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RESEARCH**

*APPLICATION NUMBER:*

**22-387**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

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NDA: 22-387	Submission Dates: 06/27/08 and 08/25/08
Relevant IND	70,362
Submission Type; Code	Original NDA; N-000
PDUFA Goal Date	April 24, 2009
Brand Name	TYVASO™
Generic Name	Treprostinil sodium
Formulation; Strength	Solution for inhalation; 0.6 mg/mL
Indication	Pulmonary Arterial Hypertension
Applicant	United Therapeutics Corporation
Reviewer	Robert O. Kumi, Ph.D.
Secondary Reviewer	Angelica Dorantes, Ph.D.
OCP Division	DCP1
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Briefing Date	March 23, 2009

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# 1 Executive Summary

## Introduction

In NDA 22-387, TYVASO™ (treprostinil sodium) inhalation solution is proposed for the indication of Pulmonary Arterial Hypertension (WHO Group 1) in patients with New York Heart Association Class III — symptoms. Treprostinil is currently approved for the same indication as Remodulin injection for subcutaneous and intravenous administration (NDA 21-272). The applicant, United Therapeutics, was granted orphan designation for the stated indication in 1999.

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Treprostinil is a stable, synthetic analog of prostacyclin. The major pharmacological effects of treprostinil are vasodilatation, inhibition of platelet aggregation and inhibition of smooth muscle cell proliferation. Tyvaso will be supplied in 2.9 mL ampoules containing 0.6 mg treprostinil per milliliter and is intended for oral inhalation use with a nebulizer (Optineb). The proposed product will be dosed in four separate inhalation sessions per day, during the waking hours. Each breath is expected to deliver a dose of 6 µg. Initial therapy should begin with three breaths (18 µg treprostinil) and the maximal target dose per session is 54 µg (9 breaths).

The clinical development program for NDA 22-387 includes approximately 20 studies involving the assessment of pharmacokinetics (PK) of inhaled treprostinil, drug interactions with oral treprostinil, and in vitro metabolism. The PK studies were conducted to characterize the bioavailability of the new formulation, whereas the latter sets of studies were conducted to supplement existing information on approved or investigational treprostinil products. Nine of the 20 studies were reviewed as they are most relevant to the current application. The remaining studies submitted in NDA 22-387, including investigator sponsored studies were not reviewed as they did not provide pertinent information.

## 1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted to NDA 22-387. The clinical pharmacology and biopharmaceutics information provided in NDA 22-387 is acceptable, pending confirmation from the CDRH consultant that the inhalation device accurately delivered the dose reported in the pharmacokinetic (PK) studies. Without this confirmation, the reliability PK information is unclear and renders the PK information related to inhalation unacceptable. OCP has the following comments:

### General Comments

1. If CDRH does not confirm the precision/accuracy of the delivery system, the applicant will need to conduct a bioavailability (PK) assessment of inhaled treprostinil using the to-be-marketed formulation and device.
2. In multiple studies, some subjects (one or more) had undetectable or low treprostinil exposure compared to other subjects. The reason for these low exposures is unclear but may be related to the failure of the inhalation device (nebulizer) or factors intrinsic (e.g. CYP2C8 polymorphism) to the patients. In this reviewer's opinion, the low drug exposure is more likely due to issues related to the drug delivery device, and should be addressed by the Applicant.

### Labeling Comments

Overall, the labeling proposed by the Applicant is acceptable; the majority of information is obtained from the labeling for NDA 21-272 (Remodulin). There should be minor modifications to the pharmacokinetics section: 1) statements regarding the linear range following inhaled treprostinil administration and 2) general editorial changes to the pharmacokinetic section to make the information clearer.

### 1.2 Phase IV Commitments

None

### 1.3 Key Clinical Pharmacology and Biopharmaceutics Findings

#### General Treprostinil Pharmacokinetics Following Inhalation

The following estimates for PK measures (healthy volunteers) were obtained for inhaled treprostinil (single dose) for doses ranging from 18 to 90 µg:

- T<sub>max</sub> range = 0.12 – 0.25 hr (three studies)
- T<sub>1/2</sub> range = 0.46 – 0.62 hr (three studies)
- V<sub>z</sub>/F range = 45 - 64 L (two studies); 0.78 – 1.00 L/kg (one study)
- CL/F range = 60 - 77 L/hr (two studies); 1.01 – 1.45 L/hr/kg (one study)

#### Absolute Bioavailability

The absolute bioavailability (F) estimations for inhaled treprostinil are summarized in the following table; F appeared to depend on dose.

Table 1: Statistical Analysis in treprostinil absolute bioavailability\* study (n = 18, per group)

	Three Breaths = 18 µg	Six Breaths = 36 µg
	Bioavailability (F %)	
Mean (CV %)	61.52 (29.68)	74.05 (21.23)
Median (Range)	60.84 (13.08 – 90.69)	70.27 (52.36 – 115.99)

\* IV dose = single 15 ng/kg/min infusion for 60 minutes

#### PK Linearity (Dose Proportionality)

Based on pooled plasma exposure data from three studies, treprostinil exposure was dose proportional over the 18 to 90 µg range following single dose administration.

#### Intersubject variability

The intersubject variability in pharmacokinetic measures ranged from approximately 20 to 67 %. In some instances, subjects had low or undetectable concentrations; the source of the variability is not clear, but is likely associated with the lack of reproducibility of the inhalation device (uncertainty of the administered dose).

#### In Vitro Metabolism

The metabolism of treprostinil was evaluated in two *in vitro* studies. The results showed that;

- CYP Substrate Status: Treprostinil is metabolized primarily by CYP2C8 followed by CYP2C9 to a minor extent; other CYP enzymes do not play a role in treprostinil metabolism.

- CYP Induction Potential: Treprostinil (2 and 10  $\mu$ M) does not appear to induce the enzymatic activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4 isoforms in human hepatocytes.

### Drug-Drug Interaction Studies with Oral Treprostinil

The table below summarizes the drug interaction findings, where oral treprostinil (1 mg BID) was administered with other drugs (administered at clinically relevant dosages).

**Table 2: Drug-Drug Interaction Information for Orally Administered Treprostinil**

Compound	Basis for conducting study	Finding
Bosentan	Used in PAH as background therapy and CYP inducer, possible PK/PD	No PK effect on either compound or bosentan metabolite; possible increase in adverse events (AEs) for dual therapy (per Applicant)
Sildenafil	Used in PAH as background therapy, possible PD	No PK effect on either compound or sildenafil metabolite; possible increase in AEs for dual therapy (Per Applicant)
Rifampin	Probe CYP inducer	<ul style="list-style-type: none"> <li>• Treprostinil AUC decreases by about 30 %</li> <li>• Treprostinil Cmax decreases numerically by 20 %, but the decrease is not statistically significant</li> </ul>
Gemfibrozil	CYP2C8 inhibitor expected to inhibit treprostinil metabolism	Treprostinil AUC and Cmax increased approximately 2-fold
Fluconazole	CYP2C9 inhibitor expected to inhibit treprostinil metabolism	<ul style="list-style-type: none"> <li>• Treprostinil AUC decreased by approximately 14 %</li> <li>• No effect on Cmax</li> </ul>

### QT Prolongation

Inhaled treprostinil did not prolong the QT interval when administered as a single dose of 54  $\mu$ g (target dose per inhalation session) or 84  $\mu$ g (supra-therapeutic dose).

### Formulation and Delivery Device

Tyvaso will be supplied in 2.9 mL ampoules containing 0.6 mg treprostinil per milliliter and is intended for oral inhalation use with a nebulizer (Optineb-ir).

### Signatures

Primary Clinical Pharmacology Reviewer

Robert O. Kumi

Acting Team Leader

Angelica Dorantes

CC: NDA 22-387; Dorantes Uppoor Mehta RKumi (HFD 860)

## 2 Question Based Review

This clinical pharmacology and biopharmaceutical (CPB) review for NDA 22-387 employs an abridged version of the 'Question Based Review' (QBR) since most QBR elements were addressed in the original CPB review for treprostinil sodium for injection (NDA 21-272). Please refer to NDA 21-272 for information on human pharmacokinetics and bioavailability of treprostinil. The QBR elements addressed in detail in this Clinical Pharmacology Review are Clinical Pharmacology and Extrinsic Factors. In all, nine studies were reviewed.

### 2.1 What are the general attributes of treprostinil sodium?

#### Regulatory History

- NDA 21-272, Remodulin (treprostinil sodium) solution for injection (IV or SC) was approved in May 2002 for the treatment of pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms to diminish symptoms associated with exercise.
- The Applicant informed the Agency that the inhaled treprostinil NDA would include the Optineb nebulizer device, during the NDA review. CDRH is responsible for reviewing the suitability of the nebulizer devices. (Pre-NDA meeting held on May 16, 2008 for IND 70,362)
- The Applicant agreed to provide the missing drug interaction information for Remodulin; it was agreed that drug interaction information with oral treprostinil and a few selected compounds would be acceptable for this purpose (EOP1 meeting held on November 9, 2005 for IND 71,537, oral treprostinil)

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#### Highlights of the chemistry and physical-chemical properties of the drug substance and the formulation

Please refer to the Clinical Pharmacology Review of NDA 21-272 (treprostinil sodium solution for injection) for detailed information on the chemistry and physical-chemical characteristics of treprostinil. The only difference between the formulation in NDA 22-387 for inhaled treprostinil sodium (TYVASO™) and NDA 21-272 is the absence in the product for inhalation. Tyvaso is supplied in 2.9 mL ampoules containing 0.6 mg treprostinil per milliliter. The product is to be administered undiluted, as supplied, using the Optineb-ir.

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#### Proposed therapeutic indication and mechanism of action

TYVASO will be indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with NYHA Class III — symptoms.

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

#### Proposed route of administration and dosage

Tyvaso will be delivered via inhalation using a nebulizer, Optineb-ir. The dosage instructions follow:

General Dosage Recommendations (per label)

TYVASO is dosed in four separate inhalation sessions per day, during waking hours. The inhalation sessions should be at least 4 hours apart.

### ***Initial Therapy***

- Therapy should begin with three breaths of TYVASO (18 µg of treprostinil), per inhalation session given four times per day
- If three breaths per session are not tolerated, the dose may be reduced to one or two breaths and subsequently increased to three breaths, as tolerated.

### ***Maintenance Therapy***

- Dosage should be increased to six breaths per inhalation session given four times daily, and subsequently increased to the target maintenance dose of nine breaths (54 µg of treprostinil) per inhalation session given four times daily, as tolerated.
- If adverse effects preclude titration to this target dose, TYVASO should be continued at the highest dose that is tolerated by the patient.

The label also notes the following additional two points:

- The maximum dose used in clinical studies was 12 breaths (72 µg of treprostinil), per inhalation session.
- If a scheduled inhalation session is missed or interrupted, therapy should be resumed as soon as possible.

## **2.2 What are the general clinical pharmacology characteristics of treprostinil?**

### **Design Features of Clinical Study**

One pivotal clinical efficacy study, TRIUMPH I (TReprostinil sodium Inhalation Used in the Management of Pulmonary arterial Hypertension), was conducted. Some features of the TRIUMPH study are tabulated below.

**Table 3: Design features of pivotal clinical study**

Duration/number of subjects	12-week / 235
Description	Randomized, double-blind, placebo-controlled multi-center study
Population	PAH patients who are clinically stable, WHO Group 1, NYHA Class III and IV symptoms
Background therapy	approved therapy for PAH: bosentan (Tracleer) or sildenafil (Revatio); patients on these for at least three months prior to study initiation
Concomitant therapy	anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not prostacyclin or its analogues.
Dosage in blinded phase	four daily inhalation sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study.
Dosage in open label extension	maximum dose of 12 breaths (72 mcg) per session.

### **Clinical Response Endpoints**

The primary efficacy endpoint of the trial was the change in six-minute walk distance at 12 weeks measured at peak exposure (between 10 and 60 minutes after dosing), relative to baseline. This endpoint has been used in previous PAH clinical trials and is considered acceptable. Secondary endpoints included the following: Changes in Borg dyspnea score, PAH signs and symptoms, and NYHA functional class from Baseline to Week 12; there was also a quality of life assessment via a questionnaire.

**2.2.1 Are the active moieties in the plasma appropriately identified and measured to assess PK parameters and exposure response relationships?**

Yes, please refer to 2.6, Analytical Section.

**2.2.2. What are the characteristics of the exposure-response relationships for effectiveness and safety?**

No specific exposure-response data or quantitative analysis were collected or conducted for inhaled treprostinil; however, some useful empirical information was obtained from the various individual studies. Pharmacokinetic exposure data were not collected in the pivotal clinical trial.

**Exposure-Effectiveness Information**

Exposure-effectiveness data were not collected in the pivotal clinical trial. However, plasma exposure associated with the initial proposed dose, 18 µg, the targeted dose, 54 µg, and the maximum daily dose in clinical studies, 72 µg, (per inhalation session) are available. It should be noted that these data were obtained in healthy volunteers, rather than patients.

**Exposure-Safety Information**

In the single dose safety and tolerability study, the sponsor concluded that the maximum tolerated dose was 84 µg; the 90 µg dose was considered intolerable and was associated with chest pain, chest discomfort, nausea and vomiting. The plasma concentrations associated with 84 and 90 µg single doses are available from healthy volunteers. It should be noted that in the pivotal clinical trial, the maximum inhaled dose per session was 72 µg given on multiple occasions.

**Evaluation of QT or QTc interval prolongation**

Tyvaso does not prolong the QT interval. Following a single dose of 54 µg (recommended clinical dose) and 84 µg (supratherapeutic dose), treprostinil had no effect on cardiac conduction.

**Suitability of the sponsor's selected dose, dosing regimen, and delivery device**

The proposed initial and maintenance dosing appear reasonable from a clinical pharmacology perspective; however, it should be noted that

- a) there is no definitive exposure (dose)-response information
- b) concern remains regarding the utility of the nebulizer with respect to its ability to reliably deliver the planned dose

The first concern is somewhat alleviated by the fact that the clinical trials demonstrated that the product is effective (satisfied primary endpoint) at the proposed dose range. In all three studies, where exposure data were collected, there were one or more patients who had no or low drug exposure, suggesting that treprostinil was not delivered correctly via device or absorbed appropriately. CDRH and other CDER consulting staff have raised questions concerning the suitability of the device due to the somewhat complex nature of how the device must be operated. Please refer to attached document in Appendix 4.3. It should be noted that treprostinil is a substrate of CYP2C8 that exhibits genetic polymorphism; this can lead to differential exposure levels among subjects. The treprostinil development program did not include phenotyping or genotyping, thus the role of CYP2C8, if any, cannot be evaluated.

The Clinical Reviewer, Abraham Karkowsky, MD, has also noted the following issues regarding the suitability of the proposed dosing regimen:

- There is no demonstration of effect over the inter-dosing interval (time between inhalation sessions and during sleeping hours): walk distance was evaluated at 10 minutes and 60 minutes post inhalation
- There is no demonstration of an effect for a period greater than a year: this is a concern since there is evidence with Remodulin that “tolerance” appears to develop over time

### 2.2.3 What are the pharmacokinetics (PK) of treprostinil following inhalation?

Following inhalation, the PK of only parent drug, treprostinil, were determined; following subcutaneous and intravenous administration, five metabolites have been described (HU1 to HU5) but the biological activity and metabolic fate of these metabolites is unknown.

The accuracy of the PK information hinges on the reliability of the dose delivered via the nebulizer. In the following sections, the doses are assumed to be accurate and reflect the actual delivered dose.

#### Single dose PK measures (Studies LRX-TRIUMPH BA.001, RIN-PH-102, and RIV-PH-409)

The following table summarizes the single dose PK data obtained from three studies.

Table 4: Summary of PK measures for inhaled treprostinil\*

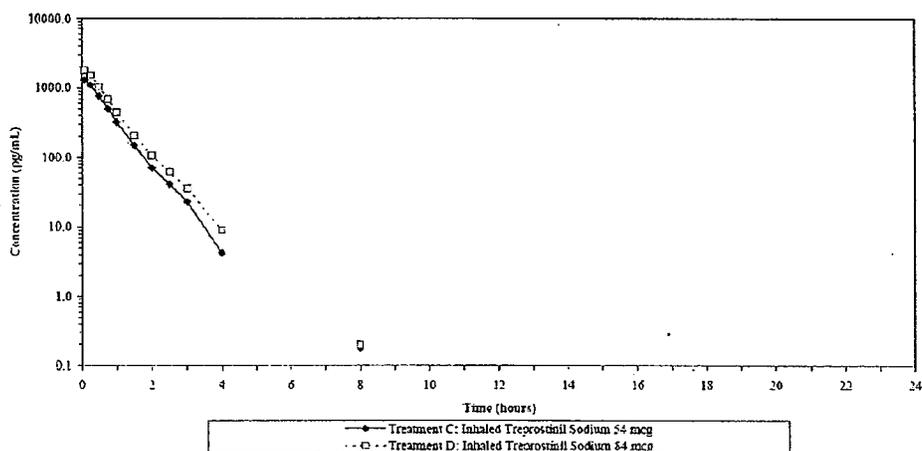
PK Measure	Value
Tmax (hr)	0.12 – 0.25
T1/2 (hr)	0.46 – 0.62
^Vz/F (L)	45 – 70
^CL/F (L/hr)	60 – 101

\* data from three studies have been recorded in the same units for ease of interpretation; where necessary, the assumed body weight was 70 kg

^ data were reported in a dose normalized fashion for one study

The inhaled treprostinil doses ranged from 18 to 90 µg and data were consistent in all three studies. A representative mean plasma concentration-time profile (QT study) following single dose administration is depicted in the figure below.

Figure 1: Treprostinil plasma concentration-time profile following inhalation of treprostinil



### Drug absorption

Following inhalation, treprostinil was absorbed in a rapid manner with maximum concentrations achieved within 15 minutes. The absolute bioavailability was approximately 68 % (data from two dose levels). The studies in this NDA did not evaluate the effect of swallowing the solution vs. Inhalation\*. It is unclear if any of the data may have been altered by subjects inadvertently or intentionally swallowing the formulation.

\* the label (Overdose Section) indicates that a patient accidentally swallowed an unknown quantity of Tyvaso

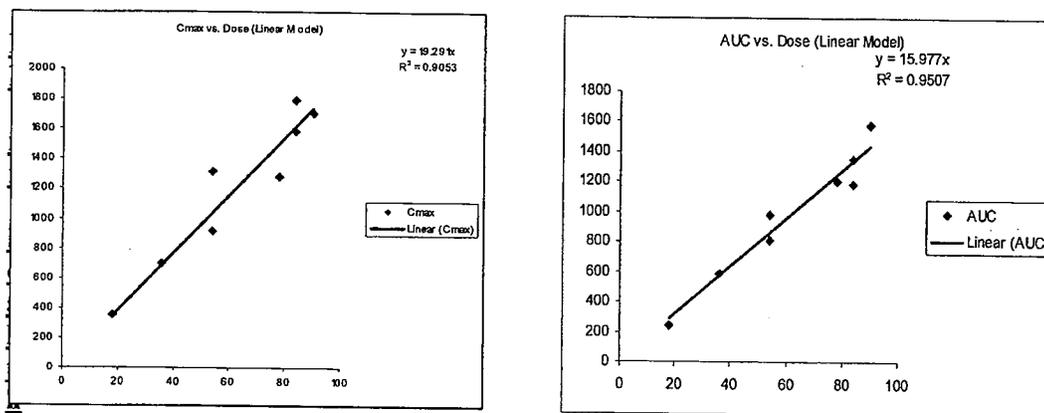
### Drug Distribution

The apparent volume of distribution ranged from 45 to 70 L

### Dose proportionality of treprostinil following inhalation

Treprostinil exhibited dose-proportional increases in exposure over the 18 to 90 µg dose range.

