <p>c. Patients will return at 8 weeks <math>\pm</math> 7 days even if prematurely discontinued.      d. As needed for patient stability and prior to discharge.</p> <p>e. A practice walk test should be performed up to 6 weeks before randomization.</p> <p>f. During the transition from Flolan to Remodulin/placebo the walk/Borg test may be performed periodically and as soon as possible for pre-mature termination</p> <p>g. After all baseline eligibility is determined.      h. Continuous monitoring during dosing and transition period.</p> <p>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.</p>					

### 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 alter performance of the study.

### Dyspnea –Fatigue Index

Signs and symptoms of pulmonary vascular disease will be evaluated by the Dyspnea Fatigue Index. This index contains three criteria each with potential values of 0-4. The change of the aggregate index between week 12 and baseline is the sum metric of effect. The lower the rating, the more symptomatic is the patient.

Dyspnea-Fatigue Rating	
Magnitude of task	
4	Extraordinary- Symptomatic only with extraordinary activity (e.g. running, carrying heavy loads on level ground)
3	Major- Becomes symptomatic only with major activities(e.g. climbing more than 3 flights of stairs, carrying a moderate or heavy load on level ground)
2	Moderate- Becomes symptomatic with moderate or average tasks (e.g. walking up a gradual hill, climbing up less than three flights of stairs, carrying a light load on level ground)
1	Light- Becomes symptomatic with light activities (e.g. walking on level ground)
0.	None- Symptomatic at rest or lying down
Magnitude of Pace	
4	Extraordinary- All tasks carried out at a normal pace
3	Major- Major tasks (see above) are performed at a reduced rate
2	Moderate-moderate tasks performed at a reduced rate
1	Light- Light tasks are performed at a reduced rate
0.	None- Symptomatic at rest
Functional Impairment	
4	None- Can carry out usual activities and occupation
3	Slight- Distinct impairment in at least one activity . No activities re completely abandoned.
2	Moderate-Changed jobs or abandoned at least one activity
1	Severe-Unable to work or has given up most of usual activities
0	Very severe- unable to work and has given up most or all usual activities.
If the component measurement is either 2, 1 or 0 the reason should be due to shortness of breath.	

### Borg Index-

As part of the exercise test, the degree of shortness of breath (the Borg Scale) is also to be administered. The patient is to be given the following set of instructions:

“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 should chose from 0.5 to 2; if you were somewhat short of breath you should select 3 and if the breathing was very difficult, you would choose 4 to 9, depending on just how hard it was; 10 represent the greatest shortness of breath that you have ever experienced in your life, and if you feel more short of breath than you have ever been in your life 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 higher the Borg scale the more symptomatic is the patient.

### Result

**Table 5 Investigators Sites and number of subjects**

Site	Investigator and Site	# patients (# PBO)
#02	Robyn J Barst, M.D., Columbia Presbyterian Medical Center and Babies and Children's Hospital; NY, NY	0
#03	Vallerie McLaughlin, M.D., Rush Presbyterian-St. Luke's Medical Center; Chicago, IL	0
#04	Ronald J. Oudiz, M.D., Harbor-UCLA Medical Center; Torrence, CA	0
#09	Adaani Frost, M.D., Baylor College of Medicine and The Methodist Hospital; Houston TX	0
#15	Greg Elliott, M.D. LDS Hospital; Salt lake City, UT	2 (2)
#19	Robert Schilz, DO, Ph.D; .University Hospitals of Cleveland; Cleveland, OH	7 (3)
#24	Shelley Shapiro, M.D., Ph.D., USC, Los Angeles, CA and LAC and USC outpatient departments; Los	0

	Angeles, CA	
#28	Melvyn Rubenfire, MD University of Michigan Health System; Ann Arbor, MI	9 (2)
#29	Dianne L Zwicke, M.D., St Luke's Medical Center; West Allis, WI	0
#33	Myung Park, M.D., Ochsner Clinic Foundation; New Orleans, LA	2 (0)
#35	Steven Nathan, M.D., Inova Fairfax Hospital; Falls Church VA	0
#36	Roblee P. Allen, M.D.; UC Davis Medical Center; Sacramento CA	2 (1)

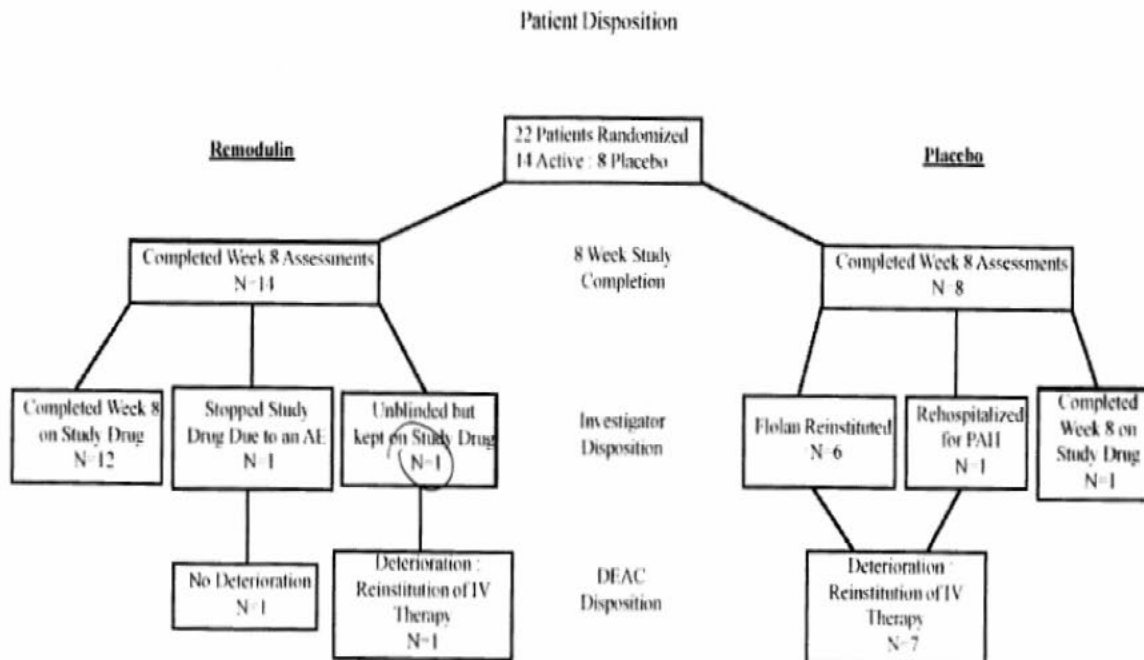
Only five centers enrolled patients. One of the sites enrolled 9 subjects and contributed half of the active-treated patients. (b) (6)

