CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

MEDICAL REVIEW(S)

MEMORANDUM

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

DATE: July 26, 2009.

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

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

SUBJECT: Follow-up CDTL memo to Tyvaso™ (inhaled treprostinil NDA 22-387, United Therapeutics Corporation).

This memo is a follow up document to my CDTL review dated April 18, 2009. Please also refer to Dr. Stockbridge's Division Director's complete-response memo.

Although some of the residual issues that were raised in the initial memos have been successfully resolved, other issues remain outstanding. Despite the unresolved issues, the current drug-device combination may be approved, subject to the post-marketing requirement and commitments as outlined below.

With respect to the resolved issues, the sponsor has submitted the results of the biocompatibility information for the device components. CDRH considered the biocompatibility information acceptable. The residual CMC issues have also been resolved. The Agency recommends a 36-month shelf-life when the drug is stored at controlled room temperature in the foil outer packets, In-use stability data allow for a maximum of 24 hours of use once the LDPE ampoules are opened and the drug placed in the nebulizer. The drug is photosensitive and it must be protected from light by the storage inside the foil packages. There are still minor issues related to the carton and containers that should be readily resolvable and should not further delay the approval of this drug.

The Trade-name Tyvaso™ is still considered acceptable.

With respect to the yet unresolved issues, the most salient of these is related to the inhalation device. CDRH requested that sponsor define the most critical tasks for the safe and effective use of the inhalation device. Once these critical tasks were defined, the sponsor was to submit a protocol and perform a human factor study, to assess whether subjects could safely and effectively use the device as is. The tasks to be assessed included the assembly of the device and preparation and administration of the inhaled drug. Instead of submitting a protocol to CDRH and incorporating their comments, the sponsor performed a human factor study in advance of defining the critical steps in the

use of the device and in advance of concurrence by CDRH with the protocol. CDRH considered the study with its results, as performed by the sponsor, inadequate.

Nevertheless, major problems with the ability of the rarified population to assemble, clean and administer this drug were detected by this less than acceptable study.

Despite obvious inadequacies in the design of the device, the Division and United Therapeutics arrived at a time line to address some of the major deficiencies, allowing the marketing of the current device until that time. The underlying rationale behind allowing the marketing of the Tyvaso (drug-device combination) before the device is completely acceptable, is the lack of a device-related safety signal in the clinical study that enrolled of 235 subjects that were treated with either active drug or placebo using the current device.

The sponsor has agreed to a post-marketing commitment with a deadline of one year to alter the current Optineb-IR device. The alteration is limited to problems with the device that are already known. These changes would not alter the hardware or software that generates the inhalation aerosol.

b(4)

The baffle plate is also to be altered to fit more securely.

Once the new device has been re-engineered, the sponsor is then tasked with defining the most critical elements in the use of the device that are most vulnerable to either mitigating the benefit of drug or provoking unnecessary risk to the patient. This human factor study as outline in the previous CDTL review would consist of two separate studies. The first is an analysis of the tasks related to the care, assembly and sham administration of the drug with the new device. In this study the key metrics would be observational and determine whether the above tasks can be acceptably performed.

The second study would be to incorporate a pharmacokinetic study to assess whether with the re-engineered device reproducible serum concentrations are generated.

In addition, a CRF should be added to all ongoing study to obtain real-use information on the patient-related difficulties in the use of the delivery device. The prototype of a Device-related CRF as submitted by United Therapeutics on July 7, 2009, queries the subjects as to difficulties with the assembly care and use of the device and appears an acceptable CRF to be added to those of the ongoing studies.

The sponsor also has a post-marketing requirement to determine the consequence of the novel route of treprostinil administration on the respiratory tract. The specific concern is derived from the following considerations:

- There were several respiratory-tree related events that were of a serious nature during the small clinical and open-label trial database.
- Pre-clinical observations in rats and dogs demonstrated that when treprostinil was administered by the inhalation route, the drug provoked respiratory tract lesions that were still present after a 4 week washout period.
- Treprostinil by the subcutaneous route of administration is highly irritating.

The sponsor, therefore, has agreed to perform a pharmacovigilance study with at least an additional 1,000 patient-years of exposure as well as matched controls. The specific protocol as well as the most appropriate comparative group still needs to be defined. The intent of this requirement is to assess the frequency and ultimate consequence of the inhaled route of administration of Tyvaso to the respiratory system.

The reviews utilized in this memo were:

- A follow-up memo from Monica D. Cooper Ph.D., ONDQA pre-Marketing Assessment Division I/Branch I, dated July 6, 2009.
- A follow-up CDRH memo from Sugato De, Biomedical Engineer (ODE/DAGID/ARDB) lead reviewer; and Ronald Kaye, Human Factors Specialist (ODE/DAGID/GHDB), dated June 10, 2009.
- A follow-up memo from Judy Park, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis, dated June 29, 2009.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22387	ORIG 1	UNITED THERAPEUTICS CORP	TREPROSTINIL FOR INHALATION

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/s/

ABRAHAM M KARKOWSKY
07/27/2009

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-387 (inhaled treprostinil for pulmonary hypertension)

Sponsor: United Therapeutics

Review date: 25 April 2009

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

Distribution: NDA 22-387
HFD-110/Brum/Karkowsky

This memo conveys the Division's recommendation to issue a Complete Response letter for inhaled treprostinil for pulmonary arterial hypertension.

Most issues have been addressed in Dr. Karkowsky's CDTL memo (18 April 2009). I acknowledge reviews by Drs. Karkowsky (medical; 3 April 2009), Lawrence (statistics; 7 April 2009), Kumi (clinical pharmacology and biopharmaceutics; 24 March 2009), Joseph (pharmacology/toxicology; 25 March 2009), Cooper (chemistry and manufacturing; 24 March 2009), and Metcalfe (microbiology; 24 March 2009), and consults performed by the QT Interdisciplinary Review Team (30 January 2009) and Mr. De of CDRH (nebulizer; 1 April 2009).

Treprostinil or remodulin is approved for the treatment of pulmonary arterial hypertension with administration by subcutaneous and intravenous routes. Both routes carry serious safety issues. Subcutaneous administration is very painful; in studies, many subjects required narcotics. The intravenous route carries the risk of infection.

The inhaled route has been studied in a trial that established effectiveness with regard to 6-minute walk, but the effect is small and diminishes substantially by the end of the recommended inter-dosing interval. Inability to dose continuously and the temporal variability means that the inhaled route will not be appropriate to all who now use other routes of administration, but it may be adequate for some of them and certainly is a more convenient route on which to start treprostinil.

The inhaled route moves local irritation effects to the nasopharynx and the rest of the respiratory tract. The available experience is up to 13 weeks; post-marketing data will show how well this mode of delivery is tolerated in the long term.

The associated OptiNeb nebulizer is not "opti"mized for this use. Patients are required to take three breaths on cue (else drug is delivered anyway), then power the device off and on, take three more breaths, power the device off and on, and take three more breaths. The complexities may have led to low or undetectable plasma levels of drug in some subjects, but the sponsor has asserted that observed low levels were appropriately low, because they were collected at trough.

The sponsor asserts (letter dated 17 April 2009) that they can get the nebulizer re-engineered, a human factors study conducted with the new model, and a report generated for submission within one year.

One issue critically affecting approval is that a manufacturing site —— of the drug substance was closed in 2006 and the replacement site has not been approved. b(4)

Our Complete Response letter will identify three deficiencies:

1. The sponsor must resolve all remaining issues with manufacture of the drug substance.
2. The sponsor must address unresolved issues with biocompatibility of nebulizer parts that come into human contact.
3. I am willing to have the existing device on the market for a short period while the changes are made. There are no real engineering uncertainties that could make the process take longer than expected, so the sponsor will be asked to provide a timetable for their response, along with appropriate landmarks, and a compelling demonstration of their commitment to meet the timetable.

Labeling still needs to be negotiated. This will proceed while the sponsor is addressing deficiencies.

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/s/

Norman Stockbridge
4/25/2009 10:29:43 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: April 18, 2009.

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

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

SUBJECT: Complete response memo to Tyvaso® (inhaled treprostinil NDA 22-387, United Therapeutics Corporation).