Figure 2: Evaluation of PK linearity\* (dose proportionality) following inhaled treprostinil administration (C<sub>max</sub> vs. Dose, left panel and AUC vs. Dose, right panel: Reviewer Generated)



\* The power model yielded the same conclusion regarding dose proportionality (not included)

### PK in healthy volunteers vs. patients

PK data were obtained only in healthy volunteers, thus no comparison with patients is possible. Treprostinil is administered via a nebulizer with inherent complexity in usage that may pose some challenges for people who have breathing difficulty, such as patients with PAH. Consequently, it is unclear if patients and healthy volunteers will have similar PK following the inhalation of treprostinil.

### Intersubject variability of PK parameters in volunteers

Following inhalation of treprostinil, intersubject variability in CL/F and V<sub>z</sub>/F ranged from 25 to 120 %; as expected the highest variability was associated with cohorts with a small number of subjects (n = 6 was smallest size). However, even with n = 60 in the QT study, CV for the PK parameters was 42 to 62 %. This finding indicates that the absorption or delivery of treprostinil following inhalation is highly variable.

The variability of exposure is further highlighted in the following table that provides a summary of treprostinil concentrations at given dose levels and time points.

**Table 5: Example of intersubject variability in concentrations at the same point (Reviewer Generated)\***

Concentration	n = 59			Dose = 54 microgram			n = 6		
	T1	T2	T3	L1	L2	L3			
Min	262.00	143.00	18.00	34.00	134.00	136.00			
Max	2210.00	1177.00	356.00	473.00	1616.00	998.00			
Mean	1324.00	777.00	153.00	250.00	845.00	666.00			
Standard Dev.	407.00	186.00	64.00	179.00	542.00	362.00			
CV (%)	30.74	23.94	41.83	71.60	64.14	54.35			
Ratio (Max/Min)	8.44	8.23	19.78	13.91	12.06	7.34			

Concentration	n = 60			Dose = 84 microgram			n = 6		
	T1	T2	T3	L1	L2	L3			
Min	331.00	331.00	50.00	179.00	820.00	649.00			
Max	3589.00	1722.00	209.00	1011.00	2508.00	1142.00			
Mean	1776.00	1042.00	467.00	529.00	1619.00	846.00			
Standard Dev.	652.00	289.00	82.00	347.00	739.00	185.00			
CV (%)	36.71	27.74	17.56	65.60	45.65	21.87			
Ratio (Max/Min)	10.84	5.20	4.18	5.65	3.06	1.76			

\* T1 and L1 represent time point with first measurable concentration; T2 and L2 represent intermediate time point; T3 and L3 represent terminal time point (last time point with measurable concentration)

Overall, the concentration data suggest that at any given time there is a great variation in the concentrations among patients. It should be noted that one subject in the 54 µg cohort (n = 59) did not have any detectable concentrations. This finding may pose clinical concern because *a priori* one could not determine which subjects would have inadequate exposure to treprostinil; consequently, it is possible that some subjects receiving Tyvaso may not receive a therapeutic dose and be unresponsive to treprostinil therapy.

### **2.3 What intrinsic factors affect treprostinil exposure?**

The effect of intrinsic factors on treprostinil exposure was not evaluated in NDA 22-387. However, the intrinsic factors that were identified for Remodulin should be applicable to Tyvaso, as they contain the same active, major circulating moieties.

### **2.4 What extrinsic factors affect treprostinil exposure?**

Extrinsic factors related to metabolic drug interactions were found to alter treprostinil exposure following oral administration; these factors in addition to those identified previously for Remodulin will be applicable to treprostinil exposure resulting from Tyvaso administration.

#### **In vitro metabolism**

##### ***CYP Substrate Status (Study 49251)***

Treprostinil was metabolized primarily by CYP2C8 and CYP2C9 to a lesser extent. The other evaluated CYP enzymes CYP1A2, 2A6, 2C19, 2D6, 3A4 and 4A11 do not metabolize treprostinil to a significant extent.

Studies conducted with microsomes confirmed CYP involvement in treprostinil metabolism. Subsequently, studies with c-DNA enzymes identified two main enzymes, CYP2C8 and CYP2C9, as being primarily responsible for treprostinil metabolism (Table 6). CYP2C8 was confirmed as the main metabolic pathway for treprostinil using two specific chemical inhibitors: quercetin (CYP2C8 – prevented treprostinil metabolism) and sulfaphenazole (CYP2C9 – 35 % of treprostinil was metabolized.)

**Table 6: Treprostinil metabolism with c-DNA expressed enzymes**

Isozyme	Peak Areas				% Remaining
	0 min		15 min		
	Average	%CV	Average	% CV	
1A2	932467	9.57	1056000	4.27	113%
2A6	1132000	0.81	1189667	6.18	103%
2C8	1081700	9.74	54550	12.27	5%
2C9	733500	10.29	570100	19.90	78%
2C19	1098333	7.19	1143000	7.89	104%
2D6	1282333	4.21	1142667	6.18	89%
2E1	1135333	10.13	1180667	10.44	104%
3A4	1286667	4.00	1364333	6.35	106%
4A11	711266	7.68	781767	4.42	110%

% Remaining = Peak Area at 15 min / Peak Area at 0 min

Note: Values greater than 100% of Treprostinil Remaining are not significantly different from the negative control values

***CYP Induction Potential (Study 7049-122)***

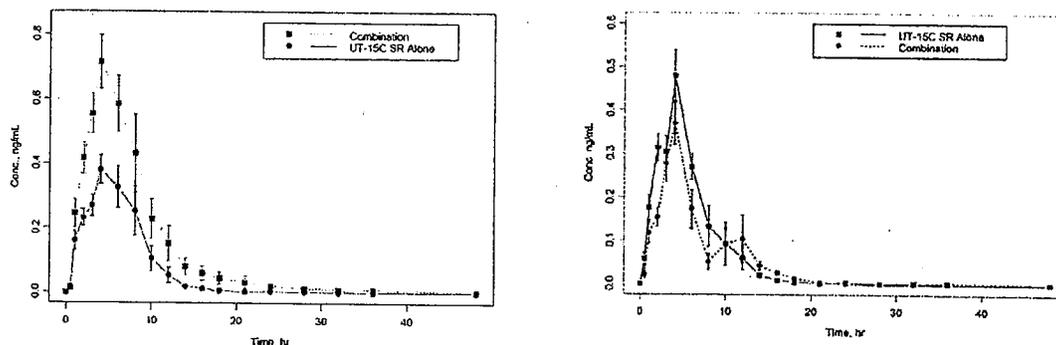
Treprostinil (2 and 10 µM) does not appear to induce the enzymatic activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4 isoforms in human hepatocytes (*in vitro*). This finding suggests that clinically, treprostinil will not alter the exposure of substrates for these enzymes.

### In vivo Drug Interaction Studies

Orally administered tadalafil underwent a drug interaction when coadministered with gemfibrozil (CYP2C8 inhibitor) and rifampin (CYP inducer); whereas there was no clinically significant interaction with sildenafil, bosentan or fluconazole.

The following figures depict tadalafil exposure changes with gemfibrozil and rifampin.

**Figure 3: Plasma concentration time profiles of tadalafil in drug interaction studies (gemfibrozil, left panel and rifampin, right panel)**



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The following table summarizes the findings in the tadalafil drug interaction studies: coadministration of oral tadalafil (1 mg BID) with probe compounds (administered at clinically relevant dosages).

**Table 7: Tadalafil drug interaction profile (pharmacokinetic/PK and pharmacodynamic/PD)**

Study/Drug	Basis for conducting study	Finding	Conclusion
TDE-PH-105/ Bosentan	Used in PAH as background therapy and CYP inducer; possible PK/PD	No PK effect on either compound or bosentan metabolite; possible increase in adverse events (AEs) for dual therapy (per Applicant)	No adjustment needed for either compound
TDE-PH-106/ Sildenafil	Used in PAH as background therapy; possible PD	No PK effect on either compound or sildenafil metabolite; possible increase in AEs for dual therapy (per Applicant)	No adjustment needed for either compound
TDE-PH-109/ Rifampin	Probe CYP inducer that can decrease tadalafil exposure	Tadalafil AUC decreases by about 30 % Tadalafil Cmax decreases numerically by 20 %, but the decrease is not statistically significant	In presence of rifampin Tadalafil may not be as effective as in absence of rifampin
TDE-PH-110/ Gemfibrozil	Probe CYP2C8 inhibitor expected to inhibit tadalafil metabolism	Tadalafil plasma AUC and Cmax increased approximately 2-fold	Tadalafil dose should be reduced to avoid high exposure
TDE-PH-110/ Fluconazole	Probe CYP2C9 inhibitor that may inhibit tadalafil metabolism	Tadalafil AUC decreased by approximately 14 % No effect on Cmax	No adjustment needed for either compound

## 2.5 What are the biopharmaceutical characteristics of treprostinil solution for inhalation?

Tyvaso, Treprostinil for inhalation, 0.6 mg/mL, is a solution dosage form for inhalation that is administered by a portable ultrasonic nebulizer. The sodium salt of treprostinil, the active ingredient, is formed during the solution formulation of the drug product. Treprostinil for inhalation is packaged into ampoules with nominal fill volumes of 2.9 mL. The filled ampoules are further packaged into foil pouches with four ampoules per pouch.

b(4)

The components of treprostinil for inhalation, 0.6 mg/mL, along with the quality standard, function and amount of each component per mL and per ampoule are provided in the following table.

**Table 8: Composition of treprostinil for inhalation, 0.6 mg/mL**

Component	Quality Standard	Function	Amount	
			Per mL	Per Ampoule
Treprostinil	In-house standard	Drug substance	0.6 mg*	1.74 mg*
Sodium Chloride	USP, EP, JP	b(4)		18.9 mg
Sodium Citrate (Dihydrate)	USP, EP, JP		18.3 mg	
1N Hydrochloric Acid**	NF, EP, JP		11.7 mg†	
Sodium Hydroxide	NF, EP, JP		0.58 mg	
1N Sodium Hydroxide**	NF, EP, JP		As needed§	
Water for Injection	USP, EP, JP			

\* This is the theoretical weight. The actual weight is adjusted based on a chemical purity factor to account for total volatiles and total related substances.

\*\* HCl, NF, EP, JP, and NaOH, NF, EP, JP, are prepared as 1 N solutions with Water for Injection, USP, EP, JP, for use in formulation.

† An additional quantity may be used to adjust the pH of the product.

§ A quantity may be used to adjust the pH of the product

The described formulation was used in the clinical pharmacology studies as well as the pivotal clinical trial.

## 2.6 What assay was used to measure treprostinil plasma concentrations in clinical pharmacology studies?

A validated LC/MS/MS method was used in the TYVASO development program. The characteristics of the assay were as follows:

- Linear range: 10 – 5000 pg/mL; R > 0.997
- Accuracy (relative error): within 15 %
- Precision (coefficient of variation): within 15 %
- Specificity: chromatograms provided

Overall the assay performance was acceptable.

### **3 Detailed Labeling Recommendations**

The proposed labeling for TYVASO (treprostinil sodium) solution for inhalation is included in Appendix 4.1 . The labeling comments are as follows:

Overall, the labeling proposed by the Applicant is acceptable; the majority of information is obtained from the labeling for NDA 21-272 (Remodulin). There should be minor modifications to the pharmacokinetics section: 1) statements regarding the linear range following inhaled treprostinil administration and 2) general editorial changes to the pharmacokinetic section to make the information clearer.

## 4 Appendices

#### ***4.1 Proposed Labeling***

14 Page(s) Withheld

       Trade Secret / Confidential (b4)

X Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

## ***4.2 Individual Study Reviews***

**4.2.1 An open-label, randomized, three-period crossover comparative pharmacokinetics and steady state absolute bioavailability study of treprostinil sodium for inhalation administration of Remodulin® by continuous infusion to normal healthy volunteers (LRX-TRIUMPH BA.001)**

INVESTIGATOR	Frederick A. Bieberdorf, M.D.
STUDY SITE	
STUDY PERIOD	October 2006

b(4)

**Objectives:**

To compare the pharmacokinetic profiles and assess the absolute systemic bioavailability of treprostinil sodium solution for inhalation to Remodulin administered by continuous intravenous infusion in normal healthy volunteers.

**Study Design**

This was a single-center, open-label, randomized three-period crossover study in normal healthy adult subjects. Eighteen healthy subjects received three separate single-dose administrations of the study drug after a 10-hour overnight fast followed by a standardized low-fat breakfast one hour prior to the beginning of study drug administration. Each drug administration was separated by a washout period of at least seven days. The treprostinil treatments administered were as follows:

- a single 15 ng/kg/min infusion for 60 minutes dose (Treatment A)
- an 18 mcg (3 breaths) inhaled dose (Treatment B)
- a 36 mcg (6 breaths) inhaled dose (Treatment C) in a randomized

Treatments B and C were administered using a Nebu-Tec OPTINEB® nebulizer.

***Inhalation Process***

To begin inhalation of study drug, subjects placed nose clips on their noses. After hearing two short beeps, subjects were instructed to inhale with their mouths off of the mouthpiece. After hearing a long beep, subjects were instructed to exhale with their mouths off the mouthpiece. Next, after hearing one short beep, subjects were instructed to inhale deeply through the mouthpiece (this was the first breath of study drug). Between inhalations, subjects breathed normally for a few seconds with their mouths off of the mouthpiece.

***Reviewer's Comments on the Inhalation Process***

The inhalation process appears complicated and imprecise and appears dependent on a subject's breathing patterns, potentially leading to different doses administered to subjects. Consequently the reliability and, or utility of the administered dose and resulting PK information is unclear, if different doses were administered to individual patients.

It should be noted that CDRH has been consulted on the acceptability of the inhaler. Furthermore, the Review team is concerned about the reliability of the inhaler.

**Pharmacokinetic sampling times**

Blood samples (7 mL each) were collected for pharmacokinetic analysis during each dosing period by venipuncture from each subject. In each dosing period where inhaled treprostinil was administered, blood samples were collected prior to study drug administration and at 5, 10, 15, 30,

60, and 90 minutes and 2, 3, 4, 5, 6, and 8 hours after study drug administration. In the dosing periods where Remodulin was administered via IV infusion, samples were collected at predose, 0.25, 0.5, and 1.0 hr after the start of the infusion, and post infusion at 5, 10, and 15 minutes and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours.

### Formulation

- Treatment A: Remodulin® (treprostinil sodium) Injection; United Therapeutics Corp. Lot No. 904290.
- Treatment B: treprostinil sodium solution for inhalation (0.6 mg/mL in 3 mL ampoules) using a Nebu-Tec OPTINEB® by Lung Rx, Inc. Lot No. 02704D
- Treatment C: treprostinil sodium solution for inhalation (0.6 mg/mL in 3 mL ampoules) using a Nebu-Tec OPTINEB® Lung Rx, Inc. Lot No. 02704D

### Bioanalytical methods

Treprostinil (UT-15) concentrations were determined using a validated LC-API<sup>#</sup>/MS/MS method (<sup>#</sup> atmospheric pressure ionization). The assay performance was acceptable as illustrated in the following table.

**Table 9: Performance of treprostinil assay<sup>^</sup> in absolute bioavailability study**

Parameter	Measure	Reviewer Comment
	<i>Treprostinil Assay</i>	
Linearity	The assay was linear over the 0.01 to 10.0 ng/mL range; R <sup>2</sup> > 0.993	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were within 10 % of nominal concentration	Satisfactory
LLOQ	0.01 ng/ml	Satisfactory
Specificity*	Chromatograms were not provided, but sponsor indicates that they are available upon request.	Could not be assessed

\*The validation report for the assay included chromatograms that suggest the assay was specific analyzed plasma samples for treprostinil.

b(4)

#### *Reviewer's Note on Location of Assay Information:*

The bioanalytical report was not included in the body of the study report, but it was provided in a separate document and section: Reports of Biopharmaceutic Studies. The sponsor should be advised to include the bioanalytical reports in the appropriate section (for future submissions). Note that this incorrect placement occurred throughout the dossier.

### Pharmacokinetics

The following treprostinil pharmacokinetic measures were determined after each treatment: T<sub>max</sub>, C<sub>max</sub>, AUC<sub>last</sub>, AUC<sub>inf</sub>, AUC<sub>extrap</sub>, λ<sub>z</sub>, T<sub>1/2</sub>, T<sub>last</sub>, C<sub>last</sub>, MRT, V<sub>z</sub> (after IV administration), V<sub>z</sub>/F (after inhalation), V<sub>ss</sub> (after IV administration), CL (after IV administration), CL/F (after inhalation), and absolute bioavailability (AbsF).

### Statistical methods

Concentration-time data and pharmacokinetic parameters were summarized by treatment using descriptive statistics. The Abs F values were analyzed for differences between treatments (Treatment B vs. Treatment C) using an ANOVA model with factors for sequence, subject within

sequence, period, and treatment: The 90% confidence interval for the ratio of the geometric means of the two treatments (B vs. C) was calculated.