No form 483, however, was issued.

### Patient Disposition

There were 428 patients screened; with 22 were randomized; 14 allocated to Remodulin and 8 patients to placebo. Of the Remodulin patients, one patient deteriorated and one temporarily discontinued Remodulin due to an adverse event. Of the placebo patients, six were reported as having deteriorated and one re-hospitalized. One placebo completed the study.

**Figure 1 Patient disposition**



**Table 6 Demographics**

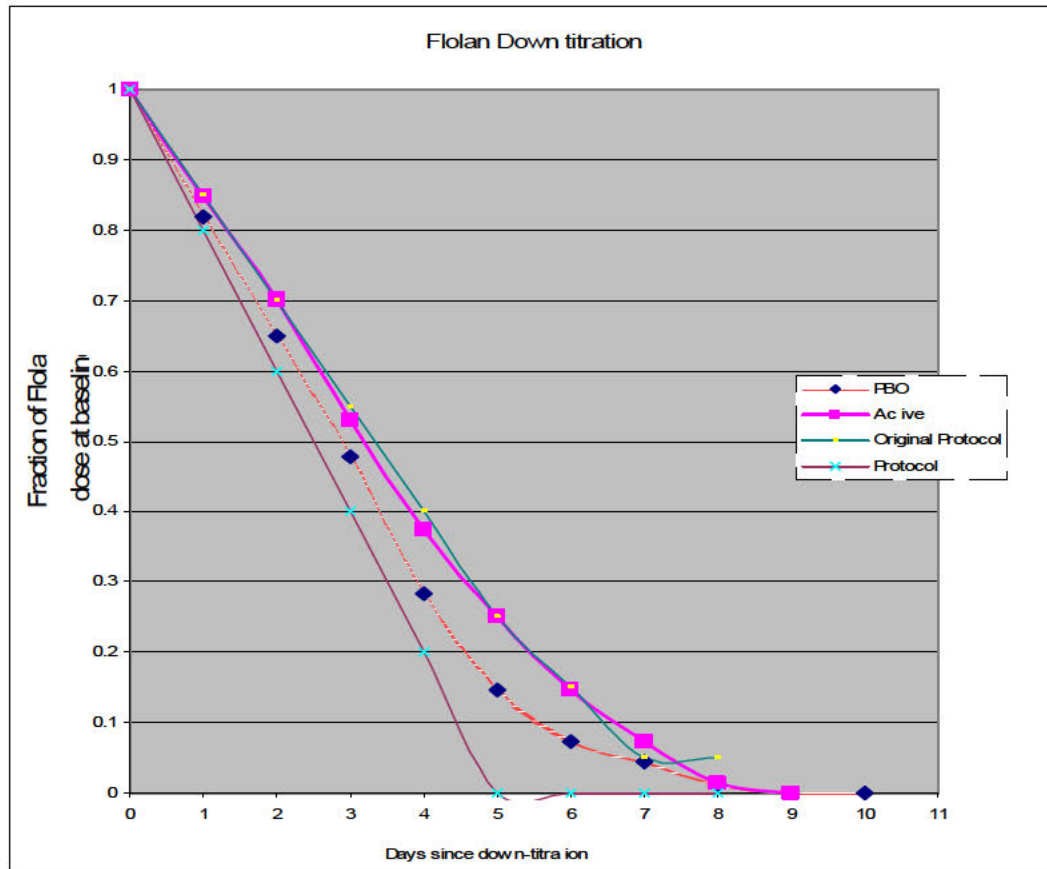
Parameter	Remodulin	Placebo
Age (years $\pm$ SD)	47 $\pm$ 12	43 $\pm$ 12
Gender male/female	2/12	1/7
Race (Caucasian/Black/Asian/Hispanic)	10/3/0/1	5/1/1/1
Etiology of PAH PPH/Scleroderma/ Congenital Shunt/ porto-pulmonary hypertension	10/2/1/1	6/1/0/1
WHO functional Class (I/II/III)	0/9/5	1/3/4
Flolan Dose ng/kg/min at Randomization (Mean $\pm$ SEM)	22.3 $\pm$ 3	30 $\pm$ 6
Duration on Flolan (years) (Mean $\pm$ SD)	3.2 $\pm$ 2.6	3.4 $\pm$ 2.7
Anticoagulants	9 (64%)	7 (88%)
Vasodilators	4 (29%)	2 (25%)
Digoxin	8 (57%)	5 (63%)
Diuretics	10 (71%)	6 (75%)

**Dose:**

The mean ( $\pm$  SEM) baseline Flolan doses differed at baseline; it was 22  $\pm$  3 in the Remodulin group and 30  $\pm$  6 in the placebo group. The dose reduction of Flolan is shown below. The average dose for those still being weaned from Flolan was somewhat faster in the placebo group than in the Remodulin group. The difference in weaning rate is largely due to one placebo patient #1315002 who was weaned from Flolan dose on day 2 to 0.7, 0.4, and 0 as a fraction of the initial Flolan dose. Neither treatment was as aggressive as the revised protocol allowed.