This memo outlines the current deficiencies in the application for inhaled treprostinil NDA 22-387. I therefore, recommend that a complete response letter be transmitted to the sponsor. The specific deficiencies for this application and the remedy for these deficiencies are summarized in this memo. I have also included in this memo, some labeling considerations.

This subject of this application consists of an active drug (treprostinil sodium for inhalation) and an inhalation device the OptiNeb nebulizer. The two can only be approved as a single entity. The drug has not been assessed in controlled clinical trials when administered by any other nebulizer and the nebulizer is not approved as a general purpose nebulizer.

The complexities in both the assembly and use of the device as well as the cumbersome nature of administering the appropriate dose (the counter only counts down from "3" then the patient must reset this device and repeat the process an additional two times), makes it important to assess how reliably an individual can learn and perform the complex processes in putting together, cleaning and administering the active drug substance. In addition, the biopharmaceutic reviewer noted that there were several subjects who either had no active drug measured or had very low measurements of these concentrations. Whether these low concentrations of drug reflect an inability of the user to accurately administer the drug or whether these subjects had inordinate variability in the absorption of the drug is unclear.

A human factor study is therefore, needed. The basis of the information to be collected would depend upon those processes that pose the greatest likelihood of provoking harm or that are most likely to diminish any benefit of the drug-delivery system. The human factor study would include two separate sub-studies. One study (in normals without the administration of medication) to assess the physical process of cleaning, assembling and pseudo-administering the drug with particular attention to the

process that are most critical for the safe and effective use of the drug system. The second study would assess whether the drug itself is effectively inhaled (based on serum concentrations) and whether under optimum learning conditions, more reliable exposure to treprostinil is obtained.

Several biocompatibility tests are still incomplete. These include the implantation tests for the medicine cup [redacted] and sealing ring materials [redacted] mouse lymphoma and chromosomal aberration tests for the [redacted] mouthpiece material. Furthermore, the tests which the sponsor has previously completely still need to be submitted as a completed study report. These deficiencies should be corrected, and the reports submitted prior to approval. b(4)

There are additional issues that will be included into the complete response. The drug substance information for NDA 22-387 is referenced to the subcutaneous formulation of treprostinil (NDA 21-272). The sponsor submitted a supplement for a new treprostinil drug substance manufacturing facility and process [redacted]. The previously approved site for that process was closed in 2006. Since treprostinil for inhalation cannot be currently manufactured until the referenced NDA supplement is approved, treprostinil for inhalation cannot currently be approved. b(4)

The clinical reviewer (me) noted that the effect of treprostinil in increasing walk-distance was small. The benefit was about half that of the other approved prostacyclin for inhalation (Ventavis®), in a broadly equivalent population. There is no reason to believe (no controlled data) that the inhaled route of administration would supplant either the subcutaneous or the intravenous route for the administration of treprostinil. There is also no reason to believe that there would be added effects on adding the inhaled drug to the drug when administered by the SC or IV route.

Since the parentral (SC or IV) routes of drug delivery is more flexible than when delivered by the inhaled route, I can't recommend substituting the inhaled route for treprostinil as an alternative to long term treatment with the parentral routes.
When treprostinil is administered by the parentral route concentrations are fairly stable (input is constant). For the inhaled route, however, concentrations in plasma are not constant and likely wane at the site of action (the pulmonary vascular sites) during the interdosing interval. Consequently, it is likely that with the inhalation route the benefit is asymmetric during the dosing interval with greater effects early on and lesser effect just immediately prior to the next dose. For these reasons, the lack of flexibility in dose and the inconstant effect during the dosing interval, the inhaled treprostinil would not necessarily be an alternative to the subcutaneous route of administration.

There is only a modest benefit of inhaled treprostinil, limited to a benefit on peak 6MWD (six-minute walk distance). This benefit, however, wanes at the interdosing interval, with the loss of approximately 30% of the effect at trough at 12-weeks compared to the peak effect at 12-weeks. Furthermore, the persistence of benefit to patients in excess of 12-weeks studied in this development program is unclear.

The down-side of this drug is mostly related to site-related irritation. This irritation is not surprising given the near universal pain at the infusion site when treprostinil is administered by the subcutaneous route. When treprostinil is administered by the inhalation route, drug delivery is irritative to the nasopharynx, oropharynx and lungs. Animal studies demonstrate that after 13-weeks of treatment with a 4 week washout there were residual lesions in the oropharynx, and lung in both species and the heart in rats.

There does not appear to be an adequate database to currently assess the relative respiratory and cardiac hazard of treprostinil by the inhaled route, particularly when compared to modest benefit in walk distance. Adverse events in the treated group during the double blind and open label phase included those related to the oro- and naso-pharynx and respiratory tree including; cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. These events were greater among treated than placebo patients.

Serious adverse events during the open-label portion of the study included pneumonia (in 8 subjects). There were three serious episodes of hemoptysis noted during the double-blind and open-label experience. One was lethal and two required invasive maneuvers to stem bleeding.

It should however, be noted that similar hemoptysis events were noted when treprostinil was administered parentrally.

Given the modest database and small benefit, as well as the pre-clinical studies indicating irreversible lesions in the oropharynx and respiratory tree, additional data should be gathered perhaps as a post-marketing commitment.

There are several limitations to the use of this drug, which should be included within labeling. The current application contains a single placebo-controlled study that demonstrated that the inhalation of treprostinil increases walk distance relative to placebo in WHO type I patients with functional class NYHA III who are on stable doses of bosentan or sildenafil. The benefit is more obvious when the concomitant medication was bosentan. Dosing is limited to the 9 puffs (breaths), approximately 54 μg/dosing four times a day, with no dosing at night. There is insufficient experience with higher doses to warrant including this recommendation in the label.

The effect on repolarization (QT effect) is small and dissipates rapidly, as the concentration of treprostinil wanes. These effects should also be included within labeling.

The drug has been granted "orphan" status and as such, pediatric studies are waived.

Since I did the original medical review, I will refer you to that review for additional information. In addition, the following reviews were consulted in the construction of this memo.

- Pharmacology/Toxicology review by Dr. Xavier Joseph D.V.M., dated March 25, 2009.
- Clinical Pharmacology and Biopharmaceutic Review by Robert O Kumi, Ph.D., dated march 24, 2009.
- Statistical review by John Lawrence, Ph.D., dated April 7, 2009.
- A single DSI audit dated January 8, 2009 by Tejashri Purohit-Sheth, regarding the inspection of Dr. Robert C. Bourge, M.D., University of Alabama.
- Thorough QT study-team review by Drs. Atul Bhattaram, Qianyu Dang, Joanne Zhang, Suchitra Balakrishnan and Christine Garnett dated January 30, 2009.
- Chemistry review by Monica D. Cooper, Ph.D., dated March 23, 2009.
- Proprietary name review by Judy Park, PharmD., dated, February 18, 2009.
- Microbiology review by John W. Metcalfe, Ph.D., dated March 23, 2009.
- Regulatory device consult review by Sugato De, Biomedical Engineer, CDRH dated April 1, 2009. The CDRH consult incorporated comments on the human factor study review by Ron Kaye (ODE/DAGID/ GHDB).

Proprietary name:

The proprietary name Tyvaso® is acceptable. The name was not found to be easily amenable to provoke mediation errors.

Chemistry:

The drug substance is currently approved for subcutaneous and intravenous administration (NDA 21,272). That application, however, has a currently pending supplement for a treprostinil drug substance manufacturing site (NDA 21-272/SCM-010). The old manufacturing site ——— was closed in 2006. Consequently, the drug substance for this application cannot be acceptably produced and until the supplement for NDA 21-272 is approved. b(4)

The chemist recommended a 36-month shelf life if stored at controlled temperature (room temperature) and protected from light (in the foil pouches as proposed).

Microbiology:

The product is sterilized ——— prior to final seal. There were no microbiology deficiencies.

Device: b(4)

The device performs acceptably. The output of the nebulizer during four tests of three cycle assessments averaged —— close to the —— breath cycle which is the labeled output of the nebulizer. The distribution of the particle sizes averaged —— which the CDRH reviewers considered acceptable.