**Reviewer's Note on Relative BA comparison:**

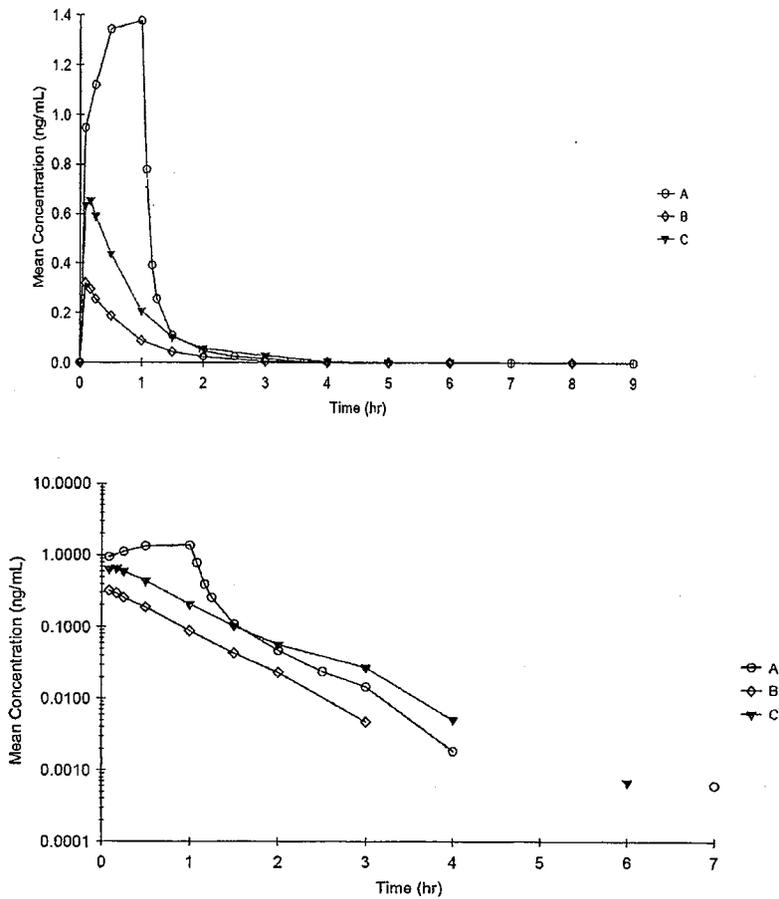
The report includes data for a comparison of C to B, rather than B to C, stated in the statistical methods.

**Results**

Treprostinil Pharmacokinetics

The mean treprostinil plasma concentration-time profiles are shown in the following figure.

**Figure 4: Mean treprostinil plasma concentration-time profile following IV administration and inhalation ----- Remodulin IV (Treatment A), 3 Breaths Inhaled Treprostinil (Treatment B), and 6 Breaths Inhaled Treprostinil (Treatment C) Linear (upper panel) and Semi-Logarithmic Scales (lower panel)**



Treprostinil PK measures following the three treatments are presented in the following table.

**Table 10: Treprostinil PK measures for the three treatments**

Parameter	<b>Treatment A: Remodulin IV</b>				<b>Treatment B: 3 Breaths Inhaled Treprostinil</b>				<b>Treatment C: 6 Breaths Inhaled Treprostinil</b>			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T <sub>max</sub> (hr)	18	0.81	0.26	31.50	18	0.15	0.11	70.61	18	0.15	0.07	46.77
C <sub>max</sub> (ng/mL)	18	1.46	0.284	19.38	18	0.354	0.137	38.76	18	0.698	0.141	20.19
AUC <sub>last</sub> (hr*ng/mL)	18	1.411	0.2336	16.55	18	0.2432	0.08149	33.50	18	0.5896	0.1769	30.01
AUC <sub>inf</sub> (hr*ng/mL)	18	1.427	0.2367	16.59	18	0.2556	0.08430	32.98	18	0.6115	0.1751	28.64
AUC <sub>Extrap</sub> (%)	18	1.07	0.37	34.99	18	5.27	2.35	44.60	18	3.85	2.55	66.14
λ <sub>z</sub> (hr <sup>-1</sup> )	18	1.1472	0.3132	27.30	18	1.3927	0.3597	25.83	18	1.0068	0.2426	24.10
T <sub>1/2</sub> (hr)	18	0.70	0.43	61.41	18	0.53	0.14	26.87	18	0.76	0.34	44.84
T <sub>last</sub> (hr)	18	3.19	1.00	31.37	18	2.28	0.57	25.22	18	3.44	0.78	22.76
C <sub>last</sub> (ng/mL)	18	0.0159	0.00458	28.83	18	0.0163	0.00543	33.43	18	0.0206	0.0125	60.67
MRT (hr)	18	0.28	0.09	33.7	18	0.74	0.18	23.93	18	0.90	0.21	23.20
V <sub>z</sub> (L/kg)	18	0.6320	0.2965	46.91								
V <sub>z</sub> /F (L)					18	62.86	37.69	59.96	18	67.69	28.73	42.44
V <sub>ss</sub> (L/kg)	18	0.1788	0.04926	27.55								
CL (L/hr/kg)	18	0.6504	0.1269	19.51								
CL/F (L/hr)					18	92.44	89.91	97.26	18	63.06	16.14	25.59

The absolute bioavailability estimations are tabulated below.

**Table 11: Statistical Analysis in treprostinil absolute BA study**

Bioavailability	F (%) for Treatment B; n = 18	F(%) for Treatment C; n = 18
Mean (CV %)	61.52 (29.68)	74.05 (21.23)
Median (Range)	60.84 (13.08 – 90.69)	70.27 (52.36 – 115.99)

According to the report two subjects had values that could be considered “outliers”; these values are reflected in the table above (13.08 – lowest value and 115.99 – highest value, respectively). Consequently, the sponsor repeated the analysis eliminating the two outlier values, but not all the data from the two patients. This approach is not robust (selective deletion) as it may introduce bias; each patient is to serve as a control in a crossover study. Statistically, removal of data obtained from the two patients renders the treatments equivalent in terms of relative BA (see table below), but inequivalent if all data are removed. One would expect the Absolute BA to be comparable for the same route of administration if PK are linear.

**Table 4: Analysis of Variance Comparing Systemic Bioavailability (Abs F) of Treprostinil for**

Population	Ratio (C/B)	90% Confidence Interval	
	(%)	Lower	Upper
n = 18	120.36	104.75	135.97
n = 16*	109.90	97.42	122.38

\* Subjects 102 and 114 had anomalous Abs F values and were excluded as potential outliers during statistical analysis

#### **IV Data: Cross Study Comparison of IV data (half-life)**

The IV T1/2 estimate obtained in this study (< 1 hr) was significantly shorter than in previous IV studies (~ 4 hr\*). Per report, the decreased half-life may not be representative of the actual terminal T1/2 of treprostinil; suggesting that the observed T1/2 in the current study was influenced by the distribution phase or treprostinil after IV administration. This explanation appears reasonable as the sampling for the IV treatment did not cover three-to-four half-lives that are needed for reliable half-life estimates.

\* reported T1/2 is 4.41 hr (Laliberte et al., J Cardiovasc Pharmacol Volume 44, Number 2, 2004),

#### **Applicant's Safety Summary**

A total of 53 treatment emergent adverse events (AEs) were reported over the course of the study. All of the 53 AEs were mild. Nineteen of the AEs were possibly associated, 27 of the AEs were reasonably attributable, and 7 were unrelated to the study treatment. The most commonly reported AEs were cough (n=21; 9 following Treatment B and 12 following Treatment C) and headache (n=3; 2 following Treatment B and 1 following treatment A).

#### **Conclusions**

- Inhalation
  - After inhalation of 18 µg (3 breaths) and 36 µg (6 breaths) doses, peak and overall exposure to treprostinil, based on Cmax and AUCinf, respectively, increase proportional to dose.
  - Mean estimates (n = 18) of the absolute systemic bioavailability of treprostinil after inhalation average 62 % (18 µg, 3 breaths) to 74 % (36 µg, 6 breaths).
  - The following mean PK measures were estimated for both doses: Tmax = 0.15 hr; T1/2 ~ 0.6 hr; Vz/F ~ 64 L; CL/F ~ 77 L/hr

- IV Data

Based on the pharmacokinetic results of this study, the following mean PK measures were estimated: CL = 0.6504 ± 0.1269 L/hr/kg; Vz = 0.6320 ± 0.2965 L/kg; Vss 0.1788 ± 0.04926 L/kg

**4.2.2 A randomized, double-blind, placebo-controlled, single dose, phase 1 dose-escalating study to determine the maximum tolerated dose of inhaled treprostinil sodium in healthy volunteers (RIN-PH-102)**

INVESTIGATOR	Craig R. Sprenger, M.D.
STUDY SITE	
STUDY PERIOD	September to October 2007

b(4)

**Objectives:**

- To determine the maximum tolerated dose of inhaled treprostinil sodium
- To determine the safety, tolerability, and pharmacokinetics (PK) of escalating doses of inhaled treprostinil sodium in healthy subjects. The maximum tolerated dose defined will be used in the thorough QT study
- To determine the PK profile of inhaled treprostinil sodium in healthy volunteers, as well as, to assess the dose-proportionality of the parameters  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ .

**Study Design**

This was a randomized, double-blind, placebo-controlled, single dose and escalating-dose study in 40 healthy volunteers. Treprostinil sodium or placebo (randomized 3:1) was delivered via nebulization in the morning using a Nebu-Tec OPTINEB® nebulizer. The doses administered were; 54 (Cohort 1), 72 (Cohort 2), 78 (Cohort 4), 84 (Cohort 5), and 90 (Cohort 3) µg or mcg.

***Interim Analysis (According to Sponsor Report)***

After a review of the safety information from Cohort 3, the 90 mcg dose was determined to be intolerable and, thus, dose escalation did not continue above 90 mcg. In order to determine the maximum tolerated dose (MTD) for inhaled treprostinil sodium in healthy volunteers, Cohort 4 received a 78 mcg dose and, provided the administration of study drug in Cohort 4 was tolerated, Cohort 5 was scheduled to receive an 84 mcg dose.

***Doses Administered: Reported vs. Corrected (Actual)***

Based upon documentation provided by the sponsor after the study was completed, the dose per inhalation was calculated at a rate of 6 mcg per breath, rather than 5 mcg per breath as described in the protocol.

***Reviewer's Note on Dose Administered***

Controversy remains as to what dose is actually delivered in each inhalation; there is uncertainty as to the how consistent the delivery is via the nebulizer. For this PK study the corrected dose will be used; however, this reviewer still is unclear about the reliability of the reported dose.

**Pharmacokinetic blood sampling times**

Blood samples were collected within one hour prior to dosing (0 hour), at the end of the dose administration interval, and at 0.083, 0.167, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours following the dose for each subject.

## Formulation

- **Test Product:** Treprostinil Sodium for Inhalation via Nebulizer; Lot #: 03306C; Expiration Date: 10/30/09; Sponsor: United Therapeutics Corp
- **Placebo Product:** Placebo for Treprostinil Sodium for Inhalation via Nebulizer; Lot #: 00607A; Sponsor: United Therapeutics Corp

## Bioanalytical methods

Treprostinil (UT-15) concentrations were determined using a validated LC-API<sup>#</sup>/MS/MS method (<sup>#</sup> atmospheric pressure ionization). The assay performance was acceptable as illustrated in the following table. . . . . analyzed plasma samples for treprostinil.

b(4)

Table 12: Performance\* of treprostinil assay

Parameter	Measure	Reviewer Comment
	<i>Treprostinil Assay</i>	
Linearity	The assay was linear over the 10 to 5120 pg/mL range; R > 0.999	Satisfactory
Between day Precision	CV was < 11 %	Satisfactory
Accuracy	QC samples were between 1 and 9 % of nominal concentration	Satisfactory
LLOQ	10 pg/ml	Satisfactory
Specificity	Chromatograms were provided and demonstrated specificity	Satisfactory

\*The plasma samples were analyzed

b(4)

## Pharmacokinetics

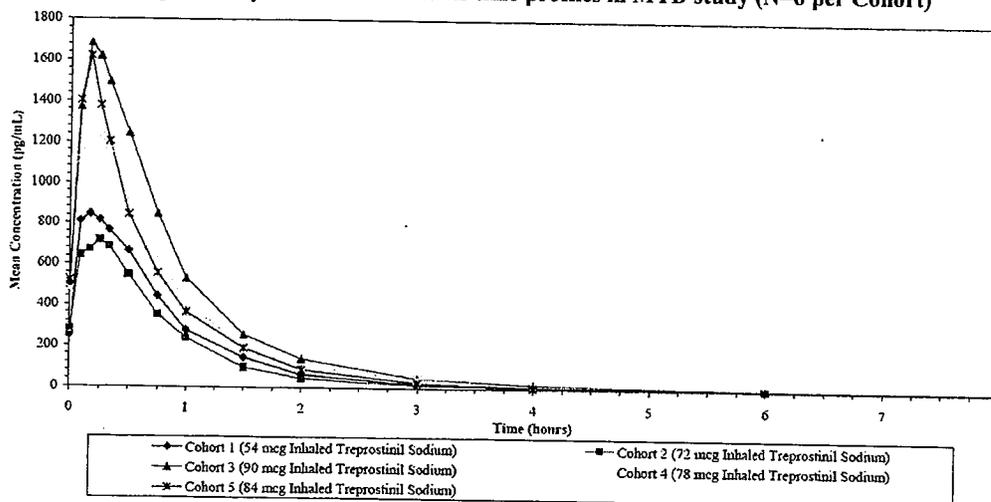
The following treprostinil pharmacokinetic measures were determined after each treatment: AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, λ<sub>z</sub>, t<sub>1/2</sub>, CL/F, and V<sub>d</sub>/F. Natural logarithmic (ln) transformations were computed for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub>. In addition, a dose proportionality analysis was performed on AUC<sub>0-∞</sub>, AUC<sub>0-t</sub>, and C<sub>max</sub> using SAS<sup>®</sup> software. ANOVA was used to evaluate the pharmacokinetic parameters for differences due to treatments, period, dosing sequence, and subjects within sequence.

## Results

### Treprostinil Pharmacokinetics

The mean treprostinil plasma concentration-time profiles are shown in the following figure.

Figure 5: Mean treprostinil plasma concentration-time profiles in MTD study (N=6 per Cohort)



Inspection of the plasma concentration-time profiles suggests that plasma exposure does not systemically increase with dose; this deviation is most pronounced for the 72  $\mu\text{g}$  cohort that had lower exposure than the 54  $\mu\text{g}$  cohort. This anomaly may be explained by two subjects in the 72 mcg cohort with unusually low concentrations of treprostinil. The lower concentrations may be due to a number of factors including poor technique in the use of the nebulizer for administration of treprostinil. It is unclear if one can determine which subjects will have low treprostinil exposure after inhalation.

Treprostinil PK measures following inhalation of various doses are summarized in the following table.

Table 13: Treprostinil PK measures in MTD study

The following table is a summary of the pharmacokinetics of inhaled treprostinil sodium.

PK Measure	Treprostinil Inhaled Doses				
	54	72	78	84	90
AUC (ng.hr/mL)	0.812 (58.13)	0.661 (67.27)	1.206 (44.29)	1.182 (20.20)	1.579 (51.72)
Cmax (ng/mL)	914.67 (59.64)	789.67 (60.76)	1284.00 (44.56)	1582.17 (52.89)	1708.33 (61.77)
Tmax* (hr)	0.25 (0.15)	0.18 (0.11)	0.18 (0.06)	0.19 (0.11)	0.21 (0.05)
T1/2 (hr)	0.55 (0.18)	0.46 (0.08)	0.58 (0.15)	0.54 (0.14)	0.57 (0.11)
CL/F (L/hr/kg)	1.45 (1.4)	3.37 (3.53)	1.19 (0.75)	1.01 (0.27)	1.41 (1.87)
VZ/F (L/kg)	1.00 (0.78)	2.20 (2.38)	0.95 (0.63)	0.78 (0.28)	1.00 (1.05)

\* reported as mean by applicant- typically tmax measure of central tendency is best reflected by median value

The data indicate that plasma concentrations and subsequent PK measures exhibited high inter-patient variability (CV > 50 %) at each given dose level. The source of the variability is not clear, but is likely associated with the uncertainty of the administered dose. The inhaled dose appears to

be highly correlated with a patient's breathing pattern. In each cohort there were significant differences among patients:

- AUC: at 54 µg- range from 150 to 1400 units; at 90 µg- range 247 to 2400 units
- C<sub>max</sub>: at 54 µg- range from 170 to 1600 units; at 90 µg- range 62 to 2900 units

It should be noted that CL and V<sub>z</sub> estimates were normalized by body weight; the basis for this normalization is not clear as the dosing of inhaled treprostinil will not be weight dependent.

#### ***Dose Proportionality***

The p-values for the ln-transformed AUC<sub>0-∞</sub>, AUC<sub>0-t</sub>, and C<sub>max</sub> were 0.1589, 0.1735, and 0.1531 respectively. These p-values suggest that there is no significant deviation from dose proportionality as differences were declared statistically significant at the 5% level (per protocol). However, a limitation of the data is that the doses cover a fairly narrow dose range (~ 2-fold).

#### **Applicant's Safety Summary**

All adverse events (AEs) were mild to moderate in severity and resolved by the end of the study. There were no deaths or serious adverse events in the study. Eighteen (18) subjects experienced a total of 48 AEs over the course of the study. Among these subjects, 16 (53.3%) who received inhaled treprostinil sodium and 2 (20.0%) who received placebo reported experiencing at least one AE over the course of the study. AEs were reported across all cohorts. There were no clinically significant treatment-emergent changes in vital signs, laboratory parameters or ECG results following dosing in any treatment cohort. Across all five cohorts, the most commonly reported AE was dizziness which was reported by 1/6 (16.7%) subjects in Cohort 1, 2/6 (33.3%) subjects in Cohort 3, and 2/6 (33.3%) subjects in Cohort 5. Dizziness was not reported by subjects in either Cohort 2 or Cohort 4. Adverse events occurring in the 90 mcg cohort (chest pain, chest discomfort, nausea, vomiting) were determined to be intolerable thus prohibiting dose escalation above 90 mcg. Therefore, the maximum tolerated dose for inhaled treprostinil sodium in healthy volunteers was determined to be 84 µg.

#### **Conclusions**

- The following PK measures were estimated for inhaled treprostinil over the 54 to 90 µg range (excluding 72 µg): CL/F = 1.01 to 1.45 L/hr/kg; V<sub>z</sub>/F = 0.78 – 1.00 L/kg; T<sub>1/2</sub> = 0.46 – 0.58 hr; T<sub>max</sub> 0.18 – 0.25.
- Overall, treprostinil PK appear linear over the evaluated dose range, exhibiting dose-proportional increases in exposure.
- There was high intersubject variability in AUC and C<sub>max</sub> values suggesting that differing dosages were delivered to subjects

**4.2.3 A double blind randomized parallel group trial to define the ECG effects of inhaled treprostinil sodium using a clinical and suprathreshold dose compared to placebo and moxifloxacin (a positive control) in healthy men and women: A thorough ECG trial (RIN-PH-103)**

INVESTIGATOR	Craig R. Sprenger, M.D.
STUDY SITE	
STUDY PERIOD	February – March 2008

b(4)

**Objectives:**

To determine whether inhaled treprostinil sodium had any effect on electrocardiogram (ECG) parameters with specific focus on cardiac repolarization as determined by the individually corrected QTc duration (QTcI).

**Reviewer's Note**

This review focuses on the PK data; the effects of QT prolongation were reviewed by the QT group within CDER.

**Study Design**

This was a randomized, double-blind, and 4-arm parallel design study. Two hundred forty-one healthy subjects (one group of 61 subjects and three groups of 60 subjects; males: females approximately 1:1) were randomized in this trial to receive one of the following four treatment regimens\* on Day 1:

- **Treatment A:** Subjects received placebo for inhaled treprostinil sodium delivered as 14 pulses (14 breaths) plus moxifloxacin placebo.
- **Treatment B:** Subjects received placebo for inhaled treprostinil sodium delivered as 14 pulses (14 breaths) plus moxifloxacin 400 mg tablet
- **Treatment C:** Subjects received inhaled treprostinil sodium 54 mcg delivered as 9 pulses (9 breaths) plus moxifloxacin placebo.
- **Treatment D:** Subjects received inhaled treprostinil sodium 84 mcg delivered as 14 pulses (14 breaths) plus moxifloxacin placebo.