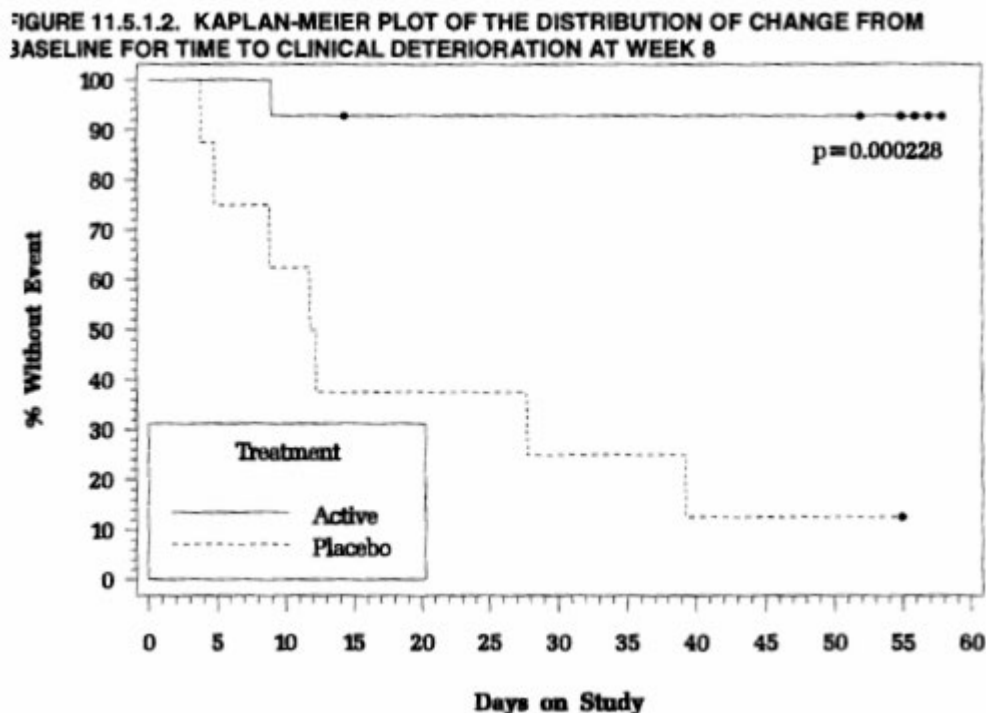


**Figure 2 Protocol (original and amended) for Flolan decrease in dose for Placebo and Remodulin treatments**



#### Time to clinical worsening:

The primary measure of efficacy was the time to first clinical deterioration (worsening PAH necessitating reinstitution of Flolan therapy or increasing the weaned dose of Flolan, rehospitalization or death). The time to deterioration, based on the randomization date and time favored Remodulin ( $p=0.00023$ ). Using the initial time of Flolan termination instead of randomization time yields a ( $p=0.00035$ ). Analysis based on a categorical yes/no using the Fisher's Exact Test resulted in a  $p=0.00035$  favoring Remodulin. Lastly a reanalysis including the patient who was a discontinued and adjudicated by the DEAC (Data Events Adjudication Committee) to have withdrawn without deterioration using the maximum instead of the minimum of the date Flolan institution the  $p=0.00022$ .

**Figure 3 Time to deterioration**

Subjects who were deemed by the investigators to have deteriorated had their cases evaluated by the DEAC. Those deemed by the investigator as not deteriorated were never adjudicated. The assessments of the DEAC did not therefore have the capability to assess whether placebo and active treatment groups were equivalently dealt with by the investigator.

[Comment:

*This metric as well as all other metrics are largely driven by the assessment of the dropouts for deterioration. I will review patient by patient outcomes based on the CRFs (see below). ]*

Exercise capacity (six-minute walk):

The analysis of the six-minute walk test was mostly reflective of the large imbalance among those who discontinued due to deterioration.

**Table 7: Six-minute walk distance.**

Treatment	N=	Baseline	Change	p-value
Remodulin	14	437 ± 26	-35 ± 40	0.00413
Placebo	8	424 ± 31	-357 ± 69	
P-value derived from ANCOVA with imputed values of 0 for deterioration and LOCF for discontinuation due to AE. Results are Mean ± SE (in meters).				

**Table 8 six-minute walk distance, worst distance imputed by ranks**

Treatment	N=	Baseline	Change	p-value
Remodulin	14	437 ± 26	-35 ± 40	0.07
Placebo	8	424 ± 31	-115 ± 50	
A secondary analysis of p-value assessed by ANCOVA? Worst rank limited to those too ill to walk and LOCF for to others. Results are Mean ± SE (in meters).				

In 5 patients allocated to placebo who because of deterioration were re-started on Flolan, those with 8 week data (n=5) now on Flolan showed essentially no change in baseline measurements relative to baseline (1.6  $\pm$  12 meters).

### Borg Dyspnea scale

The Borg dyspnea index is also largely driven by the imputed values for those who discontinue.

**Table 9 Borg dyspnea scale**

Treatment	N=	Baseline	Change	p-value
Remodulin	14	3.4 $\pm$ 0.6	0.6 $\pm$ 0.6	0.0017
Placebo	8	3.3 $\pm$ 0.6	5.63 $\pm$ 1.0	
P-value derived from ANCOVA with imputed values of 0 for deterioration and LOCF for discontinuation due to AE. Results are Mean $\pm$ SE.				

### Dyspnea-fatigue Index:

The results of the Dyspnea Fatigue index are also driven by the discontinuations.

**Table 10 Dyspnea-fatigue index**

Treatment	N=	Baseline	Change	p-value
Remodulin	14	6.9 $\pm$ 0.6	0.1 $\pm$ 0.6	0.000157
Placebo	8	7.3 $\pm$ 1.0	-5.8 $\pm$ 1.1	
P-value derived from ANCOVA with imputed values of 0 for deterioration and LOCF for discontinuation due to AE. Results are Mean $\pm$ SE.				