Of note, the output of the nebulizer was diminished when the amount of drug in the nebulizer cup was less than the —— dispensed in a single ampoule (it was slightly b(4)

diminished when only ——— was in the cup). The diminished delivery with lower cup volumes should be included in the package insert. b(4)

Several biocompatibility tests are still incomplete. These were described above.

Also as noted above, the human factor study including the prioritization of user tasks (that is the tasks most susceptible to compromising either the safe or effective use of the combination drug-device product), is still pending. Given the complex processes in the assembly and administration of the inhaled drug, such a study is required prior to the approval of the application.

Pharmacology/toxicology:

The current submission bridges the information from the use of treprostinil by either the SC or IV route of administration to the inhalation route as proposed here. One short-term and two longer-term studies one in rat and one in dog were performed to assess the specific toxicity of the new route of treprostinil administration. The key observations are the effects of aerosolized treprostinil on the naso-pharyngeal, respiratory tracts and myocardium (in rats).

In the one short-term study when nebulized treprostinil sodium, at concentration of 50 µg/L, was administered to male rats for 2, 3 and 4 hours with estimated exposure of 300, 416 and 569 µg/kg via nose-only inhalation, there was a significant decrease in respiratory rates and minute volumes (baseline controlled). The change reverted 24 hours after completion of the exposure.

Longer term exposure (13 weeks) in rats exposed to aerosol by nose only at the following exposures 7.1 µg/L for 20 min/day, 44 µg/L for 30 min/day and 40.3 µg/L for 225 minutes/day [total exposure of 7 (low), 67 (mid) and 464 (high) µg/kg/day;] control animals were not exposed to any inhalation therapy.

Lesions in the respiratory tract included: squamous metaplasia in the larynx (all doses); hemorrhage and macrophage accumulation in the lungs (all doses); hyperplasia/hypertrophy of goblet cells in the nasal cavity (all doses); degeneration/regeneration of the respiratory epithelium in the nasal cavity (mid and high doses), respiratory epithelial ulceration (high dose) and finally olfactory epithelial degeneration in the nasal cavity (high doses). Also noted was myocardial degeneration/fibrosis (all doses). There were degenerative changes observed in the testes and adrenal adrenal glands. Of these changes, only the changes in the epididymal lesions appeared reversible.

In dogs 13-weeks exposure by the oro-nasal route of inhalation at exposures of 0.025 mg/L for 15 minutes and 0.224 mg/L for either 6 or 30 minutes daily for 13 weeks, with estimated exposure of 107 (low), 322 (mid) and 1558 (high) µg/kg/day. Microscopic related lesions in the respiratory tract in nasal cavity and larynx in the mid and high doses groups included focal or multifocal respiratory epithelial degeneration/regeneration in the nasal cavity (mid and high dose). Other lesions included goblet cell

hyperplasia/hypertrophy (high dose), ulceration in the squamous and respiratory epithelium (high dose) and degeneration/necrosis in the squamous epithelium (high dose); degeneration in the larynx (mid and high doses). Lung hemorrhage was observed in 1 of 6 low dose dogs but this incidence was within the historical experience.

The C_{max} in venous blood, of the low doses of both dogs and rats are less than a log-unit higher than generated by the humans by the inhalation route.

Biopharmaceutics:

The current information for treprostinil inhaled relies heavily on the labeling of the subcutaneously administered route.

Treprostinil when administered by the inhaled route is rapidly detected in the plasma. The T_{max} of the treprostinil is between 7-15 minutes after the end of the inhalation. The concentrations rapidly dissipate with a $T_{1/2}$ of approximately 45 minutes to 1 hour. In a cross-over study comparing the AUC of a single dose of 3 or 6 breaths to a dose of 15 ng/kg/min administered intravenously for 60 minutes, the absolute bioavailability based on venous blood was determined to be between 62-74%.

Treprostinil by the oral route (treprostinil ethanolamine) was studied in five drug-drug interaction studies. There were no interactions with either bosentan or sildenafil. When administered with gemfibrozil a CYP2C8 inhibitor, exposure and Cmax of treprostinil was approximately doubled. There was a small 14% change in exposure when co-administered with fluconazole (a CYP2C9 inhibitor). In the presence of rifampin, treprostinil's AUC decreases by 30%.

It is unlikely that any of the drug interactions would alter the effectiveness of treprostinil, since exposure at the active site occurs in advance of systemic exposure. Increase or decrease in systemic related adverse events such as vasodilation, however, may be provoked by the concomitant use of drugs that either increase or decrease serum levels of treprostinil.

QT study:

With respect to the thorough QT study, there were small increases in QTcI intervals (as well as other rate-corrected QT interval measurements) after inhalation of 14 breaths, at the initial assessment points (approximately 5 minutes) with the effect dissipating fairly rapidly. The inhaled dose of treprostinil was only 55% higher than the recommended dose. The predicted values of QT measurements at C_{max} are shown below. Of note, the venous plasma concentrations generated by the inhalation route of administration generates concentrations of approximately 12 ng/ml. Concentrations generated by the subcutaneous route of administration can be approximately a log unit higher than the concentrations generated by the inhalation route.

Table 1: Modeled effects of inhaled treprostinil on measurements of repolarization at Cmax for the 14 puff dose. Slope is unit change per pg/ml treprostinil concentration.

QT Parameter	Slope of Plasma Concentration	Standard Error of Plasma Concentration	p-value	Predicted QTc at Average C_{max}	One-sided Upper 95% Confidence Bound of Predicted QTc	Overall Model Fit
QTcI	0.0040	0.0004	0.0000	6.8977	8.0418	<.0001
QTcF	0.0040	0.0004	0.0000	7.3455	8.4696	<.0001
QTcB	0.0065	0.0006	0.0000	13.3221	14.7745	<.0001

[1] Linear Mixed Model if fit for change from baseline (not placebo-correct) versus the plasma concentration as a fixed effect with subject included in the model as a random effect.
[2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

Medical/Statistical;

The application consisted of a single placebo-controlled, single regimen study in patients who were WHO class I and nearly all NYHA class III subjects who were on stable does of either bosentan or later sildenafil as an alternative.

The randomized treatments were either placebo or treprostinil administered by the OptiNeb® nebulizer. The initial dose was 3 puffs (with each puff dispensing 6 μg of drug). Doses were repeated 4 times during waking hours at approximately 0, 4, 8 and 12 hours. If the initial first administration was tolerated, the dose was to be gradually up-titrated to a target dose of 9 puffs QID.

Subjects were stratified based on study center.

6MWD were performed at screening (visit 1), first dose (visit 2), week 6 (visit 3) and immediately prior to the last dosing (visit 4) and after 4 hours following the last dose (visit 5). The timing of the 6MWD was to be 3 and 5 hours after a bosentan and 30-120 minutes after a sildenafil dose (these are approximately peak effects of those therapies). On visits 2, 3 and 4 the 6MWT was carried out to capture peak inhalation effects (10-60 minutes post inhalation) at visits 1 and 5 the effects will be measured at trough (approximately 4 hours post inhalation).

The primary endpoint of the study was 6MWT at peak inhalation effect on week 12 (visit 4). For subjects with missing information values (i.e., ranks) will be imputed based on whether the subject discontinued for worsening of disease or for non-disease related events. For those who discontinued for adverse events the algorithm employed a LOCF or last rank carried forward analysis. For those who discontinued due to worsening disease, a worst value or worst rank was imputed.

Secondary end points were:

- Time to worsening[1].

[1] Time to death, transplantation, hospitalization for PAH or transition to IV or SC prostacyclin therapy.

- The Borg Dyspnea score.
- Change in NYHA functional class as assessed by the investigator.
- Change in walk distance walked at the week 12 trough walking distance.
- Change in distance walked at the week 6 peak walking distance.
- QOL as of week 12 (Minnesota Living with Heart Failure, MLWHF questionnaire).
- Signs and symptoms of PAH
- Troponin T and proBNP levels
- Change in walk distance at day 2 (peak walking distance after the initial dose)
- The PK of treprostinil.

For the secondary endpoints, alpha was allocated sequentially. Should the hierarchy of parameters no longer attain significance, the residual analyses then become exploratory in nature.