\* Blinding was maintained in each group by including placebo and over-encapsulated moxifloxacin, as needed.

Placebo and inhaled treprostinil sodium were delivered by nebulization using Nebu-Tec OPTINEB® nebulizers. No food was administered for at least 8 hours prior to dosing through at least 4 hours after dosing.

**Dose Delivered**

The report states that the sponsor provided documentation during the study that indicated the dose per inhalation was calculated at a rate of 6 mcg per breath, rather than 5 mcg per breath as described in the protocol.

**Subject Disposition**

Of the 241 normal healthy subjects who participated in the study, 240 completed the study as planned. Subject 207 was discontinued due to a dosing error (prior to Day 1, study hour 6 activities) and was replaced by Subject 707.

## Pharmacokinetic sampling times

Blood for pharmacokinetic sampling was obtained from all subjects on Day 1 of this trial. The pharmacokinetic sampling time points on Day 1 were: pre-dose (0 hour), and at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 23.5 hours from the initiation of dose administration. Blood sample collection occurred following ECG measurements.

## Formulation

The formulation details are summarized in the following table.

**Table 14: identity of products (formulations) in QT Study**

Treatment A Products:	Treatment B Products:
Placebo for Overencapsulated AVELOX® (moxifloxacin hydrochloride) Lot #: 08A0002K Expiration Date: 03-2010 Sponsor: United Therapeutics Corp <i>and</i> Placebo for Treprostinil Sodium for Inhalation via Nebulizer Lot #: 00607A Expiration Date: 10-30-09 Sponsor: United Therapeutics Corp	Overencapsulated AVELOX® (moxifloxacin hydrochloride) 400 mg Lot #: 08A0001K Expiration Date: 03-2010 Sponsor: United Therapeutics Corp <i>and</i> Placebo for Treprostinil Sodium for Inhalation via Nebulizer Lot #: 00607A Expiration Date: 10-30-09 Sponsor: United Therapeutics Corp
Treatment C Products:	Treatment D Products:
Placebo for Overencapsulated AVELOX® (moxifloxacin hydrochloride) Lot #: 08A0002K Expiration Date: 03-2010 Sponsor: United Therapeutics Corp <i>and</i> Treprostinil Sodium for Inhalation via Nebulizer Lot #: 03306C Expiration Date: 10/30/09 Sponsor: United Therapeutics Corp	Placebo for Overencapsulated AVELOX® (moxifloxacin hydrochloride) Lot #: 08A0002K Expiration Date: 03-2010 Sponsor: United Therapeutics Corp <i>and</i> Treprostinil Sodium for Inhalation via Nebulizer Lot #: 03306C Expiration Date: 10/30/09 Sponsor: United Therapeutics Corp

## Bioanalytical methods

Treprostinil (UT-15) concentrations were determined using a validated LC/MS/MS method. The assay performance was acceptable as illustrated in the following table.

Job Number: 171920 (Lots: 001, 004, 006 – 009 and 012) conducted the analysis for this study.

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**Table 15: Performance of treprostinil assay in QT study**

Parameter	Measure	Reviewer Comment
	<i>Treprostinil Assay</i>	
Linearity	The assay was linear over the 10 to 5120 ng/mL range; $R^2 > 0.997$	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were between 4 and 8 % of nominal concentration	Satisfactory
LLOQ	ng/ml	Satisfactory
Specificity	Representative chromatograms were provided and demonstrated assay was specific	Satisfactory

\*The validation report for the assay included chromatograms that suggest the assay was specific

**Reviewer's Note:**

The bioanalytical report was provided in separate document (not in body of report) in Appendix 16.5 (summary of Bioanalytical reports).

**Pharmacokinetics**

The analytical data were used to calculate the following pharmacokinetic parameters:  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $T_{max}$ ,  $\lambda_z$ ,  $t_{1/2}$ ,  $CL/F$ , and  $V/F$ . Natural logarithmic (ln) transformations were computed for  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$ .

**Statistical Analysis**

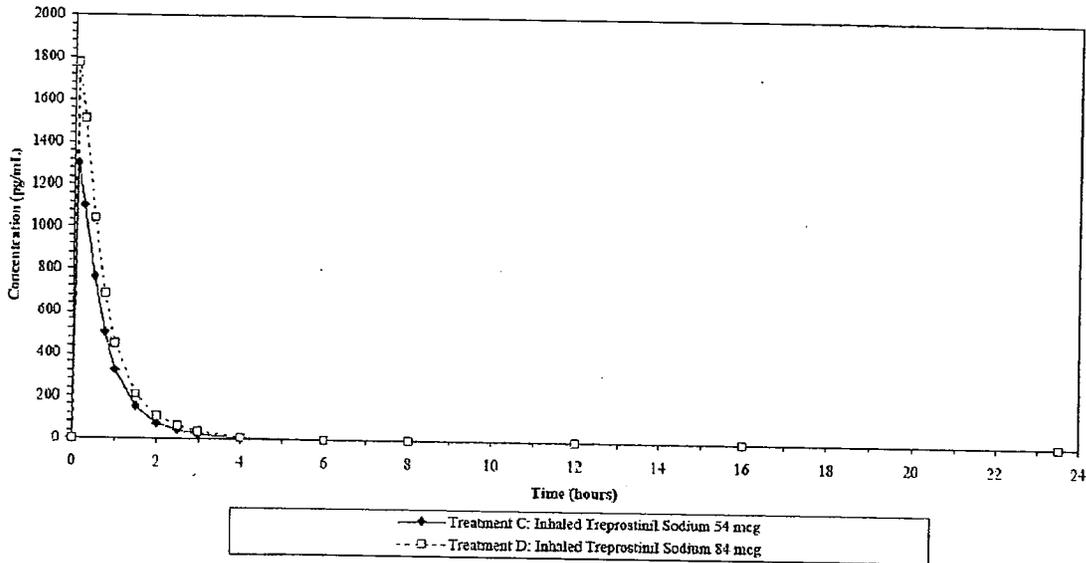
The lower limit of quantitation for treprostinil was 10.0 pg/mL. For statistical analysis, subject samples with values below the lower limit of quantitation (BLQ) were reported as zero. Plasma concentration data from all 60 subjects who were assigned Treatment C (Inhaled treprostinil sodium 54 mcg) and from all 60 subjects who were assigned Treatment D (Inhaled treprostinil sodium 84 mcg) were used in the statistical analysis.

## Results

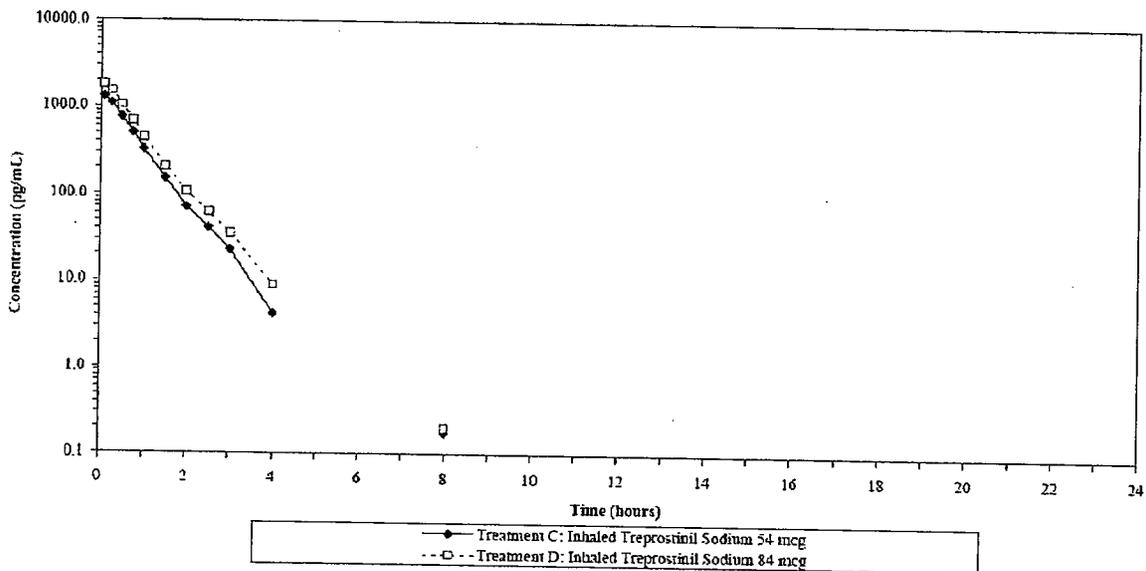
### Treprostinil Pharmacokinetics

The mean treprostinil plasma concentration-time profiles for subjects receiving treprostinil are depicted in the following figure (upper panel on Cartesian scale and lower on semi-log scale).

Figure 6: Mean Plasma Concentration on Linear Scale (Treatment C: N=60; Treatment D: N=60)



Mean Plasma Concentration on semi-logarithmic scale (Treatment C: N=60; Treatment D: N=60)



Treprostinil concentrations were detected in 59 out of 60 subjects in the 54 mcg group and all subjects in the 84 mcg group. One subject in the 54 mcg group had undetectable concentrations

of treprostinil for all samples collected with no known explanation.

The treprostinil PK measures in the QT study are summarized in the following table.

**Table 16: Treprostinil PK measures in QT study Arithmetic mean  $\pm$  SD**

PK Parameter	Treatment C: Inhaled Treprostinil Sodium 54 mcg	Treatment D: Inhaled Treprostinil Sodium 84 mcg
AUC <sub>0-t</sub> (hr*pg/mL)	974.67 ( $\pm$ 280.53)	1352.21 ( $\pm$ 356.05)
AUC <sub>0-∞</sub> (hr*pg/mL)	1005.14 ( $\pm$ 253.48)	1368.03 ( $\pm$ 357.44)
C <sub>max</sub> (pg/mL)	1315.83 ( $\pm$ 430.44)	1795.92 ( $\pm$ 634.55)
T <sub>max</sub> (hr)	0.12 ( $\pm$ 0.07)	0.12 ( $\pm$ 0.08)
$\lambda_z$ (1/hr)	1.3477 ( $\pm$ 0.26)	1.2352 ( $\pm$ 0.30)
t <sub>1/2</sub> (hr)	0.54 ( $\pm$ 0.13)	0.62 ( $\pm$ 0.30)
V/F (L)	45.37 ( $\pm$ 21.13)	58.86 ( $\pm$ 32.53)
CL/F (L/hr)	60.30 ( $\pm$ 37.34)	67.93 ( $\pm$ 29.09)

### Applicant's Safety Summary

Eighty-two (82) subjects experienced a total of 131 adverse events (AEs) over the course of the study. Following Treatment A, four subjects (6.6%) reported experiencing at least one AE; following Treatment B, 12 subjects (20.0%) reported experiencing at least one AE; following Treatment C, 31 subjects (51.7%) reported experiencing at least one AE; and following Treatment D, 34 subjects (56.7%) reported experiencing at least one AE. Adverse events were mild to moderate in intensity and reported across all cohorts.

### Conclusions

Pharmacokinetic data collected in this study were generally consistent with previous studies where doses of 54 and 84 mcg of inhaled treprostinil sodium have been administered in healthy volunteers.

**4.2.4 Effect of an evaluation of the steady state pharmacokinetics of UT-15C SR (treprostinil diethanolamine) with Tracleer® (bosentan) following oral co-administration in healthy adult volunteers (TDE-PH-105)**

INVESTIGATOR	David D. Hoelscher, MD
STUDY SITE	
STUDY PERIOD	13 January 2006 - 08 February 2006

b(4)

**Objectives:**

- To determine the steady-state pharmacokinetics of treprostinil (UT-15C SR) when treprostinil is administered concurrently with Tracleer® for 4.5 days, as compared to the steady-state pharmacokinetics of treprostinil when UT-15C SR is given alone.
- To assess the safety of UT-15C SR and Tracleer® when administered concurrently for 4.5 days, compared to the safety of each agent given alone for 4.5 days.

**Sponsor's Note**

The sponsor indicates that although not a primary objective at the time of the protocol's finalization, the steady-state pharmacokinetics of bosentan and its primary metabolite Ro 48-5033 were estimated in this study due to the subsequent availability of bioanalytical assays.

**Reviewer's Note: Purpose of drug interaction studies**

The drug interaction studies were conducted with oral treprostinil and concomitant medications to evaluate a worst-case scenario for inhaled treprostinil. In general, following administration of inhaled treprostinil, fewer interactions are likely to occur than with oral administration; as inhaled treprostinil is not subject to as high a degree of presystemic metabolism or gut-related interactions. Overall, the drug-drug interaction findings from the oral administration route may not be clinically relevant for inhaled treprostinil, but they will provide qualitative information.

**Study Design**

This was an open-label, three-period, and three-sequence crossover study in which healthy adult male and female subjects were randomly allocated to one of three sequences of the following three treatments:

- Treatment A: UT-15C (treprostinil diethanolamine), 1 mg\* BID SR tablets alone for 4.5 days;
- Treatment B: Tracleer® alone, 125 mg QD for 4.5 days,
- Treatment C: combination of UT-15C SR and Tracleer® for 4.5 days (dosed as above).

\* 1 mg of treprostinil (free acid)

Each treatment was separated by a 5-day washout period. Subjects received all doses with water following a standard breakfast and dinner. Twenty-four healthy adult volunteers were enrolled in the study and 22 subjects completed the study in its entirety.

**Blood (Pharmacokinetic) sampling times**

Blood (PK) samples were collected at the following times on Days 5 (Treatment 1), 15 (Treatment 2) and Day 25 (Treatment 3): 0 hour (prior to last morning dose of study drug) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hrs post- dose.

## Formulation

- UT-15C SR 1 mg tablets were manufactured by Shire Laboratories (now Supernus). Product batch # B05042. Each UT-15C SR tablet contained 1.27 mg of treprostinil diethanolamine salt, equivalent to 1 mg of the free acid of treprostinil.
- Tracleer® (bosentan) was supplied as tablets containing 125 mg bosentan and was provided to the CRU directly from Actelion Pharmaceuticals as commercially packaged product. Batch Lot # BP054P0101.

## Bioanalytical methods

The concentrations of bosentan and its metabolites, Ro 48-5033, Ro 47-8634, and Ro 64-1056, were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in the following table.

**Table 17: Bosentan\* assay performance**

Parameter	Bosentan			Reviewer Comment
Linearity	The assay was linear over the to 1 to 4000 ng/mL range; R > 0.9942			Satisfactory
Between day Precision	CV was < 8.2 %			Satisfactory
Accuracy	QC samples were between -2 and +7 % of nominal concentration			Satisfactory
LLOQ	1.0 ng/mL			Satisfactory
Specificity	Chromatograms were provided that demonstrated specificity			Satisfactory
	Bosentan Metabolites			
	Ro 48-5033	Ro 47-8634	Ro 64-1056	
Linearity (range of assay 2 to 512 ng/mL)	R > 0.9967	0.9959	0.9947	Satisfactory
Between day Precision	CV < 5.3 %	CV < 4.2 %	CV < 4.0 %	Satisfactory
Accuracy QC samples were with range of nominal concentration	-3 to +5 %	-4 to +6	-9 to +7	Satisfactory
LLOQ (all metabolites)	2.0 ng/mL			Satisfactory
Specificity	Chromatograms were provided that demonstrated specificity			Satisfactory

\* Bosentan assay conducted by \_\_\_\_\_

Treprostinil concentrations were determined using a validated LC-MS/MS method (\_\_\_\_\_\_). The treprostinil assay performance was acceptable as illustrated in the following table.

**Table 18: Performance of Treprostinil Assay**

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 10 to 5120 pg/mL range; R > 0.997	Satisfactory
Between day Precision	CV was < 9 %	Satisfactory
Accuracy	QC samples were between -5 and -2 % of nominal concentration	Satisfactory
QC sample concentrations	30, 1920 and 4416 pg/ml	Satisfactory
LLOQ	10 ng/mL	Satisfactory
Specificity	Chromatograms were provided that demonstrated specificity	Satisfactory

## Pharmacokinetics

The pharmacokinetic evaluation included the determination of C<sub>max</sub> of the parent drug (treprostinil or bosentan) or metabolite (Ro 48-5033), corresponding T<sub>max</sub>, T<sub>1/2</sub>, AUC<sub>0-12h</sub>, CL/F, CL/F<sub>m</sub>\*, V<sub>z</sub>/F, and V<sub>z</sub>/F<sub>m</sub>\*, as appropriate.

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\*F<sub>m</sub> is the fraction metabolized

### **Statistical methods**

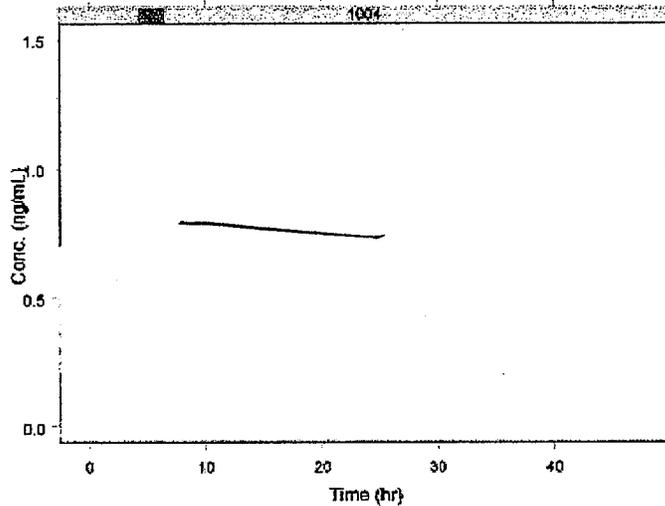
The existence of drug-drug interactions was evaluated by standard pharmaco-statistical methods. The effect of co-administration of Tracleer® on treprostinil steady-state pharmacokinetics was determined by ANOVA of logarithmically transformed AUC<sub>0-12h</sub> and C<sub>max</sub> values and computation of the 90% confidence interval around the ratio of the geometric mean results observed after administration in combination and alone. The effect of coadministration of UT-15C SR on bosentan and its major metabolite Ro 48-5033 was determined in the same manner.

## Results

### Treprostinil Pharmacokinetics

Representative treprostinil plasma concentration-time profiles for an individual subject are shown in the following figure (open triangles represent Tracleer alone and open circles represent the combination).

Figure 7: Treprostinil plasma concentration-time profile for Subject 1004



Treprostinil PK measures are summarized in the following table.