### PAH symptoms:

The symptoms at baseline for those receiving placebo and those receiving Remodulin at baseline and week 8 are shown below. In addition, of those receiving Remodulin the change in the presence of these symptoms at week 8 is also tabulated.



**Table 11 PAH symptoms for placebo at baseline and for Remodulin at baseline and week 8**

	Placebo (N= 8)			Remodulin (N=14)						
				Baseline (n=14)			Week 8 (n=12)			
	none	mild	moderate	none	mild	moderate	none	mild	moderate	severe
dyspnea	5	2	1	4	7	3	4	6	1	1
Fatigue	4	2	2	3	4	7	2	8	1	1
Edema	8	0	0	12	1	1	11	1	0	0
Syncope	8	0	0	14	0	0	12	0	0	0
Dizziness	7	1	0	12	0	2	7	3	2	0
Palpitations	7	1	0	10	1	3	5	6	1	0
Chest pain	6	2	0	11	1	2	11	1	0	0

Some of the symptoms in the Remodulin group appear to worsen over the 8 week period comparing baseline to week 8. There were three patients with no dizziness at baseline developing dizziness at week 8. Palpitations also appeared to worsen.

The following section consists of this reviewer's analysis of the treatment effect based on the CRFs. The review was not done completely blinded to treatment.

#### Patient Analysis

(b) (4), (b) (6)

FDA's additional analyses:

I asked Dr. Lawrence, FDA statistician to perform a sensitivity/robustness analysis by treating all those patients with a  $\sqrt{\phantom{x}}$  mark as having been discontinued at the early point of the decrease in walk distance for patients #1319001; 1319004; 1319005 1328009; 1333001. The analysis by Dr. Lawrence suggests a persistent benefit despite treating these patients as early failures ( $P=0.025$ ).

I also asked Dr. Lawrence to exclude the two patients with porto-pulmonary hypertension, since these patients are not indicated for treatment either with Flolan or UT-15. There was one patient excluded in each group. The one placebo patient was the only placebo patient to complete the 8-weeks of study in the placebo group.

No analyses were requested excluding either of the two sites. There would be inadequate number of patients should Dr. Rubenfire's or Dr. Schilz's patient group be excluded.

## **Safety:**

### Deaths

There were no deaths during the 8 weeks of study. One patient, however, died 15 days. During the course of the study this 53 year old female subject had been hospitalized for a Hickman catheter infection for which she was treated with vancomycin (for approximately 4 weeks) and the Hickman catheter was removed and a PICC line placed. Cultures were negative.

This patient was hospitalized 2 weeks post-study for pneumonia and pancreatitis, leading to sepsis and death. No additional data as to how the diagnosis of pancreatitis was made. It is also unclear if the subject continued on therapy.

### Dropouts

Dropouts were in general for the primary outcomes and are described above. There was one additional patient in the Remodulin group who discontinued due to site pain (# 1328005) .

### Serious adverse events

The sponsor notes there were eight subjects with serious adverse events; five (36%) in the Remodulin group and 3 ( 38%) in the placebo group.

Patient # 1319001 (Remodulin) The patient was a 38 year old female with primary pulmonary hypertension who at the week 8 visit had increased dyspnea, chest pain fatigue, pallor and dizziness. The sponsor noted that the patients pump was not on. She was subsequently hospitalized, restarted on Flolan (3 ng/kg/min).

Patient # 1319004 (Remodulin) was a 73 year old female with primary pulmonary hypertension (NYHA Class III) had a syncopal episode. The sponsor attributes this to a vaso-vagal event. (This reviewer suspects the syncopal episode might be worsening of disease). The patient was at her week 4 visit. During the routine 6-minute walk test (after approximately 3 minutes), she complained of tiredness and sat down. She became clammy diaphoretic and stared without responding. She was placed on 6 L/min O<sub>2</sub>, laid supine on the floor. She subsequently became unresponsive and had no palpable pulse. She recovered spontaneously approximately 10 sec later. BP after the event was 180/100 and heart rate was 76 BPM. She was sent to the ER and kept overnight. An MI was ruled out.

Patient #1328005 (Remodulin) was a 66 year old with primary pulmonary hypertension and PAH WHO class II. The subject discontinued study medication and withdrew consent on day on day 14 because of pain and erythema at the infusion site.

Patient # 1336001 was a 44 year old female with primary pulmonary hypertension and PAH WHO class III. She was initially treated with Flolan at an infusion rate of 15.5 ng/kg/min. The first day of Flolan decrease was 22 March (day 2). The subject was weaned from Flolan on 25 March (day 6) but was hospitalized and restarted on Flolan on (b) (6) because of severe dyspnea and fatigue.

**Table 12 Adverse events listed as “severe” in intensity**

Active	Patient #	Event
	1319001	Infusion site pain; PAH; erythema
	1319004	Infusion site pain; infusion site induration; infusion site erythema; syncope vaso-vagal; hypertension (NOS); infusion site warmth
	1319005	Infusion site pain;
	1319007	None-
	1328001	Infusion site pain
	1328003	Arthralgia
	1328004	None.
	1328005	None
	1328007	Back pain;
	1328008	Intermittent headache; infusion site pain; right groin swelling; Hickman catheter infection; intermittent headache; pericarditis lupus; polyserositis; lower extremity edema
	1328009	Infusion site pain; intermittent diarrhea; Jaw pain; Hickman catheter infection; Dizziness; Migraine headache
	1333001	None
	1333002	Syncope; Headache
	1336002	None
Placebo	1315001	None
	1315002	None
	1319002	None
	1319003	Nausea, headache
	1319006	Infusion site pain, worsening of pain
	132002	Pulmonary hypertension worsening
	1328006	Headache
	136001	Headache

In the treated group six of 14 subjects had adverse events related to the infusion site were labeled as “severe”. An additional 5 subjects treated with treprostinil had infusion site pain as “moderate”. Only one placebo patient had infusion pain as either “moderate” or “severe”.