There was a difference in walk distance comparing placebo at peak

Table 2: Effect at 12-week peak walk distance comparing inhaled treprostinil to placebo

Baseline (median)	359	361
Change at Week 12	+21.6	+3.0
Treatment effect (Hodges-Lehmann estimate) (95%CI)	+ 20.0 (8.0, 32.8) P=0.006	

The first secondary endpoint, the time to clinical worsening was not different between treatments. Other secondary endpoints are therefore only descriptive in nature.

With respect to the effect at the interdosing interval at week 12, there was a 13 meter difference comparing the treprostinil to placebo. This effect is approximately 2/3 of that observed at peak.

Safety:

During the 12-week placebo controlled study, the majority of adverse events could be attributed to either to the route of administration, adverse events of prostacyclin use (vasodilatation and joint pain), and events associated with the pulmonary artery hypertension disease process. The adverse events during the double blind phase are shown below:

Table 3: Adverse events and (%) occurring during the Double-blind portion of TRIUMPH 001

Adverse event	Treprostinil (N=115)	Placebo (N=120)	Difference in %
Patient with any event*	101 (88%)	100 (83%)	5
Cough	62 (54%)	35 (29%)	25
Headache	47 (41%)	27 (23%)	18
Nausea	22 (19%)	13 (11%)	8
Dizziness	20 (17%)	18 (15%)	2
Flushing	17 (15%)	1 (< 1%)	15
Throat irritation	16 (14%)	10 (8%)	6
Pharyngeal pain	13 (11%)	7 (6%)	5
Diarrhea	11 (10%)	9 (8%)	3
Chest discomfort	7 (6%)	4 (3%)	3
Syncope	7 (6%)	1 (<1%)	6
Epistaxis	6 (5%)	2 (2%)	3
Jaw pain	6 (5%)	5 (4%)	1
Extremity pain	5 (4%)	4 (3%)	1
Lower respiratory tract infection	5 (4%)	1 (< 1%)	4
Urinary tract infection	5 (4%)	1 (< 1%)	4
Chest pain	4 (3%)	3 (3%)	0
Pulmonary hypertension	3 (3%)	2 (2%)	1
Chills	3 (3%)	1 (< 1%)	3
Hemoptysis	3 (3%)	0	3
Stomatitis	3 (3%)	0	3
Wheezing	3 (3%)	0	3

*Sum of adverse events greater than this number

Adverse events in the treated group during the double blind phase reflecting irritation to the oro- and naso-pharynx and respiratory tree including; cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. During the double-blind study, discontinuations for oro-pharyngeal and respiratory issues were noted in five treprostinil and two placebo-patients. There was a small but not significant decrease in FEV1 and FVC in the treated group compared to the placebo group among those were available at the end of the study (excluded dropouts). The sponsor was asked to fully evaluate adverse events during the double blind phase by an ENT examination.

During the long term open-label exposure, the second most common cause for discontinuation was cough. Serious adverse events during the open-label portion of the study included pneumonia (in 8 subjects). There were three serious episodes of hemoptysis noted during the double-blind and open-label experience. One was lethal and two required invasive maneuvers to stem bleeding.

Although similar hemoptysis events were observed when treprostinil was administered by the subcutaneous route, it is unclear if the event rate by the inhaled route of administration increases the risk of these adverse events to an intolerable level. I therefore, recommend that prior to or as a commitment for approval a method for fully assessing the pulmonary and orophayngeal risk is in place.

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/s/

Abraham Karkowsky
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MEDICAL OFFICER
CDTL memo

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-387 serial 0000
Submission Code	5/S
Letter Date	June 26, 2008
Stamp Date	June 30, 2008
PDUFA Goal Date	April 30, 2009
Reviewer Name	Abraham M. Karkowsky, M.D., Ph.D.

Review Completion Date

Established Name	Treprostinil for inhalation
(Proposed) Trade Name	Tyvaso®
Therapeutic Class	Prostacyclin antagonist
Applicant	United therapeutics
Priority Designation	S
Formulation	Liquid for inhalation
Dosing Regimen:	Up to 9 breaths four times daily during awake hours
Indication	To increase walk distance
Intended Population	PAH patients WHO class I disease with WHO functional class III

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Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

Pending acceptable performance and labeling of the OptiNeb® device (including an human factor study), the drug can be approved for its use in conjunction with either bosentan or sildenafil to increase walk distance in subjects with WHO functional Class III as a consequence of idiopathic/familial pulmonary arterial hypertension (PAH), PAH as a consequence of collagen vascular disease, left to right congenital cardiac shunts or anorexigens. The label should make it clear that the effect at the interdosing interval has waned relative to the effect at peak.

Labeling should also make it clear that there is limited information regarding the persistence of a drug effect at time points in excess of the duration of the controlled clinical studies (12 weeks). There is no credible dose ranging data, for this drug. The lack of an adequate dose-range for the inhaled route is important since with either subcutaneously or intravenously administered treprostinil, there is substantial drift to higher treatment doses as time passes. It is unclear if the need for higher doses reflects a worsening of disease and, therefore, the need for additional pulmonary artery vasodilation or whether the need for higher doses reflects some degree of tolerance development. There is no such flexibility with the inhaled formulation.

The effect at the interdosing interval, largely measured after an overnight hiatus suggests that a portion of the drug's effect persists throughout the interdosing interval. The metric, however, was in the hierarchy of endpoints placed below the clinical worsening, which was not significant, consequently, the assessment of interdosing interval can only be considered as descriptive.

The major safety concern is that treprostinil is highly irritating. When administered by the inhalation route the irritation is particularly notable on the oro-nasopharynx and respiratory tree. There have been cases of hemoptysis that are of particularly serious, requiring invasive maneuvers to control bleeding. These events, however, cannot definitely be attributed to treprostinil by inhalation since these events occur with other drugs for PAH even when the route of administered is not by the inhalation route.

Risk Benefit Assessment

The benefit of inhaled treprostinil treatment is that there is a increase in functional performance as demonstrated by an increased six-minute walk distance (6MWD). There is no credible evidence that the course of PAH is altered by use of inhaled treprostinil. The magnitude of the 6MWD was no better and perhaps less than the only other approved prostacyclin drug for inhalation.

The safety for treprostinil by the inhaled route is largely described by the safety experience for treprostinil when it is administered systemically (SC or IV). The data, even for

this route of administration are limited because of the small exposed population who utilize this drug as therapy for PAH.

With respect to treprostinil when administered by the inhaled route, preclinical data (see review by Dr. X. Joseph), indicate some risk to the respiratory (pulmonary hemorrhage and squamous metaplasia in the larynx and hyperplasia/hypertrophy of the goblet cells of the nasal cavity and other irritation-related changes) in mice (13-week study). Also noted was degeneration and fibrosis in the heart. In dogs, (13-week study) lesions were noted in the oral and respiratory tract. Among the canine lesions noted, was one animal with pulmonary hemorrhage (within the historical controls) and degeneration and regeneration in the nasal cavity including goblet cell hyperplasia/hypertrophy and degeneration of the squamous epithelium with degeneration of the ciliated epithelium in the larynx. These lesions were not seen pre-clinically for treprostinil when it was administered by the subcutaneous route. In addition, there were suggestions that the inhaled route of administration of treprostinil had effects on spermatogenesis, also not observed when treprostinil is administered subcutaneously or intravenously. The sum of the risks for treprostinil by the inhalation route can likely be described by the risks of systemic exposure plus the additional risks to direct toxicity to the pulmonary and cardiac systems.

In clinical studies, there were episodes of pulmonary hemorrhage noted among those treated with treprostinil by the inhaled route. Several of there events were serious in nature and led to death or required invasive maneuvers or required prolonged hospitalization. These events and outcomes included: intrapulmonary hemorrhage that resulted in death, and hemoptysis that required bronchoscopy or embolization. It should be noted that events such as these were also noted with the use of treprostinil by the SC route. Hemoptysis was also noted with Iloprost when administered by the inhaled route and with sildenafil (a PDE V inhibitor). Whether the frequency and severity of the pulmonary events with inhaled treprostinil is more severe or more frequent than comparative treatments is not possible with the data at hand.

Liver abnormalities were also noted but these events were largely confounded by the concomitant use of bosentan. I can't tell whether the frequency or intensity of such events are increased or worsened by the concomitant use of treprostinil.