Table 19: Treprostinil PK measures in bosentan interaction study

Treprostinil Pharmacokinetic Parameters at Steady State (n = 22)  
Arithmetic Mean (CV)

Parameter	UT-15C SR Alone	UT-15C SR and Tracleer® in Combination
UT-15C SR Dose	1.0 mg bid	1.0 mg bid
$C_{max}$ (ng/mL)	0.790 (33.9%)	0.784 (44.5%)
$T_{max}$ (hr) <sup>†</sup>	3.00	3.00
$AUC_{0-12h}$ (hr*ng/mL)	3.838 (30.4%)	3.559 (32.0%)
CL/F (mL/hr/kg)	3873 (29.6%)	4229 (31.6%)
$V_z/F$ (mL/kg)	107341 (76.3%)	105086 (63.7%)
$T_{1/2}$ (hr)	18.89 (66.6%)	17.39 (54.9%) <sup>□</sup>

<sup>†</sup> median value

<sup>□</sup> It should be noted that Tracleer® dosing was discontinued after the morning dose on the fifth day and the treprostinil  $T_{1/2}$  was determined when plasma bosentan levels had declined to relatively low levels (i.e., no longer at steady state).

The statistical comparisons of exposure are summarized in the following table.

**Table 20: Treprostinil geometric mean ratios and associated 90 % confidence intervals in bosentan interaction study**

Effect of Tracleer® on Treprostinil Pharmacokinetic Parameters at Steady State  
(90% Confidence Intervals)

Treprostinil Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Combination	Alone		
C <sub>max</sub> (ng/mL)	0.722	0.751	0.961	(0.830, 1.112) <sup>†</sup>
AUC <sub>0-12h</sub> (hr*ng/mL)	3.392	3.673	0.923	(0.831, 1.026) <sup>†</sup>

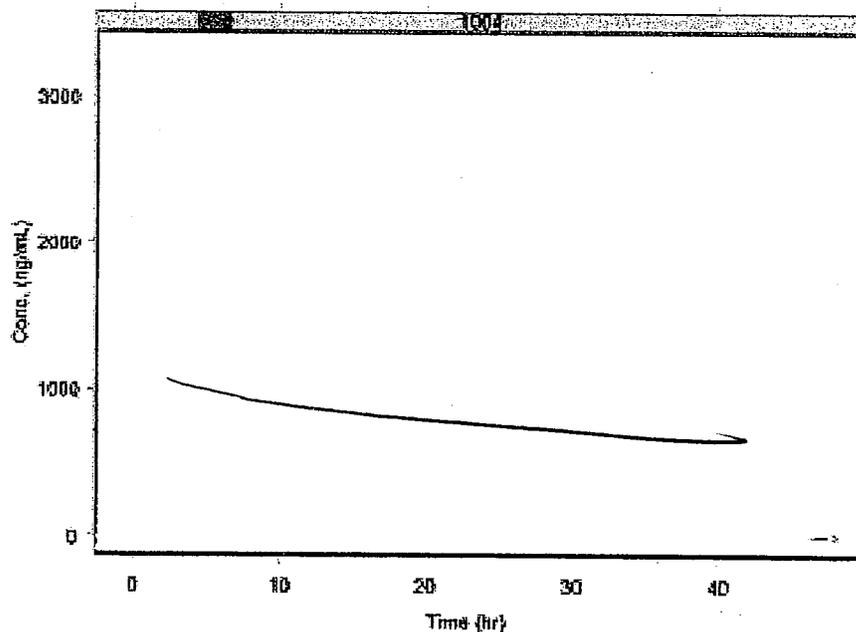
<sup>†</sup> The 90% confidence intervals for the C<sub>max</sub> ratio and AUC<sub>0-12h</sub> ratio fell within the equivalence interval of 0.800 to 1.250.

The data indicate that bosentan does not alter treprostinil exposure.

### Bosentan Pharmacokinetics

Representative bosentan plasma concentration-time profiles for an individual subject in the bosentan drug interaction study are depicted in the following figure (open triangles represent Tracleer alone and open circles represent the combination).

**Figure 8: Bosentan plasma concentration-time profile for Subject 1004**



The bosentan PK measures are summarized in the following table.

**Table 21: Bosentan PK measures in drug interaction study**

Bosentan Pharmacokinetic Parameters at Steady State (n = 23)  
Arithmetic Mean (CV)

Bosentan Parameter	Tracleer® Alone	Tracleer® and UT-15C SR in Combination
Tracleer® Dose	125 mg bid	125 mg bid
C <sub>max</sub> (ng/mL)	1392.7 (33.1%)	1537.6 (50.1%)
T <sub>max</sub> (hr) <sup>†</sup>	3.00	4.00
AUC <sub>0-12h</sub> (hr*ng/mL)	5826.6 (27.9%)	6093.0 (34.7%)
CL/F (L/hr/kg)	23.2 (28.7%)	22.9 (34.1%)
V <sub>z</sub> /F (L)	396 (49.0%)	499 (64.2%)
T <sub>1/2</sub> (hr)	12.35 (54.8%)	14.91 (57.4%) <sup>□</sup>

<sup>†</sup> median value

<sup>□</sup> It should be noted that UT-15C dosing was discontinued after the morning dose on the fifth day and that the bosentan T<sub>1/2</sub> was determined when plasma treprostinil levels had declined to relatively low levels (i.e., no longer at steady state).

The data in the following table indicate that bosentan exposure was not altered by treprostinil coadministration.

**Table 22: Bosentan statistical comparisons in drug interaction study**

Effect of UT-15C SR on Bosentan Pharmacokinetic Parameters at Steady State  
(90% Confidence Intervals)

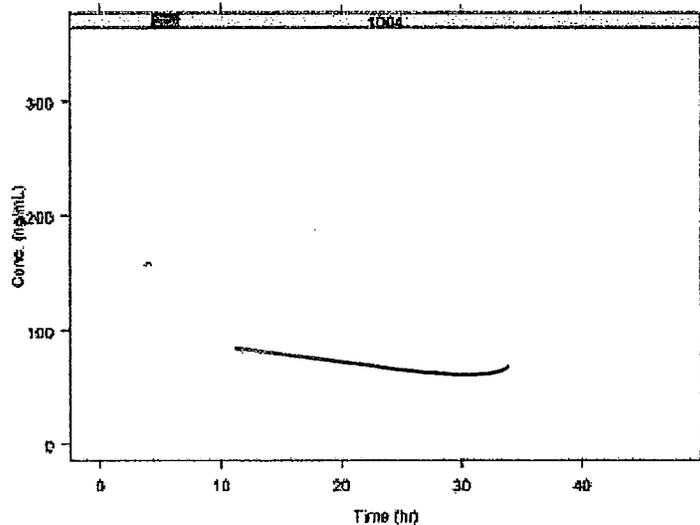
Bosentan Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Combination	Alone		
C <sub>max</sub> (ng/mL)	1384	1327	1.043	(0.942, 1.153) <sup>†</sup>
AUC <sub>0-12h</sub> (hr*ng/mL)	5744	5623	1.021	(0.951, 1.097) <sup>†</sup>

<sup>†</sup> The 90% confidence intervals for the C<sub>max</sub> ratio and AUC<sub>0-12h</sub> ratio fell within the equivalence interval of 0.800 to 1.250.

### Ro 48-5033 Pharmacokinetics

Representative R 48-5033 plasma concentration time profiles for an individual subject in the drug interaction study are depicted in the following figure (open triangles represent Tracleer alone and open circles represent the combination).

Figure 9: Ro 48-5033 plasma concentration-time profile for individual in drug interaction study



Ro 48-5033 PK measures in the study are shown in the following table.

Table 23: Ro 48-5033 PK measures in the drug interaction study

Ro 48-5033 Parameter	Tracleer® Alone	Tracleer® and UT-15C SR in Combination
Tracleer® Dose	125 mg bid	125 mg bid
$C_{max}$ (ng/mL)	138.5 (37.8%)	145.7 (40.1%)
$T_{max}$ (hr) <sup>†</sup>	4.00	4.00
$AUC_{0-12h}$ (hr*ng/mL)	786.8 (30.7%)	798.9 (35.8%)
$CL/F_m$ (L/hr)	176.8 (27.6%)	181.3 (34.6%)
$V_z/F_m$ (L)	3719 (63.7%)	3120 (102.8%)
$T_{1/2}$ (hr)	14.34 (50.8%)	11.25 (67.6%) <sup>□</sup>

<sup>†</sup> median value

<sup>□</sup> It should be noted that UT-15C dosing was discontinued after the morning dose on the fifth day and that the Ro 48-5033  $T_{1/2}$  was determined when plasma treprostinil levels had declined to relatively low levels (i.e., no longer at steady state).

The data in the following table indicate that Ro 48-5033 PK were not altered by treprostinil coadministration.

**Table 24: Ro 48-5033 Geometric mean ratios and associated confidence intervals**

Ro 48-5033 Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Combination	Alone		
C <sub>max</sub> (ng/mL)	134.3	130.6	1.028	(0.935, 1.131) <sup>†</sup>
AUC <sub>0-12h</sub> (hr*ng/mL)	750.1	755.0	0.993	(0.930, 1.062) <sup>†</sup>

<sup>†</sup> The 90% confidence intervals for the C<sub>max</sub> ratio and AUC<sub>0-12h</sub> ratio fell within the equivalence interval of 0.800 to 1.250.

It is noted that there were period effects for C<sub>max</sub> and AUC of Ro 48-5033, but the source of this effect is unclear.

Ro 48-5033 Parameter	p Values <sup>†</sup>	
	Treatment Effect	Period Effect
C <sub>max</sub> (ng/mL)	0.615	0.014 <sup>Δ</sup>
AUC <sub>0-12h</sub> (hr*ng/mL)	0.867	0.019 <sup>Δ</sup>

<sup>†</sup> p < 0.05, statistically significant

<sup>Δ</sup> The contributing factor to this statistically significant period effect is unknown.

### Applicant's Safety Summary

There was a greater overall incidence of treatment-emergent adverse events during the combination treatment of UT-15C and Tracleer® (38 events in 58% of subjects) as compared to both UT-15C alone (8 events in 23% of subjects) and Tracleer® alone (13 events in 30% of subjects). It is doubtful that the slight increase in number of subjects completing the combination therapy contributed greatly to the incidence of events. Additionally, although the overall number of adverse events was greater in the combination arm, it is worth noting that there were a number of events which were reported as a single occurrence. The significance of this is not clear.

Headache, flushing, nausea, and abdominal pain were the most frequently occurring AEs judged as possibly or reasonably attributable to study drug, with headache being the most frequent event reported. All AEs were mild in severity with the exception of two moderate events reported in one subject. Subject 001011, who withdrew consent and was discharged on dosing Day 4, experienced moderate nausea and vomiting during Period 1 while receiving UT-15C and Tracleer® in combination. These events were reported approximately 6 and 50 hours, respectively, following first dosing. The nausea resolved approximately 57 hours following the first dosing; vomiting appeared to last less than one hour. Both events resolved and no treatment was required for these AEs. No events were classified as severe.

### Conclusion

Exposure of bosentan, Ro 48-5033 (bosentan's major circulating metabolite) and treprostinil, respectively, exhibited similar PK during monotherapy and combination therapy over a 4-day period.

### Reviewer's Comment

There is no clinically significant interaction between bosentan and treprostinil, thus the compounds can be concomitantly administered without dose adjustment.

**4.2.5 An Evaluation of the steady state pharmacokinetics of UT-15C SR (Treprostinil Diethanolamine) and Revatio™ (Sildenafil Citrate) following oral co-administration in healthy adult volunteers (TDE-PH-106)**

INVESTIGATOR	David D. Hoelscher, MD
STUDY SITE	
STUDY PERIOD	January 2006 – March 2006

b(4)

**Objectives**

- To determine the steady-state pharmacokinetics of treprostinil (UT-15 C SR) and sildenafil when UT-15C SR is administered concurrently with Revatio™ for 4.5 days, as compared to the steady-state pharmacokinetics of treprostinil and sildenafil when UT-15C SR and Revatio™ are given alone.
- To assess the safety of UT-15C SR and Revatio™ when administered concurrently for 4.5 days compared to the safety of each agent given alone for 4.5 days.
- To characterize the pharmacokinetic profile of the primary metabolite of Revatio™, N-desmethyl-sildenafil, following 4.5 days co-administration of Revatio™ and UT-15C SR

**Study Design**

This was an open-label, three-period, and three-sequence crossover study in which 18 healthy subjects were randomly allocated to one of three sequences of the following three treatments:

- UT-15C SR 1 mg\* twice daily alone for 4.5 days;
- Revatio™ 20 mg three times daily alone for 4.5 days;
- or the combination of UT-15C SR 1 mg\* twice daily and Revatio™ 20 mg three times daily for 4.5 days.

One subject withdrew consent prior to the Period 3, thus 17 subjects completed the study in its entirety.

**Blood (Pharmacokinetic) sampling times**

In each dosing cohort blood samples were collected at pre-dose (prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hours after the administration of study drug.

**Formulation**

- UT-15C SR 1 mg tablets were manufactured by Shire Laboratories (now Supernus); Product Batch # B05043. Each UT-15C SR tablet contained 1.27 mg of treprostinil diethanolamine salt, equivalent to 1 mg of the free acid of treprostinil.
- Revatio™ (sildenafil citrate) was supplied as tablets containing 20 mg sildenafil citrate (Lot # 5108607) and was obtained from a commercial source by the clinical site.

**Pharmacokinetics**

Pharmacokinetic evaluation included the determination of C<sub>max</sub> of the parent drug (treprostinil and sildenafil) or N-desmethyl-sildenafil metabolite, T<sub>max</sub>, T<sub>1/2</sub>, treprostinil AUC<sub>0-12h</sub>, sildenafil and N-desmethyl-sildenafil AUC<sub>0-8h</sub>, CL/F, CL/F<sub>m</sub>, V<sub>z</sub>/F, V<sub>z</sub>/F<sub>m</sub>, as appropriate.

## Statistical methods

The effect of co-administration on steady-state pharmacokinetics of the two study drugs, UT-15C SR and Revatio™, was determined by an analysis of variance (ANOVA) of relevant AUCs and Cmax after logarithmic transformation followed by computation of the 90% confidence intervals of the relevant ratios (single drug administration versus both study drugs in combination). The results were compared to the interval of equivalence (0.800, 1.250) for describing the effect of the drug interaction of Revatio™ on the systemic exposure to tadalafil and of UT-15C SR on the systemic exposure to sildenafil and N-desmethyl-sildenafil. The ANOVA model tested for treatment effect and period effect but not sequence effect or carryover effect because this study used a half-block design.

## Bioanalytical methods

Determinations of individual plasma sample concentrations of tadalafil, sildenafil and N-desmethyl-sildenafil were performed using validated LC-MS/MS bioanalytical methods. The performance of the assays was acceptable as illustrated in the following two tables.

**Table 25: Performance of Tadalafil Assay**

Parameter	Tadalafil	Reviewer Comment
Linearity	The assay was linear over the 10 to 5120 pg/mL range; R > 0.999	Satisfactory
Between day Precision	CV was < 7 %	Satisfactory
Accuracy	QC samples were between -4 and -1 % of nominal concentration	Satisfactory
QC sample concentrations	30, 1920 and 4416 pg/ml	Satisfactory
LLOQ	10 ng/mL	Satisfactory
Specificity	Chromatograms were provided that demonstrated specificity	Satisfactory

**Table 26: Performance of Sildenafil Assay**

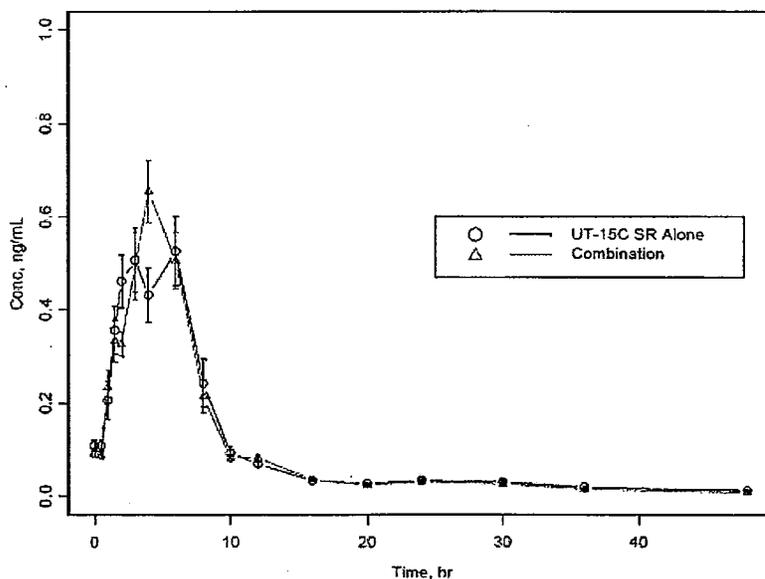
	<i>Sildenafil</i>	
Linearity	The assay was linear over the 1 to 1000 ng/mL range; R > 0.998	Satisfactory
Between day Precision	CV was < 6 %	Satisfactory
Accuracy	QC samples were between -1 and -3 of nominal concentration	Satisfactory
LLOQ	1.0 ng/mL	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory
	<i>Desmethyl-sildenafil</i>	
Linearity	The assay was linear over the 1 to 1000 ng/mL range; R > 0.997	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were between -5 and 1 % of nominal concentration	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

## Results

### Treprostinil Pharmacokinetics

The mean treprostinil plasma concentration-time profiles following administration of treprostinil +/- sildenafil are shown in the following figure.

Figure 10: Mean treprostinil plasma concentration-time profiles in presence or absence of sildenafil



Treprostinil PK measures are presented in the following table.

Table 27: Treprostinil PK measures in the sildenafil interaction study

Treprostinil Parameter (n=17)	UT-15C SR Alone	UT-15C SR and Revatio™ in Combination
UT-15C SR Dose	1.0 mg bid	1.0 mg bid
C <sub>max</sub> (ng/mL)	0.776 (33.2%)	0.756 (38.5%)
T <sub>max</sub> (hr) <sup>†</sup>	3.00	4.00
AUC <sub>0-12h</sub> (hr*ng/mL)	3.663 (36.6%)	3.731 (33.4%)
CL/F (mL/hr/kg)	4230 (39.2%)	4123 (41.8%)
V <sub>z</sub> /F (mL/kg)	128237 (72.7%)	85801 (61.0%)
T <sub>1/2</sub> (hr)	20.83 (52.6%)	15.23 (49.7%)

<sup>†</sup> median value

The reason for the discrepancy between treprostinil C<sub>max</sub> values in the plot for treprostinil alone (Figure 10) vs. that in the PK summary (Table 27) is unclear.

The statistical analysis presented in the table below indicates that sildenafil did not alter treprostinil exposure.