#### Overall adverse events

The sponsor supplies the following table of adverse events that occurred in more than 1 patient in the Remodulin group.

**Table 13 Overall adverse events**

Event	Remodulin	PBO	Event	Remodulin	PBO
Infusion site pain	13 (93%)	3 (38%)	Abdominal distension	3 (21%)	1 (13%)
Nausea	6 (43%)	6 (75%)	Pain in extremity	3 (21%)	1 (13%)
Headache	6 (43%)	5 (63%)	Dyspnea	2 (14%)	1 (13%)
Diarrhea	7 (50%)	3 (38%)	Infusion site induration	3 (21%)	0 (0%)
Infusion site erythema	10 (71%)	0 (0%)	Infusion site swelling	3 (21%)	0 (0%)

Patient #1328008 (Remodulin) was a 28 year old female with scleroderma and PAH WHO class III had a serious adverse event that the sponsor labeled as panserositis. The subject was treated for approximately 4 weeks; was successfully weaned from Flolan and was treated with 71-73 ng/kg/min of study drug. She developed nausea, vomiting epigastric and chest pain. She received NTG and was tachycardic upon arrival to the ER. She also had swelling around the infusion site. She received morphine then dilaudid that ameliorated the pain. She had persistent tachycardia. Two days later she had a positive urinary culture for *klebsiella pneumonia*, for which she received ciprofloxacin. Prior to discharge, the subject upon standing became dizzy and fell. The next day she presented with lower back pain with nausea and vomiting and was rehospitalized.

Upon rehospitalization she was treated for possible lower lobe pneumonia. She had an enlarged cardiac silhouette. She was noted to have spleenomegaly. An evaluation of her gall bladder revealed gall bladder thickening and common duct dilation. Further evaluation of the gall bladder showed no evidence of cholecystitis. Pneumonia was eventually ruled out.

Patient # 1328009 (Remodulin) was a 53 year old female with primary pulmonary hypertension and PAH WHO class III. After approximately 10 days of therapy the subject felt unwell with generalized fatigue, nausea, vomiting diarrhea and cramps. She also developed increased urinary frequency. Three days later her exercise performance was poor. Coagulase negative staphylococcus was grown from the Hickman catheter. She was treated with vancomycin for approximately 4 weeks. Treatment was complicated by the development of acute renal failure (apparently related to elevated vancomycin levels). This patient completed the study but died two weeks later of pancreatitis and sepsis.

Patient # 1333002 (Remodulin) was a 41 year old female with primary pulmonary hypertension and PAH WHO class III. Eleven days after the start of treatment with Remodulin, she had a syncopal episode was diaphoretic. The study medication was unblinded. She was, however, continued on Remodulin therapy. Two weeks later she had increased fatigue, shaking chills and vomiting. The subject was hospitalized and a diagnosis of right heart failure. A blood culture was positive for micrococcus species.

Patient #1319006 (placebo) was a 48 year old black female with a diagnosis of primary pulmonary and PAH WHO classification II. After weaning from Flolan on day 10 she developed worsening symptoms of fatigue, dizziness, dyspnea and pedal edema. She was unable to walk. She was discontinued.

Patient #1328002 (placebo) was a 44 year old female with primary pulmonary hypertension and PAH WHO Class II status. The first day of decreased dose (day 2) was Dec 12. The subject was weaned off Flolan on 20 Dec (day 10) but was restarted on Flolan on Jan 7 (day 28) for worsening symptoms including: increase shortness of breath, episodes of dizziness, lightheadedness, mild palpitations, increased fatigue, decrease in activity, decrease exercise capability and difficulty in breathing. She was restarted on Flolan.

Dizziness	6 (43%)	3 (38%)	Injection site pruritis	2 (14%)	0 (0%)
Flushing	6 (43%)	3 (38%)	Pyrexia	2 (14%)	0 (0%)
Upper Respiratory infection	5 (36%)	1 (13%)	Syncope vasovagal	2 (14%)	0 (0%)
Vomiting	4 (29%)	1 (13%)	Infusion site warmth	2 (14%)	0 (0%)
Pain in jaw	4 (29%)	1 (13%)			

Infusion site effects, excessive vasoactive effects, bone pain, and worsening of underlying disease process were the main adverse events on Remodulin.

## Labs

The data base is relatively small relative to other previously completed studies. No laboratory value was listed as an adverse event. There were two subjects in the treatment group

## Vital Signs:

There were two Remodulin subjects with syncopal events. The end of treatment values for vital signs as listed in the tables are week 8 values when a substantial number of placebo subjects had been restarted on baseline medications. The small number of patients in each group, the simultaneous decrease in Flolan during dose titration phase and the early discontinuation of placebo patients make any assessment of the comparative effect of treatment on vital signs difficult to interpret.