Recommendations for Postmarketing Risk Management Activities

The sponsor should maintain a registry of those treated with inhaled treprostinil (we suggested that his may be a possibility when we met with the sponsor of November 1, 2006). Although a registry would not allow one to assess the comparative risk of inhaled treprostinil to other treatments for PAH, a registry would allow one to assess event rates and calculate absolute bounds of risk both for pulmonary events and for liver dysfunction. The sponsor currently follows a large cohort of patients who are treated with subcutaneous or intravenous treprostinil. Since the PAH population is largely treated at specialty clinics, maintaining a registry for those who are treated with Tyvaso® is feasible.

Recommendations for other Post Marketing Study Commitments

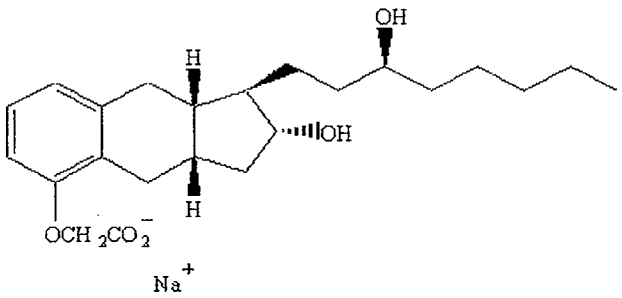
None

Introduction and Regulatory Background

Product Information:

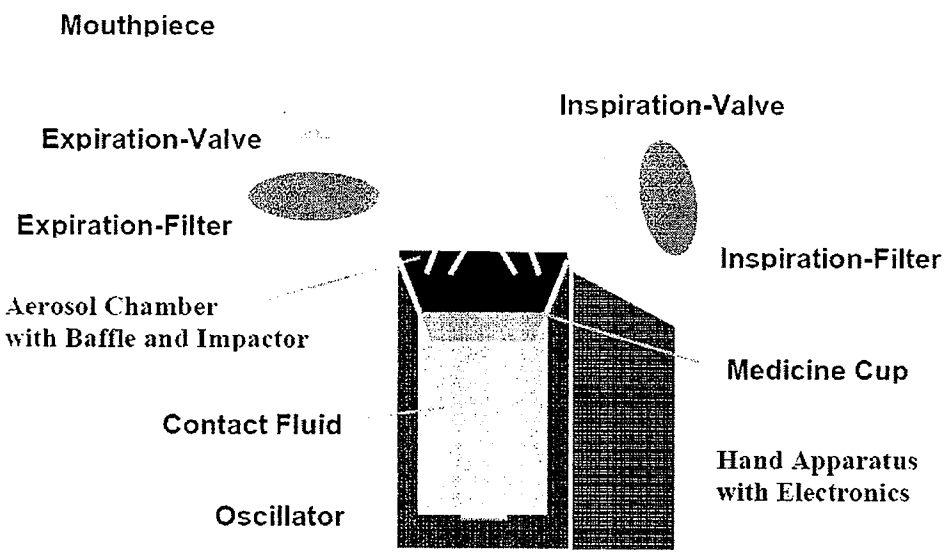
The structure of treprostinil is shown below.

Figure 1: Structure of treprostinil



The drug is currently approved for use by the subcutaneous and intravenous routes of administration. The sponsor, however, has recently added new and multiple manufacturing sites b(4) [redacted]. These sites have not yet been approved and consequently, Tyvaso has not yet been cleared by the Quality Assurance group. Tyvaso's approval would be contingent on the approval of these manufacturing sites. In this application, the sponsor submits the supporting data and request approval for the use of treprostinil in WHO I patients with WHO functional class III → (only class III patients are adequately represented) heart failure who are on concurrent therapy with either bosentan or sildenafil. Tyvaso was studied and will be marketed as a drug-device combination. The specific device that was studied was the OptiNeb® nebulizer (shown below).

Figure 2: OptiNeb device



Tables of Currently Available Treatments for Proposed Indications:

Currently, treatments for pulmonary artery hypertension include three classes of drugs that target reducing pulmonary artery pressures. There are also adjunctive therapies that include diuretics and anticoagulants, which do not act directly at the sites of the primary disease. The specific classes of drugs and their route of administration are shown in the Table below.

Table 1: Available products to treat increased pulmonary pressure in subjects with PAH

Class of drug	Name of drug	Trade name	Route of administration
Prostacyclin vasodilator	Epoprostenol sodium	Flolan®	Intravenous
	Iloprost	Ventavis®	Inhalation
	Treprostinil	Remodulin®	Subcutaneous and if not tolerated by that route intravenously
Endothelin-1 (ET_A or mixed ET_A and ET_B) antagonist	Bosentan	Tracleer®	Oral
	Ambrisentan	Letaris®	Oral
PDE V inhibitors	Sildenafil citrate	Revatio®	Oral

Availability of Proposed Active Ingredient in the United States

The active ingredient is currently approved for subcutaneous and intravenous (when the subcutaneous route is not tolerated) use. A new manufacturing site [redacted] for Tyvaso® has not yet been found acceptable. The OptiNeb® nebulizer has not been approved as a general use nebulizer.

b(4)

Important Safety Issues, With Consideration to Related Drugs

The most common adverse events attributable to the class of Prostacyclin vasodilators include: symptoms of vasodilation (flushing, headache and hypotension); gastrointestinal symptoms (nausea, vomiting and abdominal pain); musculoskeletal pain (jaw pain). For remodulin administered as a subcutaneous infusion, irritation-related adverse events at the site of the infusion were nearly universally observed. For Iloprost (Ventavis®), administered by inhalation, hemoptysis was also noted. Prostacyclin vasodilators (both Tyvaso and Ventavis), however, inhibit platelet function and bleeding episodes may be unrelated to a direct irritant effect of Tyvaso®.

Summary of Presubmission Regulatory Activity Related to Submission

The following meetings were held with the sponsor:

- December 16 2004-
  - In this meeting the sponsor was asked for greater CMC controls, to define the relative bioavailability of their product by the inhalation route relative to that when it is administered by the SC route. They were also asked to define clinical efficacy, specifically, the time course of benefit, the effect of dose, whether the first dose is effective, and whether there is a rebound after the withdrawal inhaled treprostinil for at least 24 hours. They were also asked to provide a QT study.

- April 26, 2005- This meeting was with regards to the pivotal protocol. Issues that were discussed included the recommendation that this should be a dose ranging study; that the sponsor should define the algorithm for handling discontinuations and safety issue with regards to oro-pharyngeal irritation.

- November 1, 2006- This was a guidance meting in preparation for the submission of this NDA

  - Preclinical- A carcinogenicity study would be required.
  - Clinical- A QT study will be necessary
  - All discontinued patients should be followed through the entirety of the study.
  - A registry of patients may be needed for safety because of pulmonary and cardiac toxicity
  - The 6MWD effect must be better than marginal.
  - Nebulizer-The eventual use of an alternate nebulizer.
  - An interim analysis.
  - Biopharmaceutics- drug-drug interaction study would not be specifically needed for inhaled treprostinil.
  - CMC- The sponsor noted they would be s [redacted] at different sites and asked whether additional preclinical information would be necessary. b(4)

- Asked if this submission could be considered for fast track designation – Since no benefit of clinically meaningful outcomes, the Division would not treat this application for fast-track designation.
- Format for older studies by the SC route.

- May 16, 2008- Pre-IND meeting:
  - Administrative- The meeting dealt with issues regarding the submission of this NDA.

Other Relevant Background InformationEthics and Good Clinical Practices:

Submission Quality and Integrity

Compliance with Good Clinical Practices;

DSI audited two sites. The data from the site for which Dr. Robert Bourge, University of Alabama, was the principal investigator, was found acceptable.