**Table 28: Treprostinil geometric mean ratios and associated 90 % confidence intervals in sildenafil interaction study**

Treprostinil Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Combination	Alone		
C <sub>max</sub> (ng/mL)	0.705	0.725	0.972	(0.824, 1.145) <sup>†</sup>
AUC <sub>0-12h</sub> (hr*ng/mL)	3.509	3.407	1.030	(0.900, 1.179) <sup>†</sup>

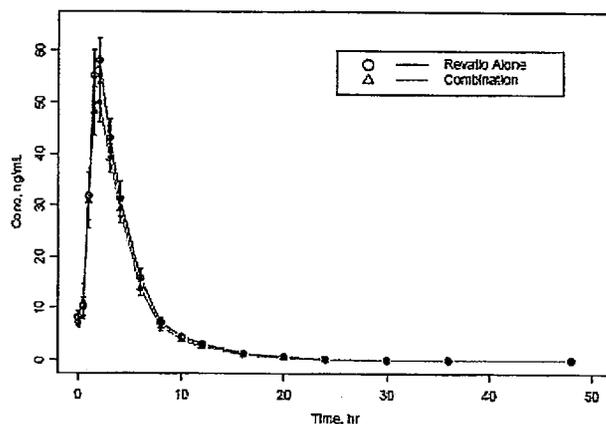
<sup>†</sup> The 90% confidence intervals for the C<sub>max</sub> ratio and AUC<sub>0-12h</sub> ratio fell within the equivalence interval of 0.800 to 1.250.

The results of ANOVA of geometric mean C<sub>max</sub> and AUC<sub>0-12h</sub> values did not show any statistically significant (p > 0.05) treatment effect or period effect.

### Sildenafil PK

The mean sildenafil plasma concentration-time profiles following administration of treprostinil +/- sildenafil are shown in the following figure.

**Figure 11: Mean sildenafil plasma concentration-time profiles in presence or absence of treprostinil**



Sildenafil PK measures are presented in the following table.

**Table 29: Sildenafil PK measures in the sildenafil interaction study**

Sildenafil Parameter (n = 18)	Revatio™ Alone	Revatio™ and UT-15C SR in Combination
Revatio® Dose	20 mg tid	20 mg tid
C <sub>max</sub> (ng/mL)	62.74 (28.0%)	55.34 (28.7%)
T <sub>max</sub> (hr) <sup>†</sup>	2.00	1.53
AUC <sub>0-8h</sub> (hr*ng/mL)	223.0 (36.1%)	202.3 (35.5%)
CL/F (L/hr)	99.7 (32.0%)	109.2 (32.0%)
V <sub>z</sub> /F (L)	617.9 (57.1%)	554.5 (36.9%)
T <sub>1/2</sub> (hr)	4.35 (47.6%)	3.68 (36.0%)

<sup>†</sup> median value

The statistical analysis presented in the following table indicates that sildenafil exposure is not altered by treprostinil.

**Table 30: Sildenafil geometric mean ratios and associated 90 % confidence intervals in sildenafil interaction study**

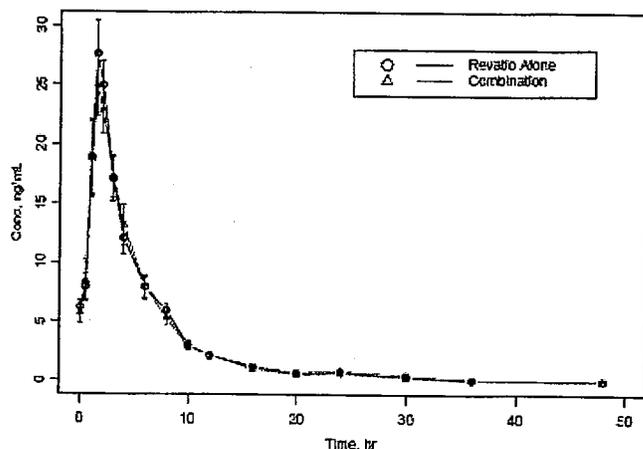
Sildenafil Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Combination	Alone		
C <sub>max</sub> (ng/mL)	53.25	60.44	0.881	(0.804, 0.966) <sup>†</sup>
AUC <sub>0-8h</sub> (hr*ng/mL)	192.1	211.0	0.910	(0.876, 0.946) <sup>†</sup>

<sup>†</sup> The 90% confidence intervals for the C<sub>max</sub> ratio and AUC<sub>0-8h</sub> ratio fell within the equivalence interval of 0.800 to 1.250.

**N-desmethyl-sildenafil**

The mean N-desmethyl-sildenafil (NDMS) plasma concentration-time profiles following administration of treprostinil +/- sildenafil are shown in the following figure.

**Figure 12: Mean NDMS plasma concentration-time profiles in presence or absence of treprostinil**



NDMS PK measures are presented in the following table.

**Table 31: NDMS PK measures in the sildenafil interaction study**

N-desmethylsildenafil Parameter (n=18)	Revatio™ Alone	Revatio™ and UT-15C SR in Combination
Revatio® Dose	20 mg tid	20 mg tid
C <sub>max</sub> (ng/mL)	30.36 (43.3%)	27.87 (36.7%)
T <sub>max</sub> (hr) <sup>†</sup>	1.50	1.51
AUC <sub>0-8h</sub> (hr*ng/mL)	104.32 (40.0%)	102.85 (45.6%)
CL/F <sub>m</sub> (L/hr)	213.7 (39.3%)	222.0 (39.9%)
V <sub>z</sub> /F <sub>m</sub> (L)	2117.2 (72.6%)	1714.2 (42.7%)
T <sub>1/2</sub> (hr)	7.99 (79.2%)	6.32 (65.1%)

<sup>†</sup> median value

The statistical analysis presented in the following table indicates that NDMS exposure is not altered by tadalafil.

**Table 32: NDMS geometric mean ratios and associated 90 % confidence intervals in sildenafil interaction study**

N-desmethylsildenafil Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Combination	Alone		
C <sub>max</sub> (ng/mL)	26.06	28.00	0.931	(0.841, 1.030) <sup>†</sup>
AUC <sub>0-8h</sub> (hr*ng/mL)	94.51	97.31	0.971	(0.920, 1.025) <sup>†</sup>

<sup>†</sup> The 90% confidence intervals for the C<sub>max</sub> ratio and AUC<sub>0-8h</sub> ratio fell within the equivalence interval of 0.800 to 1.250.

### **Period and Treatment Effects for Sildenafil and NDMS**

The following two tables summarize the period and treatment effect findings for sildenafil and its primary metabolite, NDMS.

**Table 33: Statistical Analysis of Period and Treatment Effect for sildenafil**

Sildenafil Parameter	p Values <sup>†</sup>	
	Treatment Effect	Period Effect
C <sub>max</sub> (ng/mL)	0.029 <sup>‡Δ</sup>	0.269
AUC <sub>0-8h</sub> (hr*ng/mL)	<0.001 <sup>‡Δ</sup>	0.002 <sup>‡Δ</sup>

<sup>†</sup> p < 0.05, statistically significant

<sup>Δ</sup> The contributing factor to the statistically significant treatment and period effect remain unknown.

**Table 34: Statistical Analysis of Period and Treatment Effect for NDMS**

N-desmethylsildenafil Parameter	p Values <sup>†</sup>	
	Treatment Effect	Period Effect
C <sub>max</sub> (ng/mL)	0.233	0.129
AUC <sub>0-8h</sub> (hr*ng/mL)	0.357	0.002 <sup>‡Δ</sup>

<sup>†</sup> p < 0.05, statistically significant

<sup>Δ</sup> The contributing factor to the statistically significant period effect remains unknown.

The results of ANOVA of geometric mean C<sub>max</sub> and AUC<sub>0-8h</sub> values showed a statistically significant (p < 0.05) treatment effect for both C<sub>max</sub> and AUC<sub>0-8h</sub> and a significant (p < 0.05) period effect for AUC<sub>0-8h</sub> and a non-significant (p > 0.05) period effect for C<sub>max</sub>. There was also a significant period effect with the NDMS AUC. However, the factor(s) contributing to these effects is unclear.

### **Applicant's Safety Summary**

AEs occurred more frequently during the combination treatment, with overall events reported in 29%, 44%, and 56% of subjects receiving UT-15C SR alone, Revatio alone and the combination of UT-15C SR and Revatio, respectively. The three most frequently reported events across treatment groups were headache, pain in extremity, and nausea. All AEs were either mild or moderate in intensity. No AEs were considered to be severe and there were no SAEs. There were no clinically relevant treatment-emergent changes in vital signs or laboratory parameters following dosing in any treatment group. There were no adverse trends in

vital signs or clinical laboratory parameters observed when comparing the combination and monotherapy treatment groups.

### **Conclusion**

The steady state exposure of sildenafil, N-desmethyl-sildenafil and treprostinil, respectively, were similar during monotherapy and combination therapy.

### ***Reviewer Comment***

No clinically significant drug interaction occurs between sildenafil and treprostinil, thus the agents may be coadministered without dose adjustment.

**4.2.6 An Evaluation of single oral dose UT-15C SR (treprostinil diethanolamine) pharmacokinetics following repeated dosing with prototypical cytochrome P450 2C8 and 2C9 enzyme inducer rifampin in healthy adult volunteers (TDE-PH-109)**

INVESTIGATOR	Jon Bradbury, M.D.
STUDY SITE	
STUDY PERIOD	February 2008

b(4)

**Objectives:**

- To evaluate the effect of rifampin, a model CYP2C8/2C9 inducer, on treprostinil (UT- 15C SR) pharmacokinetics following a single 1 mg oral dose of UT-15C SR in healthy volunteers.
- To assess the safety and tolerability of a single oral dose of UT-15C SR before and following repeated dosing with rifampin in healthy volunteers.

**Study Design**

This was a single-center, open-label, one-sequence, two-treatment design. Subjects received the following treatments in a pre-specified order:

- (a) a single 1 mg UT-15C SR dose on Day 1 (reference treatment)
- (b) daily rifampin 600 mg in the evening on Days 3 – 12 plus a single 1 mg UT-15C SR oral dose on Day 11 (test treatment).

All subjects received a standardized breakfast (approximately 55% carbohydrates, 30% fat, 15% protein and totaling 500 kcal) prior to single dose UT-15C SR administration on the morning of Days 1 and 11. Twenty healthy adult volunteers were enrolled and they all completed the study per protocol.

**Pharmacokinetic sampling times**

On each of the two dosing days, serial pharmacokinetic blood samples were collected at the following time points: 0 hour (prior to dosing) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 21, 24, 28, 32, 36, and 48 hours post-dose for the determination of pertinent plasma treprostinil pharmacokinetic parameters.

**Formulation**

- UT-15C SR (sustained release) 1 mg Tablets were manufactured by Catalent Pharma Solutions in Winchester, KY (Drug Product Batch # 0702276). Each 1 mg SR Tablet contained 1.27 mg of treprostinil diethanolamine salt, equivalent to 1 mg of the free acid of treprostinil.
- Rifampin 300 mg Capsules from a commercial source (Lot # 060072) was procured

b(4)

## Bioanalytical methods

Treprostinil concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in the following table. b(4)

Table 35: Performance of Treprostinil Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 10 to 5000 pg/mL range; $R > 0.994$	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were between -5 and -2 % of nominal concentration	Satisfactory
QC sample concentrations	30, 600 and 3750 pg/ml	Satisfactory
LLOQ	10 ng/mL	Satisfactory
Specificity	Chromatograms were provided in this report	Satisfactory

## Pharmacokinetics

Pharmacokinetic evaluations included the determination of  $C_{max}$ ,  $T_{max}$ ,  $T_{1/2}$ ,  $AUC_{0-48h}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $CL/F$ , and  $V_z/F$ . Noncompartmental methods were used in the determination of treprostinil pharmacokinetic parameters following each treatment (single dose oral administration of 1 mg UT-15C SR in the absence of rifampin or following repeated administration of rifampin).

## Statistical methods

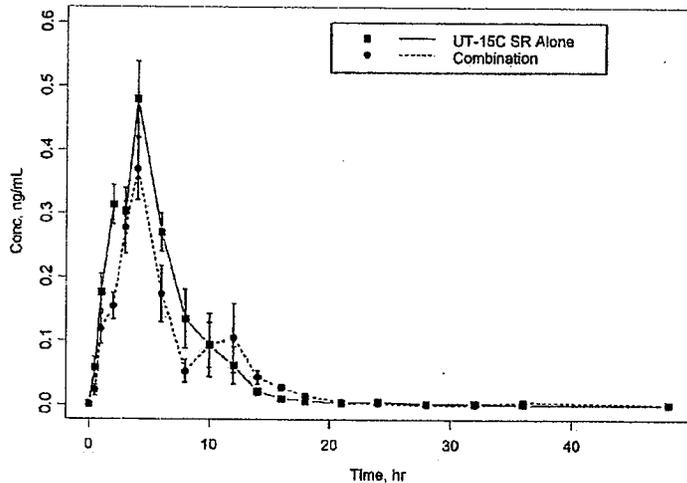
The existence of drug interactions was conducted using standard statistical methods. The effect of repeated administration of rifampin on the oral bioavailability of a single oral dose of 1 mg UT-15C SR in the presence of rifampin (test treatment) versus the same UT-15C SR dose administered in the absence of rifampin (reference treatment) was determined by ANOVA. Logarithmically transformed  $AUC_{0-48h}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  were used for ANOVA and there was a computation of the 90% confidence interval around the ratio of the geometric mean values for each of these four pharmacokinetic measures.

## Results

### Treprostinil Pharmacokinetics

The mean treprostinil plasma concentration-time profiles in the absence or presence of rifampin are shown in the following figure.

**Figure 13: Mean treprostinil plasma concentration-time profile following administration of treprostinil +/- rifampin**



Treprostinil PK measures are presented in the following table.

**Table 36: Treprostinil PK measures in rifampin interaction study (n = 20)**

Treprostinil Parameter	UT-15C SR 1 mg Tablet Administered Following Repeated Administration of Rifampin (Test Treatment)	UT-15C SR 1 mg Tablet Administered Alone (Reference Treatment)
UT-15C SR Dose	1 mg	1 mg
$C_{max}$ (ng/mL)	0.486 (51.4%)	0.548 (45.7%)
$T_{max}$ (hr) <sup>†</sup>	4.0	4.0
$AUC_{0-18h}$ (hr*ng/mL)	2.161 (69.9%)	2.737 (47.4%)
$AUC_{0-1}$ (hr*ng/mL)	2.119 (70.4%)	2.717 (47.7%)
$AUC_{0-\infty}$ (hr*ng/mL)	2.359 (67.6%)*	2.583 (39.2%) <sup>□</sup>
$T_{1/2}$ (hr)	4.24 (46.3%)*	3.2 (44.4%) <sup>□</sup>
CL/F (mL/hr/kg)	6739 (49.6%)*	5170 (31.7%) <sup>□</sup>
$V_z/F$ (mL/kg)	43555 (75.3%)*	23158 (44.8%) <sup>□</sup>

<sup>†</sup> median value

\* n = 14

<sup>□</sup> n = 13

The statistical comparisons summarized in the following table indicate that rifampin decreases treprostinil exposure, however, the effect on C<sub>max</sub> is not statistically significant.

**Table 37: Treprostinil geometric mean ratios and associated 90 % confidence intervals in rifampin interaction study**

Treprostinil Parameter	Least Square Means		Ratio of Geometric Means	90% Confidence Interval
	Test Treatment	Reference Treatment		
C <sub>max</sub> (ng/mL)	0.416	0.499	0.834	(0.673, 1.032) <sup>†</sup>
AUC <sub>0-∞</sub> (hr*ng/mL) <sup>□</sup>	1.859	2.374	0.783	(0.655, 0.937) <sup>†</sup>
AUC <sub>0-t</sub> (hr*ng/mL)	1.728	2.467	0.701	(0.599, 0.819) <sup>†</sup>
AUC <sub>0-48h</sub> (hr*ng/mL)	1.765	2.488	0.709	(0.608, 0.828) <sup>†</sup>

<sup>†</sup> The 90% confidence intervals for the C<sub>max</sub> ratio and all three AUC ratios fell outside the equivalence interval of (0.80, 1.25).

<sup>□</sup> n = 9

The decreased exposure finding may be anticipated as rifampin induces the activity of multiple CYPs, including CYP2C8; treprostinil is a CYP2C8 substrate, thus treprostinil is susceptible to rifampin drug interactions.

As shown in the following table, all AUC measures exhibited a treatment effect.

**Table 38: Statistical analysis of treatment effect (Analysis Performed on Log-Transformed Data)**

Parameter	N	p Value <sup>†</sup>
		Treatment Effect
C <sub>max</sub> (ng/mL)	20	0.157
AUC <sub>0-t</sub> (hr*ng/mL)	20	<0.001
AUC <sub>0-∞</sub> (hr*ng/mL)	9	0.035
AUC <sub>0-48h</sub> (hr*ng/mL)	20	0.001

<sup>†</sup> p < 0.05, statistically significant

### Applicant's Safety Summary

Eleven AEs were reported in 11 (55%) of 20 subjects. No events were reported by the investigator as reasonably or possibly attributable to study drug. There were no serious AEs or deaths during this investigation. All adverse events were reported as mild. Chromaturia, which accounted for 9 out of 11 overall AEs reported, occurred following initiation of rifampin dosing and is listed as an AE in the rifampin product information. There were no clinically significant or evident treatment-emergent changes or adverse trends in vital signs or laboratory parameters following dosing in any treatment cohort. All physical findings, if not reported as adverse events, were considered to be normal throughout the study.

## **Conclusions**

Rifampin and treprostinil undergo a drug interaction, resulting in a decrease in treprostinil plasma concentrations:

- AUC decreases by approximately 30 %
- C<sub>max</sub> tends to decrease by approximately 20 %, although the change is not statistically significant

## ***Reviewer Comments***

1. The drug interaction finding suggests that the effectiveness of treprostinil may be decreased in the presence of rifampin or other CYP enzyme inducers, thus, treprostinil doses may need to be increased when rifampin is present.
2. It is noted that treprostinil dosage can be adjusted, thus the potential drug interaction can be managed by careful dosage adjustment in the absence of a definitive study to identify the appropriate treprostinil dose adjustment.

**4.2.7 An Evaluation of single oral dose UT-15C SR (Trepstinil Diethanolamine) pharmacokinetics following repeated dosing with oral prototypical cytochrome P450 2C8 (Gemfibrozil) and 2C9 (Fluconazole) inhibitors in healthy adult volunteers (TDE-PH-110)**

INVESTIGATOR	Jon Bradbury, M.D.
STUDY SITE	
STUDY PERIOD	February to March 2008

b(4)

**Objectives:**

- To evaluate the effect of repeated doses of gemfibrozil, a model CYP 2C8 inhibitor, and repeated doses of fluconazole, a model CYP 2C9 inhibitor, on treprostnil pharmacokinetics following a single 1 mg oral dose of UT- 15C SR (treprostnil) in healthy volunteers.
- To assess the safety and tolerability of a single oral dose of UT-15C SR before and following repeated dosing with gemfibrozil or fluconazole in healthy volunteers.