Below are some observations related to vital signs;

- Patient 1315001 (PBO) was tachycardic (HR 110 at baseline). Maximum heart rate was 116 on day 1. During the transition phase heart rate decreased to 75 on day 5. Baseline ECG does not suggest atrial fibrillation.
- Patient 1319002 (PBO) Had a blood pressure measured as 68/33 on day 4
- Patient 1328002 (PBO) had a heart rate down to 51 on day 8.
- Patient 1328004 (Remodulin) had a heart rate up to 122 BPM on day 2 and a increase in SBP to 166/85 also on day 2 (BL 113/85)
- Patient 1328005 (Remodulin) had a low BP 88/44 on day 2 (BL 96/58)
- Patient 1328007 (Remodulin) had a single episode of tachycardia (HR 103) on day 6
- Patient 1328008 (Remodulin) was tachycardic throughout the study (BL heart rate 107) had a maximum measured heart rate of 124
- Patient

## ECGs.

Most subjects had abnormalities related to their pulmonary hypertension. The small number of patients in each group, the simultaneous decrease in Flolan during dose titration phase and the early discontinuation of placebo patients make any assessment of the comparative effect of treatment on vital signs difficult to interpret.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Abraham Karkowsky  
2/9/2006 03:00:54 PM  
MEDICAL OFFICER  
Review Subpart H commitment

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**21-272/S-005**

**OTHER REVIEW(S)**



**RHPM Overview of NDA 21-272/S-005**  
**Remodulin (treprostinil sodium) 1.0, 2.5, 5.0, and 10 mg/ml Injection.**  
March 21, 2006

**Sponsor:** United Therapeutics Corporation  
**Type:** SE7/P  
**Receipt Date:** October 13, 2005  
**User Fee Goal Date:** April 13, 2006  
**AP Letter Issued:** March 20, 2006  
**Final Draft Labeling:** March 20, 2006 (Enclosed in the AP letter)

**Background**

Remodulin Injection was approved under Subpart H on May 21, 2002. As part of the conditions for approval, the sponsor was to conduct a study demonstrating the clinical benefit of treatment.

United Therapeutic submitted S-005 to provide data from their Subpart H commitment as required in the FDA letter dated May 21, 2002 approving this application under Subpart H. The sponsor committed to the performance of a clinical study as outlined in their amendment dated April 1, 2002. This study titled Protocol P01:13, "*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*". The time-lines for completion of P01:13 as affirmed by the sponsor's April 2, 2002 submission were as follows: 50% of Planned Enrollment: by June 2, 2003, Full (100%) Enrollment: by December 2, 2003, Submission of Complete Study Report: by June 2, 2004. In this study a total of approximately 100 patients who are clinically stable on regimens for their pulmonary hypertension are to be withdrawn from Flolan and randomized to receive either placebo or Remodulin.

The sponsor submitted meeting briefing documents on April 4, 2003 and April 16, 2003 as protocol amendments (to IND 36,704) for their Subpart H, post-marketing study (Protocol P01:13). In these documents, they requested that we modify some of the terms specified in our May 21, 2002 approval letter. The timelines for completion of Study P01:13 are revised to the following: 50% of planned enrollment by June 2, 2004, Full (100%) enrollment by June 2, 2005, Submission of complete study reports by December 2, 2005. The overall sample size originally estimated at approximately 100 patients, could be reduced, based on more optimistic estimates of treatment effects. We remind the sponsor that the trial must be of sufficient size to demonstrate clinical effectiveness for Remodulin in the patient population studied.

The sponsor submitted S-005 to provide data from their Subpart H commitment which was suspended with 22 patients completing enrollment.

The primary endpoint in Protocol P01:13 was to determine whether Remodulin, compared to placebo, results in a statistically significant increase in time to clinical worsening in patients transitioned from Flolan therapy. The indication is the treatment of patients with pulmonary arterial hypertension. United Therapeutics was granted Orphan designation for the indication Pulmonary Arterial Hypertension on November 2, 1999.

**Medical Review**

In his review dated February 9, 2006, Dr. Karkowsky states that he recommends approval of this sNDA based on the results of the interim analysis of this single submitted study and based on a series of robustness assessments. He believes that there is adequate information that Remodulin has some activity in patients with pulmonary arterial hypertension. The labeling, however, should be extremely cautious in its recommendations that patients who are currently well controlled on Flolan can be switched to Remodulin.

Dr. Karkowsky concluded that this study is useful in satisfying the Phase IV commitment of Remodulin. The recommendation for use of Remodulin instead of Flolan should only be made for subjects so intolerant to Flolan that they would consider discontinuing Flolan's use.

Labeling recommendations were attached to the medical review dated February 9, 2006.

There are no additional mandatory phase 4 studies for this sNDA.

Financial Disclosure is not applicable as noted on page 7 of the medical review dated February 9, 2006.

### **Pharmacology Review**

There was no pharmacology review completed for this supplemental NDA.

### **Biopharmaceutical Review**

There was no biopharmaceutical review completed for this supplemental NDA.

### **Chemistry Review**

There was no chemistry review completed for this supplemental NDA.

### **Statistical Review**

The statistical review was combined with the medical review for this supplemental NDA.

### **DSI**

In her memorandum, Dr. Sharon Gershon concluded that in general, both sites adhered to applicable regulations and good practices governing the conduct of clinical investigations. One of the two sites was issued a 2- item FDA Form 483. The assessment for Dr. Rubenfire's site was based on the preliminary EIR that was sent by the field investigator. She indicated that the Review Division will be notified if the conclusion changes after receipt and review of the EIR from this inspection. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol and signed informed consent. No serious or significant deviations were found during the inspections at these 2 sites. The data submitted appears to be acceptable.

### **Pediatric Rule**

Remodulin was designated as an Orphan Drug product for treatment of patients with pulmonary arterial hypertension and the sponsor received an exemption for conducting studies in the pediatric population.

### **Labeling:**

The sponsor submitted the most recent draft labeling and revised labeling on February 1, 7, 8, 21 & March 6, 2006, respectively.

This sNDA will be approved on draft labeling.

### **Advisory Committee Meeting**

This application did not go before the Advisory Committee.

### **Project Manager's Summary**

To my knowledge, there are no issues that might prevent taking regulatory action on this sNDA.

John David, BSN, MS in HRM  
Regulatory Health Project Manager

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
John David  
3/21/2006 02:27:37 PM  
CSO

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA #21,272

Supplement #005

SE7

Trade Name: Remodulin Injection

Generic Name: treprostinil sodium

Strengths: 1, 2.5, 5 and 10 mg/ml

Applicant: United Therapeutics

Date of Application: October 12, 2005

Date of Receipt: October 13, 2005

Date clock started after UN: N/A

Date of Filing Meeting: November 23, 2005

Filing Date: December 12, 2005

Action Goal Date (optional): April 13, 2006

User Fee Goal Date: April 13, 2006

Indication(s) requested: Treatment of patients with pulmonary arterial hypertension.