The data from the site of Valeraie McLaughlin, University of Michigan, however, was found to have not adequately followed the timing of the measurements of walk test as stipulated by the protocol. This site enrolled 29 subjects. Of note, none of the deviations in the timing of the walk tests, corresponded to the Visit 4 pivotal walk test. As such, although the deviations could alter some of the measurements, the primary metric of the study appears to be reliable. There were five subjects whose visit 5 walk-measurements were performed at an inappropriate time. Of these 5 subjects, four were placebo-treated subjects and only one was on active treatment. The inappropriately timed measurements would have captured some effects closer to the peak drug effect. Since there was only one treprostinil-treated patient who deviated in the timing of the trough measurement, the effect would be minimal. In summary, the lack of attention to the proper timing of the 6MWD assessment in Dr. McLaughlin's site, would have little impact on the results of the study

Financial Disclosures

The sponsor in submitting form # 3455, notes the following investigators had financial arrangements with United Therapeutics Corp, and received "significant payments": [redacted]. The sponsor asserts that the payments did not alter the outcome of the study. It should be noted that the numbers of subjects enrolled in these sites is substantial [redacted]. An analysis of these [redacted] ubjects to assess their effect on the preliminary outcomes demonstrated that although the sites with financial interest had a numerically greater effect, the residual sites still demonstrated a statistical benefit on peak 6MWD at week 12.

b(6)

Of note, the results of —— studies are the sole source for dose-response data for treprostinil. These studies were, single dose hemodynamic assessment of parameters such as pulmonary pressures, pulmonary vascular resistance and cardiac output. The data generated by —> in these studies was not submitted as a complete study report. The fact that this investigator had financial interests in this product further complicates the interpretation of these dose-ranging studies. Because these studies lacked primary data including the protocol and line listings, I have given little weight to the results reported from these studies. b(6)

In summary, the reliability of the data that demonstrated a performance benefit (6MWT) would partly depend on whether the— subjects who were enrolled by investigators who had financial arrangements with the sponsor drove the study's results. I've asked Dr. Lawrence to analyze whether the —subjects enrolled in these sites so differed from the population as a whole that they drove the results of the single pivotal study.

Significant Efficacy/Safety Issues Related to Other Review Disciplines

Chemistry Manufacturing and Controls

The chemistry, manufacturing and control review will be incorporated into the CDTL review.

Clinical Microbiology

The clinical microbiology review will be incorporated into the CDTL review.

Preclinical Pharmacology/Toxicology

The complete preclinical pharmacology review will be incorporated into the CDTL review.

Clinical Pharmacology

Mechanism of Action

Treprostinil is a prostacyclin vasodilator and is currently approved for the treatment of PAH when it is administered either by the subcutaneous or, if not well tolerated because of site pain, by the intravenous route.

Pharmacodynamics

A QTc study employed a dose of 14 puffs or 8 puffs of inhaled treprostinil (approximately 6 µg/puff). The larger of these doses of treprostinil was only marginally greater than the proposed treatment dose of 9 puffs/treatment, as a single administration, and only two

puffs greater than some doses which were actually used in these clinical studies. Furthermore, the timing of the ECG measurements did not capture the effect on repolarization at the end of the inhalation and consequently, likely missed peak effects. In addition, the QTc study only used a minimal excess of dose relative to the proposed dosing regimen. Nevertheless, the small increase in QTc at the initial time point rapidly dissipates and consequently, this increase would not likely be a risk to patients.

Pharmacokinetics

The pharmacokinetic measurements of treprostinil by the inhaled route were assessed by the measurement of venous blood samples in two studies. LRX-TRIUMPH BA-001 was a preliminary study to assess the tolerable doses that could be used in a complete QTc study. There were 6 subjects/group and the kinetic constants are shown below. Although time points earlier than 5 minutes post dose were not captured, with the small number of subjects, it appears that the maximal effect occurs somewhat after the first time measurement (T_{max} = 0.25 hours, or 15 minutes).

Table 2 Pharmacokinetic parameters mean + SD. Study LRX-TRIUMPH BA-001

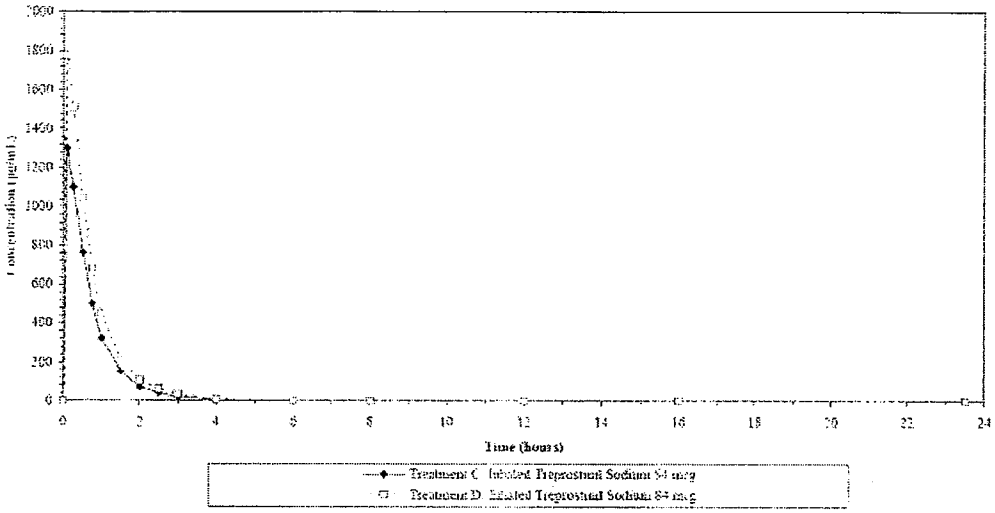
Dose	AUC $_{0-\infty}$ pg-hr/ml	C_{max} pg/ml	T_{max} (hr)	$T_{1/2}$ (hr)	Cl/F L/hr/kg
9 puffs	812 ± 472	915 ± 416	0.25 ± 0.15	0.55 ± 0.18	1.45 ± 1.4
12 puffs	660 ± 444	787 ± 479	0.18 ± 0.11	0.46 ± 0.08	3.4 ± 3.5
15 puffs	1579 ± 816	1708 ± 1055	0.21 ± 0.05	0.57 ± 0.11	1.4 ± 1.9
14 puffs	1206 ± 534	1284 ± 872	0.18 ± 0.06	0.58 ± 0.15	1.19 ± 0.75
13 puffs	1181 ± 239	1582 ± 836	0.19 ± 0.10	0.54 ± 0.14	1.01 ± 0.27

Study RIN-PH-103 (PRACS R06-028) was the thorough QTc study, pharmacokinetics were assessed in the 60 patients/treatment group treated with either 9 puffs or 14 puffs of treprostinil. The pharmacokinetic constants and curve of venous concentrations are shown below. T_{max} occurred at the first measured time period (5 minutes, 0.12 h).

Table 3: Pharmacokinetic parameters for study RIN-PH-103 (PRACS R06-028)

	Treprostinil 9 puffs	Treprostinil 14 puffs
C_{max} (pg/ml)	1316 ± 430	1796 ± 635
$AUC_{0-\infty}$ (pg*hr/ml)	975 ± 281	1352 ± 356
T_{max} (hr)	0.12 ± 0.07	0.12 ± 0.07

Figure 3: Pharmacokinetics for study RIN-PH-103 (PRACS R06-028)



Arterial concentrations were not measured and these concentrations may more reflect the concentrations of drug at the lung and heart.

Sources of Clinical Data

Tables of Clinical Studies:

Only studies with inhaled treprostinil were reviewed in this document. Previous studies with subcutaneous or intravenous treprostinil were not further reviewed. There were a large number of single investigator studies that were not submitted with the appropriate supporting material. The sponsor was asked to supply both the protocol and the line listings for these studies but was unable to obtain these documents. Consequently, the results of these studies were not seriously considered in the decision making process.

Table 4: Overview of Investigator-initiated Clinical Studies with Inhaled Treprostinil.