**Study Design**

This was an, open-label, randomized, two-cohort, two sequence, two-period, crossover design. In healthy subjects. Individual subjects in two separate cohorts of 20 each were randomized to one of two treatment sequences:

**Cohort 1 (Effect of Gemfibrozil)**

**Sequence I:**

- Period 1: Days 1 through 4: Gemfibrozil 600 mg twice daily and a single oral dose of UT-15C SR 1 mg following a standardized breakfast on the morning of Day 3 (test treatment). Days 5 through 11: 7-day at home washout period.
- Period 2: Days 12 through 13: Observation and continued washout period; Day 14: A single oral dose of UT-15C SR 1 mg following a standardized breakfast (reference)

**Sequence II:**

- Period 1: Days 1 through 2: Observation; Day 3: A single oral dose of UT-15C SR 1 mg (reference treatment). Days 5 through 11: 7-day at home washout period.
- Period 2: Days 12 through 15: Gemfibrozil 600 mg twice daily and a single oral dose of UT-15C SR 1 mg following a standardized breakfast on the morning of Day 14 (test).

**Cohort 2 (Effect of Fluconazole):**

**Sequence I:**

- Period 1: Fluconazole, 400 mg once daily in the morning on Day 1 and 200 mg once daily in the morning on Days 2 through 7, plus a single oral dose of UT-15C SR 1 mg following a standardized breakfast on the morning of Day 6 (test treatment). Days 8 through 14: 7-day at home washout period.
- Period 2: Days 15 through 19: Observation and continued washout period; Day 20: a single oral dose of UT-15C SR 1 mg following a standardized breakfast (reference treatment).

**Sequence II:**

- Period 1: Days 1 through 5: Observation; Day 6: a single oral dose of UT-15C SR 1 mg following a standardized breakfast (reference treatment). Days 8 through 14: 7-day at home washout period.
- Period 2: Fluconazole, 400 mg once daily in the morning on Day 15 and 200 mg once daily in the morning on Days 16 through 21, plus a single oral dose of UT- 15C SR 1 mg following a standardized breakfast on the morning of Day 20 (test treatment).

**Blood Sampling**

On each of the UT-15C SR dosing day in Periods 1 and 2, serial pharmacokinetic samples were collected from all subjects at the following time points: 0 (pre-dose), and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 21, 24, 28, 32, 36, and 48 hours following UT-15C SR dosing.

**Formulation**

- UT-15C SR 1 mg Tablets were manufactured by Catalent Pharma Solutions in Winchester, KY; Drug Product Batch # 0702276. Each UT-15C SR Tablet contained 1.27 mg of treprostinil diethanolamine salt, equivalent to 1 mg of the free acid of treprostinil.
- Gemfibrozil 600 mg tablets (manufactured by Teva Pharmaceutical, Lot # 01G067) were procured by the Clinical Research Unit
- Fluconazole 200 mg tablets (manufactured by Ivax Pharmaceuticals, Lot # Y70910) were procured by the Clinical Research Unit

**b(4)****Bioanalytical methods**

Treprostinil concentrations were determined using a validated LC-MS/MS method as described in previous reports. The assay performance was acceptable (data not included in this report).

**Pharmacokinetics**

Pertinent individual subject and mean pharmacokinetic parameters were calculated and included the determination of C<sub>max</sub>, T<sub>max</sub>, λ<sub>z</sub>, T<sub>1/2</sub>, AUC<sub>0-48 h</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub>.

**Statistical methods**

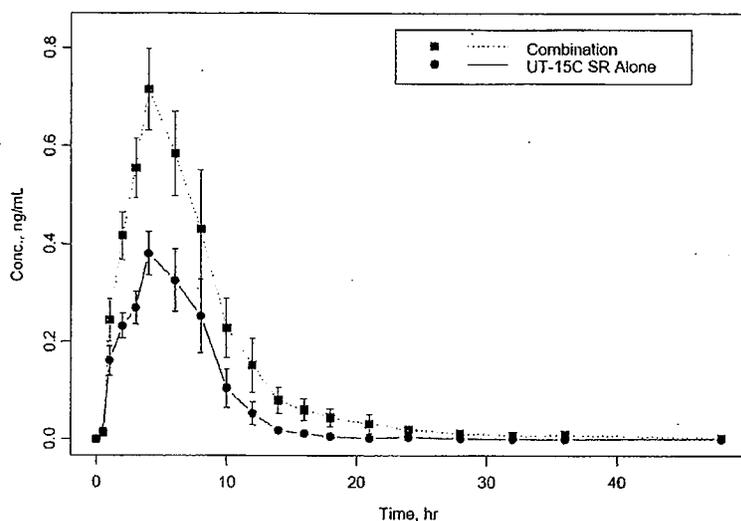
The existence of drug interactions was evaluated using standard statistical methods. The effect of repeated administration of gemfibrozil or fluconazole on the oral bioavailability of a single oral dose of 1 mg UT-15C SR (test treatment) versus the same UT-15C SR dose administered in the absence of the same inhibitor (reference treatment) was determined by ANOVA. The ANOVA was conducted with logarithmically transformed treprostinil C<sub>max</sub>, AUC<sub>0-48h</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> and computation of the 90% confidence interval around the ratio of the geometric mean values of each of these four parameters.

## Results

### Treprostinil Pharmacokinetics (effect of Gemfibrozil)

The mean treprostinil plasma concentration-time profiles in the presence or absence of gemfibrozil are shown in the following figure.

**Figure 14: Mean treprostinil plasma concentration-time profile following administration of treprostinil +/- gemfibrozil**



Treprostinil PK measures in the gemfibrozil interaction study are summarized in the following table.

**Table 39: Treprostinil PK measures in gemfibrozil interaction study (n = 20)**

Treprostinil Parameter	UT-15C SR 1 mg Tablet Administered Following Repeated Administration of Gemfibrozil (Test Treatment)	UT-15C SR 1 mg Tablet Administered Alone (Reference Treatment)
UT-15C SR Dose	1 mg	1 mg
C <sub>max</sub> (ng/mL)	1.062 (38.3%)*	0.562 (44.6%)
T <sub>max</sub> (hr) <sup>†</sup>	4.0	4.0
AUC <sub>0-48h</sub> (hr*ng/mL)	5.74 (46.3%)	2.78 (55.9%)
AUC <sub>0-t</sub> (hr*ng/mL)	5.702 (46.4%)	2.761 (56.2%)
AUC <sub>0-∞</sub> (hr*ng/mL)	5.369 (53.8%)*	2.753 (44.8%) <sup>□</sup>
T <sub>1/2</sub> (hr)	5.573 (93.7%)*	3.593 (39.5%) <sup>□</sup>
CL/F (mL/hr/kg)	2737 (38%)*	5423 (40.3%) <sup>□</sup>
V <sub>z</sub> /F (mL/kg)	21157 (104.2%)*	29268 (69.3%) <sup>□</sup>

<sup>†</sup> median value

\* n = 14 (not the same 14 as in the reference treatment)

<sup>□</sup> n = 14 (not the same 14 as in the test treatment)

The statistical comparisons presented in the following table indicate that gemfibrozil increases treprostinil exposure approximately 2-fold relative to when treprostinil is administered alone.

**Table 40: Treprostinil geometric mean ratios and associated 90 % confidence intervals in gemfibrozil interaction study**

Treprostinil Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Test Treatment	Reference Treatment		
$C_{max}$ (ng/mL)	0.992	0.505	1.964	(1.688, 2.284) <sup>†</sup>
$AUC_{0-\infty}$ (hr*ng/mL) <sup>*</sup>	5.041	2.631	1.916	(1.485, 2.471) <sup>†</sup>
$AUC_{0-t}$ (hr*ng/mL)	5.188	2.396	2.165	(1.934, 2.424) <sup>†</sup>
$AUC_{0-48h}$ (hr*ng/mL)	5.224	2.417	2.161	(1.932, 2.417) <sup>†</sup>

<sup>\*</sup> n = 8

<sup>†</sup> The 90% confidence intervals for the  $C_{max}$  ratio,  $AUC_{0-\infty}$  ratio,  $AUC_{0-t}$  ratio, and  $AUC_{0-48h}$  ratio fell outside the equivalence interval of (0.800, 1.250).

**Reviewer's Note:** This interaction is expected because gemfibrozil is a CYP2C8 inhibitor and treprostinil is a CYP2C8 substrate.

Significant treatment effects were observed during the study as presented in the following table.

**Table 41: Statistical analysis of treatment and period effect (Analysis Performed on Log-Transformed Data)**

Treprostinil Parameter	p Values <sup>‡</sup>		
	Sequence Effect	Treatment Effect	Period Effect
$C_{max}$ (ng/mL)	0.774	<0.001 <sup>‡</sup>	0.185
$AUC_{0-\infty}$ (hr*ng/mL) <sup>*</sup>	0.887	0.003 <sup>‡</sup>	0.193
$AUC_{0-t}$ (hr*ng/mL)	0.790	<0.001 <sup>‡</sup>	0.355
$AUC_{0-48h}$ (hr*ng/mL)	0.789	<0.001 <sup>‡</sup>	0.347

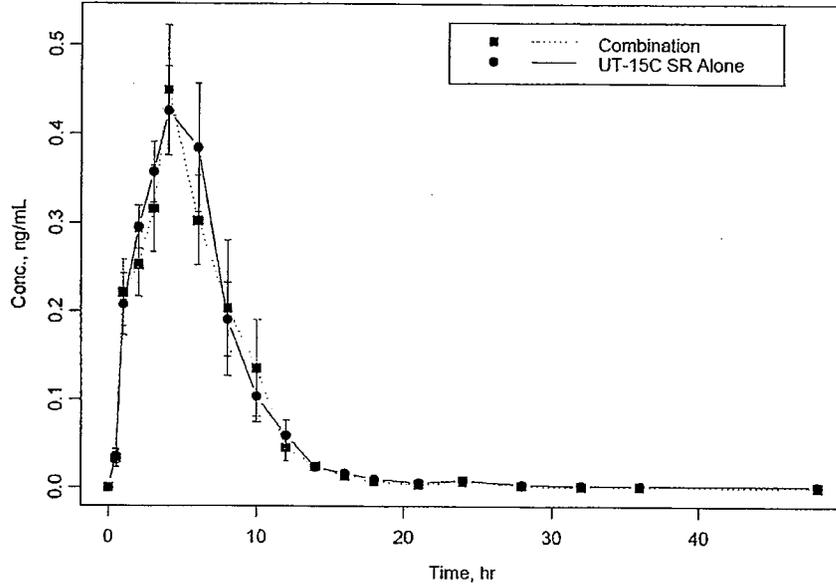
<sup>‡</sup> p < 0.05, statistically significant

<sup>\*</sup> n = 8

Treprostinil Pharmacokinetics (effect of Fluconazole)

The mean treprostinil plasma concentration-time profiles in the presence or absence of fluconazole are shown in the following figure.

**Figure 15: Mean treprostinil plasma concentration-time profile following administration of treprostinil +/- fluconazole**



Treprostinil PK measures in the fluconazole interaction study are summarized in the following table.

**Table 42: Treprostinil PK measures in fluconazole interaction study (n = 20)**

Treprostinil Parameter	UT-15C SR 1 mg Tablet Administered Following Repeated Administration of Fluconazole (Test Treatment)	UT-15C SR 1 mg Tablet Administered Alone (Reference Treatment)
UT-15C SR Dose	1 mg	1 mg
C <sub>max</sub> (ng/mL)	0.604 (54.2%)*	0.592 (40.6%)
T <sub>max</sub> (hr) <sup>†</sup>	4.0	4.0
AUC <sub>0-48h</sub> (hr*ng/mL)	2.958 (63.8%)	3.148 (40.7%)
AUC <sub>0-t</sub> (hr*ng/mL)	2.936 (64.3%)	3.13 (40.8%)
AUC <sub>0-∞</sub> (hr*ng/mL)	3.22 (63%)*	3.315 (41.7%) <sup>‡</sup>
T <sub>1/2</sub> (hr)	4.351 (91.3%)*	4.027 (60.6%) <sup>‡</sup>
CL/F (mL/hr/kg)	6041 (57%)*	4839 (38.8%) <sup>‡</sup>
V <sub>z</sub> /F (mL/kg)	33928 (76.2%)*	27202 (57.4%) <sup>‡</sup>

<sup>†</sup> median value

\* n = 15

<sup>‡</sup> n = 14

The statistical comparisons presented in the following table indicate that fluconazole tends to decrease treprostnil exposure by approximately 10 % relative to when treprostnil is administered alone.

**Table 43: Treprostnil geometric mean ratios and associated 90 % confidence intervals in gemfibrozil interaction study**

Treprostnil Parameter	Geometric Means		Ratio of Geometric Means	90% Confidence Interval
	Test Treatment	Reference Treatment		
C <sub>max</sub> (ng/mL)	0.531	0.545	0.975	(0.871, 1.090)
AUC <sub>0-∞</sub> (hr*ng/mL)*	2.582	3.023	0.854	(0.689, 1.059) <sup>†</sup>
AUC <sub>0-t</sub> (hr*ng/mL)	2.422	2.836	0.854	(0.740, 0.985) <sup>†</sup>
AUC <sub>0-48h</sub> (hr*ng/mL)	2.448	2.855	0.858	(0.744, 0.988) <sup>†</sup>

\* n = 12

<sup>†</sup> The 90% confidence intervals for the AUC<sub>0-∞</sub> ratio, AUC<sub>0-t</sub> ratio, and AUC<sub>0-48h</sub> ratio fell outside the equivalence interval of (0.800, 1.250).

The basis for the observed finding is unclear as the two compounds do not have a common interaction pathway; in vitro data suggest that treprostnil is a non-sensitive CYP2C9 substrate whereas fluconazole is a CYP2C9 inhibitor and is eliminated renally. Consequently, one would anticipate an increase in treprostnil exposure, rather than a decrease. It is noted that the change in treprostnil exposure is relatively small and unlikely to be clinically significant.

The following table summarizes the statistical analysis of treatment, period and sequence effects; period effects were significant for C<sub>max</sub> and two AUC measures, but the cause of these observed period effects is unknown.

**Table 44: Statistical analysis of sequence, treatment and period effects in fluconazole arms**

Treprostnil Parameter	p Values <sup>†</sup>		
	Sequence Effect	Treatment Effect	Period Effect
C <sub>max</sub> (ng/mL)	0.600	0.697	0.002 <sup>‡</sup>
AUC <sub>0-∞</sub> (hr*ng/mL)*	0.777	0.213	0.105
AUC <sub>0-t</sub> (hr*ng/mL)	0.950	0.072	0.031 <sup>‡</sup>
AUC <sub>0-48h</sub> (hr*ng/mL)	0.957	0.077	0.030 <sup>‡</sup>

<sup>‡</sup> p < 0.05, statistically significant

\* n = 12

The cause of the observed period effect on the C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-48h</sub> values is not known.

## **Conclusions**

- A drug interaction occurs between trestatinil and gemfibrozil, leading to an approximate two-fold increase in trestatinil exposure relative to when trestatinil is given alone. The interaction is due to inhibition of CYP2C8 enzymatic activity by gemfibrozil; trestatinil is mainly metabolized by CYP2C8.
- There appears to be a drug interaction between fluconazole and trestatinil resulting in an approximate 10 % reduction in trestatinil plasma exposure, relative to when trestatinil is given alone. The basis for the interaction is unclear.

## ***Reviewer Comments***

1. The interaction findings suggest that the dose of trestatinil should be decreased by a factor of two when initiating therapy with gemfibrozil or other CYP2C8 inhibitors to avoid excessive trestatinil exposure.
2. There does not appear to be a need to adjust the trestatinil dose with fluconazole, as the change in exposure is small and unlikely to be clinically significant.

#### 4.2.8 Evaluation of CYP450 induction by UT-15C using primary cultures of human hepatocytes (7049-122)

STUDY DIRECTORS	
STUDY SITE	
STUDY PERIOD	November 2004

b(4)

#### Objective

To measure the extent of induction of specific P450 marker isoenzymes (for CYP1A2, 2B6, 2C9, 2C19, and 3A4) following exposure of human hepatocytes to UT-15C (treprostinil diethanolamine) and to compare the effects of UT-15C with those of prototypical inducers.

#### Methodology

The induction potential of treprostinil was evaluated using standard in vitro methods; these procedures are consistent with those recommended in the Draft Drug Interaction Guidance. Fresh human hepatocytes were obtained from commercial sources; the characteristics of the four human donors are summarized in the Appendix to this study. The hepatocytes were exposed to 2  $\mu$ M (1  $\mu$ g/mL) or 10  $\mu$ M (5  $\mu$ g/mL) UT-15C, prototypical inducers, or representative solvent control for 72 hours. The CYP isoenzyme activities were evaluated by incubating appropriate probe substrates\* for 1 hour and determining the rate of production of relevant metabolites utilizing fluorimetric or liquid chromatography/tandem mass spectrometry (LC/MS/MS) detection.

\*Substrates: 7-ethoxyresorufin O-deethylase for activity (CYP1A2); bupropion hydroxylase activity (CYP2B6); diclofenac 42-hydroxylase activity (CYP2C9); mephenytoin 42-hydroxylase activity (CYP2C19); 6 $\beta$ -hydroxylase activity (CYP3A4)

#### Reviewer Note on Treprostinil Concentrations

It is noted that the doses of UT-15C used in this study were approximately 1000 fold greater than expected plasma concentrations achieved following oral dosing. Consequently, the findings of this study are not likely to be clinically relevant, but may produce qualitative information.

## Results

The following table summarizes the findings from the induction study.

**Table 45: Assessment of treprostinil induction potential in human hepatocytes**

CYP Isoform	Inducer	Concentration of Inducer ( $\mu\text{M}$ )	Fold Induction <sup>a</sup>			
			Donor 1	Donor 2	Donor 3	Donor 4
CYP1A2	UT-15C	2	0.834	1.25	0.473	ND
	UT-15C	10	0.735	0.905	0.453	ND
	Omeprazole	25	1.82	8.02	14.7	ND
CYP2B6	UT-15C	2	NA <sup>1</sup>	1.01	1.53	1.04
	UT-15C	10	NA <sup>1</sup>	1.42	1.31	1.08
	Phenobarbital	1000	NA <sup>1</sup>	37.6	16.9	1.08
CYP2C9	UT-15C	2	0.265	NA <sup>1</sup>	0.975	1.07
	UT-15C	10	0.424 <sup>b</sup>	NA <sup>1</sup>	1.08	1.49
	Rifampicin	50	22.0	NA <sup>1</sup>	2.91	1.85
CYP2C19	UT-15C	2	0.689 <sup>b</sup>	NA <sup>2</sup>	1.23	NA <sup>2</sup>
	UT-15C	10	0.834 <sup>b</sup>	NA <sup>2</sup>	2.35	NA <sup>2</sup>
	Rifampicin	50	17.0	NA <sup>2</sup>	6.03	NA <sup>2</sup>
CYP3A4	UT-15C	2	1.05	0.857 <sup>b</sup>	1.07	ND
	UT-15C	10	1.34 <sup>b</sup>	2.17	1.76	ND
	Rifampicin	50	3.45	8.05	5.13	ND

Note Fold induction is calculated relative to an appropriate solvent control. An induction response of  $\geq 40\%$  (Bjornsson *et al.*, 2003) of that of the prototypical inducer is considered significant.