Type of Original NDA: (b)(1) \_\_\_\_\_ (b)(2) \_\_\_\_\_

OR

Type of Supplement: (b)(1)   X   (b)(2) \_\_\_\_\_

**NOTE:**

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

(2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

  X   NDA is a (b)(1) application OR        NDA is a (b)(2) application

Therapeutic Classification: S \_\_\_\_\_

P   X  

Resubmission after withdrawal?   N/A  

Resubmission after refuse to file?   N/A  

Chemical Classification: (1,2,3 etc.) \_\_\_\_\_

Other (orphan, OTC, etc.)   Orphan  

Form 3397 (User Fee Cover Sheet) submitted:

YES

User Fee Status:

Paid \_\_\_\_\_ Exempt (orphan, government)   X    
Waived (e.g., small business, public health) \_\_\_\_\_

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

*product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

YES

If yes, explain: NCE 5-year exclusivity was granted until May 21, 2007.

- Does another drug have orphan drug exclusivity for the same indication?

YES

(until May 21, 2009)

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)?

NO

If yes, explain.

- If yes, has OC/DMPQ been notified of the submission?

N/A

- Does the submission contain an accurate comprehensive index?

YES

- Was form 356h included with an authorized signature?

YES

**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50?

YES

If no, explain:

- If an electronic NDA, does it follow the Guidance? Case report forms (CRF's) only  
**If an electronic NDA, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format? Case report forms (CRF's)

Additional comments:

- If in Common Technical Document format, does it follow the guidance?

N/A

- Is it an electronic CTD?

NO

**If an electronic CTD, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a?

YES

- Exclusivity requested?

NO

**NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature?

YES

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as “To the best of my knowledge . . .”

- Financial Disclosure forms included with authorized signature? YES  
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? YES  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 36,704
- End-of-Phase 2 Meeting(s)? NO  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? NO  
If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? NO  
If no, did applicant submit a complete environmental assessment? NO  
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? N/A
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: November 23, 2005

**BACKGROUND:**

United Therapeutic submitted S-005 to provide data from their Subpart H commitment as required in the FDA letter dated August 18, 2003. Protocol P01:13, "*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*", has been suspended with 22 patients completing enrollment. The primary endpoint in Protocol P01:13 was to determine whether Remodulin, compared to placebo, results in a statistically significant increase in time to clinical worsening in patients transitioned from Flolan therapy. The indication is the treatment of patients with pulmonary arterial hypertension. United Therapeutics was granted Orphan designation for the indication Pulmonary Arterial Hypertension on November 2, 1999.

**ATTENDEES:**

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Ellis Unger, M.D.	Deputy Director, HFD-110
Abraham Karkowsky, M.D.	Team Leader, Medical Officer, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Nhi Beasley, Ph.D.	Clinical Pharmacology/Biopharmaceutics, HFD-860
Edward Fromm	Chief, Project Management Staff, HFD-110
John David	Regulatory Health Project Manager, HFD-110

**ASSIGNED REVIEWERS:**

<b><u>Discipline</u></b>	<b><u>Reviewer</u></b>	<b><u>Review Due</u></b>
Medical/ Statistical:	Abraham Karkowsky, M.D.	January 23, 2006
	John Lawrence, Ph.D.	
Pharmacology:	Xaxier Joseph, Ph.D.	N/A
Chemistry:	Monica Cooper, Ph.D.	N/A
Biopharmaceutical:	Nhi Beasley, Ph.D.	N/A
DSI:	Sharon Gershon	November 14, 2005
Regulatory Project Management:	John David	
Other Consults:		
DDMAC:	Lance McLeroy	

Per reviewers, are all parts in English or English translation?  
If no, explain:

YES

CLINICAL

FILE   X  

REFUSE TO FILE           

- Clinical site inspection needed:
- Advisory Committee Meeting needed?

YES  
(completed November 14, 2005)  
NO



- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

NO

CLINICAL MICROBIOLOGY                      N/A   X      FILE                                 REFUSE TO FILE           

STATISTICS FILE   X   REFUSE TO FILE           

BIOPHARMACEUTICS                      N/A      X      FILE \_\_\_\_\_                      REFUSE TO FILE \_\_\_\_\_

- Biopharm. inspection needed:

NO

PHARMACOLOGY	N/A	X	FILE	REFUSE TO FILE
--------------	-----	---	------	----------------

- GLP inspection needed:

NO

CHEMISTRY	N/A	X	FILE	REFUSE TO FILE
-----------	-----	---	------	----------------

- Establishment(s) ready for inspection?
- Microbiology

N/A

N/A

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

\_\_\_X\_\_\_ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

X	No filing issues have been identified.
---	----------------------------------------

Filing issues to be communicated by Day 74. List (optional):

### ACTION ITEMS:

1. No filing issues will be conveyed to applicant by Day 74.

John David  
Regulatory Project Manager, HFD-110

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
John David  
12/6/2005 12:13:46 PM  
CSO

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-272/S-005**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-272

SUPPL # 005

HFD # 110

Trade Name Remodulin Injection

Generic Name treprostinil sodium

Applicant Name United Therapeutics Corp.