Protocol Number	Study Design	Sample Size	Comparison Group	Dosage of Treprostinil	Duration of Treatment
LRX-TRIUMPH BA.001	Ac, OL, 3 Period Crossover	18	Intravenous (IV) treprostinil	15 ng/kg/min IV	60 minutes
				18 ug	3 breaths
				36 ug	6 breaths
RIN-PH-102	Ac, R, DB, PC	40	Placebo	54 ug	9 breaths
				72 ug	12 breaths
				78 ug	13 breaths
				84 ug	14 breaths
				90 ug	15 breaths
RIN-PH-103	Ac, R, DB, PC, PosC	240	Placebo, Moxifloxacin	54 ug	9 breaths
				84 ug	14 breaths
LRX-TRIUMPH 001	C, R, DB, PC	235	Placebo	54 ug (9 breaths) 4 times daily	12 Weeks
LRX-TRIUMPH 001 (OL continuation phase)	C, OL	206*	None	Up to 72 ug (12 breaths) 4 times daily	Long term, ongoing

Ac = acute, C = chronic, R = randomised, SB = single blind, DB = double-blind, PC = placebo controlled, PosC = positive control, OL = open label
*206 patients that were previously randomised in the 12 week period of the study

Overview of Investigator Initiated Clinical Studies with Inhaled Treprostinil

Protocol Number	Study Design	Sample Size	Comparison Group	Dosage of Treprostinil	Duration of Treatment
LRX-TRE-INH-0001[a]	R, Ac, SB	44	Iloprost	Single dose 4 ug/mL (4 ug) 8 ug/mL (8 ug) 16 ug/mL (10 ug)	6 minutes 6 minutes 3 minutes
LRX-TRE-INH-0002[a]	R, Ac, SB	28	Placebo	Single dose 16 ug/mL(16 ug) 48 ug/mL (48 ug) 96 ug/mL (40 ug)	6 minutes 6 minutes 2 minutes
LRX-TRE-INH-0003[a]	R, Ac, SB	13	None	Single dose 96 ug/mL (80 ug) 200 ug/mL (50 ug)	2 minutes 1 minute
LRX-TRE-INH-0004[a]	R, Ac, SB	42	None	Single dose 15 ug delivered as: 100 ug/mL 200 ug/mL 600 ug/mL 1000 ug/mL 2000 ug/mL	 18 breaths 9 breaths 3 breaths 2 breaths 1 breaths
LRX-TRE-INH-0005[a]	C, OL	15	None	16 ug QID or 32 ug QID during Week 1 Up to 72 ug QID during chronic phase	Long-term
LRX-TRE-INH-0006[b]	C, OL	12	None	30 ug QID or 45 ug QID during 12 Weeks Up to 72 ug QID during chronic phase	Long-term
LRX-TRE-INH-0007[a] (called Investigation #5*)	R, Ac, SB	51	Sildenafil pretreatment	Single dose 600 ug/mL (15 ug) 600 ug/mL (30 ug)	3 breaths 6 breaths

Ac = acute, C = chronic, R = randomized, SB = Single blind, PC = placebo-controlled, OL = open label, QID = four times daily
[a] Conducted at University Hospital Giessen, Giessen, Germany
[b] Conducted at UCSD Medical Center, La Jolla, California

Review Strategy;

There was only one placebo-controlled study and it was reviewed. No dose-ranging efficacy studies were submitted for review. The duration of the placebo-controlled study was limited to 12-weeks. Dr. Lawrence, the FDA statistician, re-performed the statistical analyses for the primary metric of interest in the placebo-controlled study.

No persistence of efficacy outside that 12 week window can be assured. A safety exposure in open-label format was also reviewed but the absence of a comparator group makes any conclusion regarding persistence of the modest benefit on 6MWD difficult to quantify.

In considering safety, each case report form was reviewed, in particular for adverse events associated with irritation provoked by this novel route of administration.

There were many investigator studies all carried out by the same investigator (Dr. Seeger) as noted above, the appropriate documentation for these studies was not supplied and the results of these studies could not be critically reviewed. The graphs as supplied in these studies, nevertheless, are included for completeness.

A thorough QT study was also reviewed.

Discussion of Individual Studies

Review of Efficacy

Efficacy Summary:

The sponsor submits a single study that demonstrated efficacy when treprostinil is administered by the inhaled route. The TRIUMPH 001 study is fully reviewed under "REFERENCES". To avoid redundancy, only a summary of that study is reproduced here.

TRIUMPH 001 was a placebo-controlled, randomized, multicenter, multinational efficacy study that enrolled subjects with PAH, functional class NYHA class III or IV due either to familial/idiopathic, anorexigens, secondary to collagen vascular disease or due to HIV. These subjects were to be on stable doses of bosentan, later amended to allow for sildenafil as an alternative to bosentan. Patients had to have a cardiac catheterization within 13 months of enrollment that demonstrated PAH: PAPm $\geq$ 25 mmHg, PCWP or LVEDP of $\leq$ 15 mm Hg and a PVR of > 3 mm Hg/L/min; as well as a recent chest X-ray consistent with PAH.

The randomized treatments were either placebo or treprostinil administered by the OptiNeb® nebulizer. The initial dose was 3 puffs (with each puff dispensing 6 µg of drug). Doses were repeated 4 times during waking hours at approximately 0, 4, 8 and 12 hours. If the initial first administration was tolerated, the dose was to be gradually up-titrated to a target dose of 9 puffs QID.

Subjects were stratified based on study center.

6MWD were performed at screening (visit 1), first dose (visit 2), week 6 (visit 3) and immediately prior to the last dosing (visit 4) and after 4 hours following the last dose (visit 5). The timing of the 6MWD was to be 3 and 5 hours after a bosentan and 30-120 minutes after a sildenafil dose (these are approximately peak effects of those therapies). On visits 2, 3 and 4 the 6MWT was carried out to capture peak inhalation effects (10-60 minutes post inhalation) at visits 1 and 5 the effects will be measured at trough (approximately 4 hours post inhalation).

The primary endpoint of the study was 6MWT at peak inhalation effect on week 12 (visit 4). For subjects with missing information values (i.e., ranks) will be imputed based on whether the subject discontinued for worsening of disease or for non-disease related events. For those who discontinued for adverse events, not suggesting deterioration, the sponsor imputed values based on an LOCF analysis. For those that deteriorated the imputed values were as follows:

Table 5: Imputation Algorithm for TRIUMPH 001 Study

	Non-parametric imputation	Parametric imputation
• Death or • Clinical deterioration or • Too ill to walk or • Addition of new PAH medications	Lowest rank	Value corresponding to poorest change among randomized subjects[1]
• Adverse event or • Lost to follow up or • Protocol violation or • Consent withdrawn or • Other reasons or missing data	Last rank carried forward	Last observation carried forward[4]
• Lack of efficacy	Mean matched placebo rank[2]	Geometric means corresponding to geometric mean matched placebo change[3]

[1] To impute a walk distance value corresponding to the poorest change:
Value (for that subject) = Baseline for that subject multiplied by the minimum value for all subjects defined as the walk value/baseline for the worst measured subject.
[2] to impute a mean matched placebo rank:
Take the mean rank for all 12-week placebo patients with the same etiology of disease and same overall baseline walk quartile.
[3] To impute the geometric mean matched placebo change value for an individual subject:
The value for that subject is the baseline value for that subject multiplied by the geometric mean for all 12-week values for placebo subjects who have the same etiology of their PAH and overall walk distance quartiles.
[4] Excluding week 12 trough assessments.

Secondary end points are:

- Time to worsening[1].
- The Borg Dyspnea score[2].
- Change in NYHA functional class as assessed by the investigator.
- Change in walk distance walked at the week 12 trough walking distance.

[1] Time to death, transplantation, hospitalization for PAH or transition to IV or SC prostacyclin therapy.

[2] Dyspnea during the 6-minute walk test is assessed by the Borg dyspnea scale. The scale spans values of 0 (no dyspnea) to 10 (the worst shortness of breath ever experienced.). The scale contains markers to define to the patient, representative values thus for example, 0= Nothing at all; 2= Slight; 4= Somewhat severe; 7 Very severe; 9= Very, very severe. 10= Maximum. Lower values imply less dyspnea.

- Change in distance walked at the week 6 peak walking distance.
- QOL as of week 12 (Minnesota Living with Heart Failure, MLWHF questionnaire)[3].
- Signs and symptoms of PAH[4]
- Troponin T and proBNP levels
- Change in walk distance at day 2 (peak walking distance after the initial dose)
- The PK of treprostinil.

For the secondary endpoints, alpha was allocated sequentially. Should the hierarchy of parameters no longer attain significance, the residual analyses then become exploratory in nature.

Discontinued subjects were not followed for the entirety of the study. If a subject discontinued early, it was not possible to assess whether the subject deteriorated during the duration of the study and should be assigned the worst outcome.