NA<sup>1</sup> Not applicable, no result due to high variability between replicates.

NA<sup>2</sup> Not applicable, no result due to low inherent isoenzyme activity.

ND Not determined.

a Mean of three replicates, unless otherwise noted.

b Average of two replicates.

Overall, the data were highly variable for the study; this appeared due mainly to inherent variability in enzymatic activity among Donors:

1. in all systems, data from at least one Donor were either not applicable or could not be determined
2. the utility of data from Donor 4 was unclear

In contrast the system appeared to function acceptably based on the prototypical inducers; although the concentrations and fold increases were not always consistent with those mentioned in the Drug Interaction Guidance. Examples of the deviations are as follows:

- the 37.6-fold induction increase for CYB2B6 in Donor 2 exceeds the expected range of 5-10 fold.
- The recommended rifampin concentration for CYP2C9 and CYP2C19 induction is 10  $\mu\text{M}$  vs. 50  $\mu\text{M}$  used in this study.

Despite these deviations, the activity of the inducers suggested that the system was functional, if not optimal: all prototypical inducers produced at least a 1.8-fold increase in induction (range: 1.8- to 37-fold increase).

By inspection, relative to the prototypical inducer, treprostinil had an induction response that was  $< 40\%$  in all cases, apart from Donor 4 with CYP2C9. However, the validity of this finding with Donor 4 is unclear as data from this donor were not consistent and the other two donors did not

show a similar effect. Consequently, this reviewer concludes that treprostinil does not induce CYP2C9 activity.

## Conclusions

Treprostinil (2 and 10  $\mu$ M) does not appear to induce the enzymatic activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4 isoforms in human hepatocytes (*in vitro*). This finding suggests that clinically, treprostinil will not alter the exposure of substrates for these enzymes.

## Appendix

Demographics of human hepatocyte donors

Demographics	Donor 1	Donor 2	Donor 3	Donor 4
Supplier	Gentest	IVT	Cellzdirect	IVT
Donor Number	HH152	FHU-L10114 <sup>a</sup>	Hu192 <sup>a</sup>	FHU-L-131204 <sup>a</sup>
Age	27 years	53 years	77 years	80 years
Gender	Female	Female	Male	Female
Race	Caucasian	African-American	Caucasian	Caucasian
Height	5'4"	Not known	5'9"	Not known
Weight	43 kg	BMI 28.9	79 kg	BMI 26.7
Smoking	No	No	Former	No
Alcohol	No	No	No	Rare
Seeding Density cells/well	400,000	350,000	400,000	350,000

BMI Body mass index.

a Lot number

#### 4.2.9 Reaction phenotyping of the metabolism of UT-15C by human hepatic microsomal cytochrome P450 (49251)

Investigator	Camelia Gliser
STUDY SITE	
STUDY PERIOD	January 2005

b(4)

#### Objective

To determine the specific enzyme(s) involved in the metabolism of treprostinil diethanolamine (UT-15C) in human hepatic microsomal incubations

#### Methodology

Standard procedures for in vitro metabolism studies were used. The study had multiple stages, including time and protein dependent linearity experiments, oxidative metabolism, linearity of a reaction catalyzed by microsomal enzymes (as a function of time and protein concentration), screening by cDNA-expressed CYP enzymes, and chemical inhibition to confirm metabolic pathway. All materials, including probe compounds were obtained from commercially available sources. All incubations were performed in triplicate in a 96-well plate in a 0.5 mL reaction. The reactions were started by the addition of the NADPH-generating system, vortex mixed and then maintained in a water bath at 37 OC for their respective time of incubation. The reactions were stopped by transferring 450 pL of the reaction mixture to a pre-conditioned :

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high performance solid phase extraction disk plate. Two different sets of negative control incubations were also performed for each experiment. One set of negative control incubations consisted of a no NADPH containing sample, while the other one was considered the 0 time point, which was produced by using heat killed microsomes and/or cDNA-expressed enzymes. Treprostinil and negative controls (0 time) were analyzed by LC-MS/MS.

#### Reviewer's note on Review Focus

This report focuses on the cDNA information and chemical inhibition data, as these are the most pertinent data. Previous data indicate that treprostinil is metabolized by CYPs (per label), but the specific enzymes involved were unknown. Consequently, the current study will provide the missing CYP enzyme information.

The following tabulated specific substrates, metabolite and inhibitors were used or monitored.

CYP	Substrate	Metabolite	Inhibitors
CYP1A2	7-Ethoxyresorufin	Resorufin	NA
CYP2A6	Coumarin	7-Hydroxycoumarin	NA
CYP2C8	Paclitaxel	6 $\alpha$ -Hydroxypaclitaxel	Quercetin
CYP2C9	Tolbutamide	Hydroxytolbutamide	Sulfaphenazole
CYP2C19	S-Mephenytoin	4'-Hydroxymephenytoin	NA
CYP2D6	Bufuralol	1-Hydroxybufuralol	NA
CYP2E1	Chlorzoxazone	6-Hydroxychlorzoxazone	NA
CYP3A4	Testosterone	6 $\beta$ -Hydroxytestosterone	NA
CYP4A11	Lauric Acid	Hydroxy-Lauric Acid	NA

NA=Not Applicable

#### Compounds:

- UT-15C (treprostinil), was obtained from United Therapeutics
- CYP enzyme substrates and inhibitors were obtained from commercial sources

## Results

All control systems demonstrated that the system was functional (data are not included in this review).

### Microsomes

The key finding from the initial study was that treprostinil underwent NADPH- and time dependent metabolism at concentrations of 1 and 10  $\mu\text{M}$ , but not at 100  $\mu\text{M}$ .

Table 46: Metabolism of treprostinil in human liver microsomes (Preliminary Experiment)

UT-15C Conc.		Time of Incubation						
Replicate		0 min	20 min		40 min		60 min	
		Peak Area	Peak Area	%Remaining	Peak Area	%Remaining	Peak Area	%Remaining
1 $\mu\text{M}$	1	3148000	1177000		1410000		567200	
	2	3066000	1348000		1243000		522800	
	3	3263000	1312000		141900		627600	
	Average	3159000	1279000	40.49%	931633	29.49%	572533	18.12%
	%CV	3.13	7.05		73.86		9.19	
10 $\mu\text{M}$	1	8422000	7368000		6115000		5725000	
	2	8478000	7218000		6078000		5572000	
	3	8400000	7294000		147800 <sup>a</sup>		5581000	
	Average	8433333	7292667	86.47%	6095500	72.28%	5626000	66.71%
	%CV	0.48	1.01		0.45		1.63	
100 $\mu\text{M}$	1	22850000	23980000		147600 <sup>b</sup>		23440000	
	2	23610000	333300 <sup>a</sup>		22680000		23390000	
	3	23820000	23570000		177300 <sup>b</sup>		23570000	
	Average	23393333	23760000	101.57%	22580000	96.44%	23468667	100.31%
	%CV	2.12	1.13		NA		0.40	

a- value was excluded from the set due to failing the Q test

b- value was excluded due to erroneous results

cDNA

The following table summarizes the data obtained during incubation of treprostnil using cDNA expressed enzymes.

Table 47: cDNA data for treprostnil

Isozyme	Peak Areas				% Remaining
	0 min		15 min		
	Average	%CV	Average	% CV	
1A2	932467	9.57	1058000	4.27	113%
2A6	1132000	0.81	1169667	6.18	103%
2C8	1081700	9.74	54550	12.27	5%
2C9	733500	10.29	570100	19.90	78%
2C19	1098333	7.19	1143000	7.89	104%
2D6	1282333	4.21	1142667	6.18	89%
2E1	1135333	10.13	1180667	10.44	104%
3A4	1286667	4.00	1364333	6.35	106%
4A11	711266	7.68	781767	4.42	110%

% Remaining = Peak Area at 15 min / Peak Area at 0 min

Note: Values greater than 100% of Treprostnil Remaining are not significantly different from the negative control values

The cDNA data indicate that CYP2C8 and CYP2C9 are the major enzymes involved in treprostnil metabolism. It is noted the CYP2D6 caused an 11 % reduction in treprostnil concentration, but it is unclear if this finding is significant. The sponsor should have confirmed the lack of significance of CYP2D6, as cut-off values (e.g. < 20 % implies activity not important) were not defined *a priori*.

Effect of specific chemical inhibitors on treprostnil metabolism in human liver microsomes

The effect of quercetin (2C8 inhibitor) and sulfaphenazole (2C9 inhibitor) on treprostnil metabolism is summarized in the following table.

Table 48: Treprostnil disappearance in the presence or absence of specific chemical inhibitors

UT-15C Incubation		Inhibitor Concentration					
Replicate	0 min Incubation	No Inhibitor		3 µM Quercetin (2C8)		3 µM Sulfaphenazole (2C9)	
	Peak Area	Peak Area	%Remaining	Peak Area	%Remaining	Peak Area	%Remaining
1	1250000	661500		1373000		677500	
2	1053000	395100		1237000		776100	
3	1195000	513700		1108000		805600	
Average	1166000	523433	44.89%	1239333	106.29%	753067	64.59%
%CV	8.72	25.50		10.69		8.91	

% Remaining. = Peak Area/Average of 0 min replicates

Note: Values greater than 100% of Treprostnil Remaining are not significantly different from the negative control values

The disappearance data indicate that treprostnil is metabolized by CYP2C8 to a greater extent than CYP2C9.

**Conclusions**

Treprostnil is metabolized primary by CYP2C8 (95 % disappearance) and CYP2C9 (22 % disappearance); the CYP enzymes CYP1A2, 2A6, 2C19, 2D6, 3A4 and 4A11 do not metabolize treprostnil to a significant effect.

***4.3 Information Request Letter to Sponsor: Review Team's Comments regarding Nebulizer (inhalation Device)***



NDA 22-387

INFORMATION REQUEST LETTER

United Therapeutics Corporation  
Attention: Mr. Dean Bunce  
P.O. Box 14186  
55 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your June 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tyvaso (treprostinil) Inhalation Solution.

We are reviewing the NDA and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Device – Human Factors**

The Agency is concerned that the current design of the device and the materials supporting its use (e.g., user manual) could possibly induce or allow use-errors that could compromise the user's ability to deliver medication properly and thereby pose certain risks to the patient. Please indicate what Human Factors studies your device has undergone to identify any risks and potential consequences associated with user error, and validate the instructions. Please provide the protocols, criteria for assessing whether the instructions were vulnerable to error (pass/fail criteria), results, conclusions, and subsequent modifications to the instructions or to the device.

The Agency expects you to perform your own comprehensive analysis of use-related risk, including the following:

- Whether users can properly dose themselves with a total of nine breaths using the currently designed breath counter mechanism. This counter counts only up to three and the patient must restart the program two additional times to receive the required nine breaths.
  - The difficulty in viewing the counter in its current position relative to the user's eyes during the use of the device.
  - The ability of the user to remember where in the sequence three groups of three breaths was just completed.
  - The requirement for the user to switch the device on/off after each group of three breaths.

- Possible risk to the user should the dose be less than the prescribed dose, given the apparently challenging requirement for the user to take nine deep breaths within the specified time limit of ninety seconds.
- Whether inhalation or exhalation into the mouthpiece triggers a change in the count displayed by the breath-counter mechanism, whether this trigger is time-related, and whether the user needs to be aware of how this process operates to ensure proper use and delivered dosage.
- The ability of users to assemble your device correctly under realistic conditions consistent with home-use to include proper physical connection of device components and loading of appropriate levels of medication into the medicine cup.
- Whether the two included filters are interchangeable without impacting proper performance of your device, or if not, whether there is risk of users inadvertently reversing their location on subsequent assemblies and uses.
- The extent to which proper cleaning and maintenance is required for proper device operation, and the extent to which the user materials convey this need and the process for performing these maintenance activities in a home environment.
- The extent to which there is a risk of contamination of the medicine and the contact fluid while dropping the medicine cup into the contact fluid chamber. The medicine can be contaminated by hand or it can spill over the medicine cup into the contact fluid during this process.
- The extent of device failure or problems if non-distilled water is used as the contact fluid (e.g., tap water).

For more information regarding Human Factors, please visit <http://www.fda.gov/cdrh/humanfactors/>.

**Drug and Device – Patient/User Labeling**

With regard to labeling for the OPTINEB-ir. — device, you submitted a “user manual”. We have reviewed the user manual and believe it would be too difficult for patients and users of the device to comprehend. Additionally, the manual in its present form does not include any information about the drug, e.g., indications for use, side effects, etc.

In lieu of the OPTINEB-ir. — device user manual that you have proposed, we recommend that you instead submit 1) a Patient Package Insert (PPI) and 2) Instructions For Use (IFUs) or “user manual”. The PPI is intended to focus primarily on the drug product itself, whereas the IFU would focus on the device. PPIs are intended to enhance appropriate use of medications and provide important risk information to patients; the information should be consistent with the information presented in the full prescribing information. IFUs are intended to support the appropriate use of your device.

We are providing you with a couple of suggestions to consider as you revise your documents:

IFUs: The following sections with diagrams should be considered for inclusion:

- “preparing for your treatment”,
- “using your OPTINEB-ir. —”,
- “maintenance and cleaning”, etc.

Each diagram should be clearly labeled with references in the text that correspond to each diagram.

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PPI: Information regarding indications and usage, contraindications, and other drug-specific information are frequently included in PPIs. You may refer to 21 CFR Section 208 for a list of subheadings to consider as you develop a PPI.

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The general recommendations listed below are consistent with current research to improve risk communication to a broad audience, including those with lower literacy. Please consider these recommendations as you prepare the requested labeling revisions:

The Flesch Reading Ease and Flesch Kinkaid Grade Level scores in the DRAFT OPTINEB-ir — User Manual are 49.5% and 9.5, respectively. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). Please ensure the materials you submit for review meet these criteria.

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We recommend that you reformat the Patient Package Insert and Instructions for Use using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

#### **Label, Labeling and Packaging Configuration**

##### ***Packaging Configuration:***

We note that the inhalation solution will be packaged in four unmarked low density polyethylene (LDPE) ampules in a single foil wrap. This configuration is a concern since the four unmarked LDPE ampules may be separated from the pouch after opening. Drug products packaged in LDPE plastic ampules may be more easily confused with one another since few have distinguishing characteristics traditionally utilized on medication containers such as paper labels, color, etc. Multiple ampules in a single foil wrap lend themselves to removal or tearing also affecting the legibility of the foil overwrap itself. We have learned through post-marketing reports that the embossed/debossed lettering is difficult to read, if not poorly legible once removed from the foil overwrap. We ask you to consider foil-overwrapping each individual low-density polyethylene (LDPE) ampule to help maintain the legibility of the product name and strength.

##### ***Carton Labeling:***

Some key information (e.g., route of administration, net quantity) is not prominently displayed on the principal display panel. We suggest that you increase the prominence of this information. Consider relocating the established name beneath the proprietary name. Additionally, consider relocating the "contents" information so that the proprietary name, established name, and the dosage form can be separated from the rest of the labeling information and readily recognized.

NDA 22-387 tadalafil inhalation solution

We have completed our review of the proposed proprietary name, Tyvaso, and have concluded that it is acceptable. However, if **any** of the proposed product characteristics are altered prior to approval of the marketing application or the approval of the NDA is delayed beyond 90 days of this letter, this finding is rescinded and the proprietary name should be resubmitted for review.

We encourage you to request a teleconference to further discuss any of these issues.

If you have any questions, please call Dan Brum, PharmD, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

*{See appended electronic signature page}*

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

#### ***4.4 NDA filing and Review Form/Refusal to File Criteria***

**Office of Clinical Pharmacology**  
**New Drug Application Filing and Review Form**

**General Information About the Submission**

	Information		
<b>NDA Number</b>	22-387	<b>Brand Name</b>	TYVASO
<b>DCP (I, II, III)</b>	I	<b>Generic Name</b>	Treprostinil sodium
<b>Medical Division</b>	Cardiovascular and Renal	<b>Drug Class</b>	Vasodilator/platelet aggregation inhibitor
<b>OCP Reviewer</b>	Robert Kumi	<b>Indication(s)</b>	Pulmonary Arterial Hypertension
<b>OCP Team Leader (Acting)</b>	Angelica Dorantes	<b>Dosage Form</b>	Solution for inhalation
		<b>Dosing Regimen</b>	Varies: four inhalation sessions per day; target dose 54 µg per session
<b>Date of Submission</b>	06/27/2008	<b>Route of Administration</b>	Inhalation
<b>Estimated Due Date of CPB Review</b>	03/23/2009	<b>Sponsor</b>	United Therapeutics
<b>PDUFA Due Date</b>	04/26/2009	<b>Priority Classification</b>	Standard
<b>Division Due Date</b>	03/23/2009		

*Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			Tables not always consistent
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:	x	2-3	2	ID CYP enzymes, evaluate induction and inhibition
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:		1	1	MTD study
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	x	4	4	Studies overlapped in terms of information (total = 4)
In-vivo effects of primary drug:	x	2	x	
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>	x	1	1	PK information extracted from QTc study

Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>	x	1	1	Inhaled vs. IV
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>	11			Investigator studies that may require cursory review
<b>Total Number of Studies</b>			9	
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<b>Application filable ?</b>	X	Sufficient information to review, however will need firm to help navigate through the submission.		
<b>Comments to be sent to firm?</b>		<ol style="list-style-type: none"> <li>1. Please indicate if PK datasets were provided; if they were provided please indicate where they are located.</li> <li>2. Please provide complete study reports for investigator studies, especially where they have labeling implications.</li> </ol>		
<b>QBR questions (key issues to be considered)</b>		<ul style="list-style-type: none"> <li>• Is there clinically significant QT prolongation associated with treprostinil administration?</li> <li>• Is the proposed dosing regimen acceptable</li> </ul>		

***NDA 22-387 Treprostinil sodium:  
Evaluation of Clinical Pharmacology  
Refusal to File (RTF) Criteria***

**Criteria for Refusal to File (RTF)**

1. Has the sponsor submitted bioavailability data satisfying the CFR requirements?

Yes, it appears so.

2. Has the sponsor submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?

No, study not needed as to-be-marketed solution (inhalation) used in pivotal trials.

3. Are the clinical pharmacology and biopharmaceutical sections of the NDA organized in a manner to allow substantive and effective review?

Partially, submission loosely follows CTD format.

4. Are the data sets presented in a readable and accessible form?

No, I have not been able to locate PK datasets per se. I will ask applicant to tell me location or simply supply data.

5. Has the sponsor provided information on the metabolic fate of the drug and the activities of the circulating moieties?

Not applicable. (previous study conducted for IV administration)

6. Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?

Yes. Assay reports are available (randomly sampled studies) but not all in appropriate locations.

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

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Robert Kumi  
3/24/2009 11:41:08 AM  
BIOPHARMACEUTICS

Angelica Dorantes  
3/24/2009 12:00:59 PM  
BIOPHARMACEUTICS