Approval Date, If Known

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b)(1), SE7, United Therapeutic submitted S-005 to provide data from their Subpart H commitment as required in the FDA letter dated May 21, 2002

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### **1. Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 21-272

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐



If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol P0:13, "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"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 36,704	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☒

If yes, explain:

United Therapeutic submitted S-005 to provide data from their Subpart H commitment as required in the FDA letter dated May 21, 2002

=====

Name of person completing form: John David

Title: RHPM

Date: March 10, 2006

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
John David  
3/21/2006 03:17:58 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-272 Supplement Type (e.g. SE5): SE7 Supplement Number: 005

Stamp Date: October 13, 2005 Action Date: April 13, 2006

HFD 110 Trade and generic names/dosage form: Remodulin Injection (treprostinil sodium) 1.0, 2.5, 5.0, and 10 mg/ml

Applicant: United Therapeutics Corp. Therapeutic Class: Standard

Indication(s) previously approved:

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

**Indication #1:** Remodulin® is indicated as a continuous subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms (see CLINICAL PHARMACOLOGY: Clinical Effects) to diminish symptoms associated with exercise.

Is there a full waiver for this indication (check one)?

☒ **Yes:** Please proceed to Section A.

☐ **No:** Please check all that apply: ☐ Partial Waiver ☐ Deferred ☐ Completed

**NOTE:** More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☒ **Other:** Orphan Drug designation for the indication pulmonary arterial hypertension on November 2, 1999.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	kg	mo.	yr.	Tanner Stage
Max	kg	mo.	yr.	Tanner Stage

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

☐ Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
John David  
Regulatory Project Manager

cc: NDA 21-272  
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
John David  
3/21/2006 02:48:12 PM

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-272	Efficacy Supplement Type SE-7	Supplement Number 005	
Drug: Remodulin (treprostinil sodium) 1.0, 2.5, 5.0, and 10 mg/ml Injection.		Applicant: United Therapeutics	
RPM: John David		HFD- 110	Phone # 301-796-1059
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)            (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>N/A</p>	
❖ Application Classifications:			
Review priority			<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
Chem class (NDAs only)			
Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates			April 13, 2006
❖ Special programs (indicate all that apply)			<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information			
User Fee			<input type="checkbox"/> Paid UF ID number N/A
User Fee waiver			<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) N/A
User Fee exception			<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)			
Applicant is on the AIP			<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
This application is on the AIP			<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



Exception for review (Center Director's memo)	N/A
OC clearance for approval	N/A
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?	<input type="checkbox"/> Yes <input type="checkbox"/> No
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).	
<i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i>	
Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i>	
<i>If "No," continue with question (3).</i>	
Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	<input type="checkbox"/> Yes <input type="checkbox"/> No
(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of	



<p>receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p> <p><i>If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p> <p>Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (5).</i></p> <p>Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	<p>( ) Yes      ( ) No</p> <p>( ) Yes      ( ) No</p>
❖ Exclusivity (approvals only)	
<p>Exclusivity summary</p> <p>Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</p>	<p>Enclosed</p> <p>N/A, Subpart H, post-marketing commitment</p>
<p>Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</p>	<p>( ) Yes, Application # _____</p> <p>(X) No</p>
<p>Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</p>	<p>RHPM review 3/20/06</p>

General Information	
❖ Actions	
Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
Previous actions (specify type and date for each action taken)	
Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	3/6/06
Most recent applicant-proposed labeling	3/2/06
Original applicant-proposed labeling	October 12, 2005
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> )	DDMAC, 3/13/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
Applicant proposed	N/A
Reviews	N/A
Post-marketing commitments	
Agency request for post-marketing commitments	no
Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
Outgoing correspondence (i.e., letters, E-mails, faxes)	12/7/05 Filing Letter 10/24/06 Acknowledgement letter
Memoranda and Telecons	3/2/06 Labeling telecon
Minutes of Meetings	
EOP2 meeting (indicate date)	None
Pre-NDA meeting (indicate date)	12/15/03
Pre-Approval Safety Conference (indicate date; approvals only)	None
Other	8/24/04 Post-marketing commitment, 4/16/03; 3/7/02; 2/13/02 Discussion of post-marketing study
Advisory Committee Meeting	
Date of Meeting	N/A
48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A



Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	N/A
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	February 9, 2006
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	See pages 5 & 18 of Clin. Review
Pediatric Page(separate page for each indication addressing status of all age groups)	See peds. page
Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
Clinical studies	November 14, 2005
Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	N/A
Environmental Assessment	
Categorical Exclusion (indicate review date)	N/A
Review & FONSI (indicate date of review)	N/A
Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation (X) N/A
Methods validation	( ) Completed ( ) Requested (X) N/A
Nonclinical Pharm/Tox Information	
Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	N/A
Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
John David  
3/21/2006 02:41:42 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-272 S-005

United Therapeutics  
Attention: Dean Bunce  
One Park Drive  
Suite 400  
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your October 12, 2005 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin (treprostinil sodium) 1.0, 2.5, 5.0, and 10 mg/ml Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 23, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call:

Mr. John David  
Regulatory Project Manager  
(301) 796-1059

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Acting Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Norman Stockbridge  
12/7/2005 04:11:16 PM



NDA 21-272/S-005

**PRIOR APPROVAL SUPPLEMENT**

United Therapeutics Corporation  
Attention: Mr. Dean Bunce  
One Park Drive, Suite 400  
Research Triangle Park, NC 27709

Dear Mr. Bunce:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Remodulin (treprostinil sodium) 1, 2.5, 5, and 10 mg/mL Injection

NDA Number: 21-272

Supplement number: 005

Review Priority Classification: Priority (P)

Date of supplement: October 12, 2005

Date of receipt: October 13, 2005

This supplemental application provides data to satisfy the completion of your Subpart H commitment and confirmation of the clinical benefit of Remodulin.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 12, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 13, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Please refer to the letter dated May 21, 2002, waiving the requirement for pediatric studies for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products, Room 4173  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any question, please call;

Mr. John David  
Regulatory Health Project Manager  
(301) 796-1059

Sincerely,

*{See appended electronic signature page}*

Edward Fromm  
Chief, Project Management Staff  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research



-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Edward Fromm

10/24/2005 03:44:36 PM