The study enrolled 235 patients into the study. Approximately 60% of those enrolled were enrolled in the USA. Demographics for those enrolled are shown in Table 6. The majority of patients were female with the etiology of their PAH predominantly idiopathic/familial. Approximately 70% of those enrolled were on stable doses of bosentan with a mean dose of 125 mg BID.

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[3] The QOL questionnaire consists of 21 questions that assess various dimensions of heart failure's impact on the patient. Each question is rated from 0 to 5 with 0=no effect and 5= very much. The specific questions are :

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by-		
Causing swelling in your ankles or legs?	Making your working to earn a living difficult?	Costing you money for medical care?
Making you sit down to rest during the day?	Making your recreational pastimes, sports or hobbies difficult?	Giving you side effects from treatments?
Making your walking about or climbing stairs difficult?	Making your sexual activity difficult?	Making you feel you are a burden to your family or friends?
Making your working around the house or yard difficult?	Making you eat less of the foods you like?	Making you feel a loss of self-control in your life?
Making your going places away from home difficult?	Making you short of breath?	Making you worry?
Making your sleeping well at night difficult?	Making you tired, fatigued or low on energy?	Making it difficult for you to concentrate or remember things?
Making your relating to or doing things with your friends or family difficult?	Making you stay in a hospital?	Making you feel depressed?

4

Sign→	Loud P2 sound	Right Vent S3 sound	Right Vent S4 sound	Right ventricular heave	Murmur of tricuspid insufficiency	Murmur of pulmonary valve insufficiency	Hepatomegaly	Jugular venous distention	Edema
Symptoms→	Ascites	Dyspnea	Orthopnea	Dizziness	Syncope	Chest Pain	Palpitations	Fatigue	

Table 6: Demographics of those who enrolled into TRIUMPH 001

Characteristic	Treprostinil (N=115)	Placebo (N=120)
Age Mean ± SD	55 ± 12	52 ± 14
Male/Female (% female)	22/93 (81%)	22/98 (82%)
Etiology of PAH (%)		
Idiopathic	64 (56%)	67 (56%)
Collagen Vascular disease	40 (35%)	37 (31%)
Other	11 (10%)	16 (13%)
Background therapy		
Bosentan	77 (67%)	88 (74%)
Median Bosentan dose	125 mg	125 mg
Sildenafil	38 (33%)	32 (27%)
Mean Sildenafil dose	37.5 mg	37.8 mg
NYHA status III/IV	112/3	118/2

Subjects were titrated to the highest tolerated or maximum dose of nine puffs/dose QID. At the end of the study 87% of the placebo subjects versus 77 (74%) of the treprostinil patients were at or above the goal dose.

Of those enrolled, 89% of the treprostinil patients and 92% of the placebo subjects completed the study. There was one death (placebo) and three patients discontinued due to worsening of their PAH (all treprostinil). The rest of the subjects discontinued either due to adverse events or to withdrawal of consent.

Table 7: Disposition of patients TRIUMPH 001

	Treprostinil	Placebo
N	115	120
Completed	102 (89%)	110 (92%)
Did not complete	13 (11%)	10 (8%)
Death	0	1 (<1%)
Worsening PAH	3 (3%)	0
Adverse event	7 (6%)	4 (3%)
Withdrawal of consent	3 (3%)	5 (4%)

The primary analysis for chronic (week 12 peak walking time) is shown below:

Table 8: Peak 6MWD at week 12 TRIUMPH 001

Baseline (median)	359	361
Change at Week 12	+ 21.6	+3.0
Treatment effect (Hodges-Lehmann estimate) (95%CI)	+ 20.0 (8.0, 32.8) P=0.006	

The results show a modest benefit in walk distance in the treprostinil group relative to placebo.

Subgroup analysis indicated that patients with the lowest walk times at baseline (lowest quartile), those outside the USA and those treated with bosentan had the largest effects. Other subgroups had means effects that generally favored treprostinil (see Figure).

Subject who discontinued were censored at the time of their discontinuation. Since these subjects were not followed for the entirety of the study, they could never achieve the imputation of worst rank even if they deteriorated. I have gone through the CRFs of these subjects and listed all those who appear to have some component of worsening of disease. These subjects are shown below,

Table 9: Outcome of patients who had not completed TRIUMPH 001 Including This Reviewer's Assessment

Pt ID	Demographics Age/gender/etiology/PAH baseline med B=Bosentan; S= Sildenafil [Last Visit with walk test]	Description	Sponsor's assessment	Reviewer's assessment
Active				
10013	49/F/CVD/S [Visit 3]	Stopped for severe fatigue	Adv event	Worst value
12004	52/F/CVD/B [Visit 2]	Stopped for severe fatigue	Adv event	Worst value
13008	64/F/idiopathic PAH/B [Visit 2]	Hospitalized for worsening PAH	New PAH med-	Worst value
13010	55/M/idiopathic PAH/B [Visit 6]	No evidence of worsening disease- Withdrew consent – no deterioration in last walk- No AE c/w deterioration	Withdrew consent	LOCF
13018	59/F/idiopathic PAH/B [Visit 2]	Had increased dyspnea –not yet recovered	Withdrew consent	Worst value
17003	55/F/idiopathic PAH/S [Visit 3]	Last walk distance decreased from 362 M to 244 M supposedly discontinued due to wheezing	Adverse event	Worst value
17005	51/F/idiopathic PAH/S [Visit 2]	Adverse events consisted of decrease O_2 saturation, excessively tired, increased shortness of breath	Adverse event	Worst value
18002	58/F/idiopathic PAH/B [Visit 4]	No evidence of adverse events suggesting worsening of disease or walk distance deterioration	Adverse event	Last rank carried forth
19007	44/F/CVD/B [Visit 3]	No deterioration in walk at week 6 but had stopped meds previously. Fatigue was noted prior to D/C and continued through discontinuation.	Withdrew consent	Worst value
22002	64/F/CVD/S Completed [visit5]	Patient hospitalized for PAH	New PAH med-	Worst
31002	60/F/Anorexigens/B [Visit2]	Only AE listed is hemoptysis, but this was not listed as reason for discontinuation (only interrupted)	Adverse event	?Worst value
32015	54/F/Idiopathic PAH/S [Visit 3]	AEs suggest reason for discontinuation was due to burning in pharynx. No evidence of decreased walk distance at week 6.Subject claims not able to perform walk test due to lumboischialalgia	Adverse event	Last rank carried forward

35006	56/M/Idiopathic PAH/S [Visit 3]	Disease progression	Disease progression	Worst value
39001	72/M/Idiopathic PAH/B [Visit 5]	Protocol violation-entered open label phase. Can't tell why subject discontinued	Protocol violation	Last rank carried forward
40012	60/F/CVD/B [Visit 2]	No walk tests after first dose study. Adverse events are chest tightness and sore throat	Adverse event	Last rank carried forward
47001	60/F/CVD/B [Visit 3]	Disease progression, patient hospitalized, can't tell if patient survived.	Disease progression	Worst value
Placebo				
13004	60/F/Idiopathic PAH/B [Visit 2]	No adverse events suggestive of decompensation. No follow up 6MWD.	Withdrew consent	Last rank carried forward
15009	54/M/CVD/B [Visit 5]	Minimal change in walk distance and an increase in Borg-dyspnea score (from 9 at baseline to 5 at 6 weeks). Last dose was approximately 35 days previously.	Withdrew consent	Last rank carried forward.
15012	46/F/CVD/B [Visit 3]	Discontinued due to worsening cough, but had hypoxia that began 3 days after enrollment. Walk distance decreased from 290 to 235 M but dyspnea assessment was less from Borg sale 7 at baseline to 5 at week 6.	Adverse event	Worst value
19010	36/M/Idiopathic PAH/S [Visit 2]	Hospitalized for syncope	Withdrew consent	Worst value
23001	61/F/CVD/B [Visit 2]	Had worsening fatigue and dyspnea	Adverse event	Worst value
31006	29/F/CVD/B [Visit 3]	No evidence of worsening	Withdrew consent	Last rank carried forward
38003	56/F/Idiopathic PAH/B [Visit 2]	Discontinued for burning sensation of throat	Adverse event	Last rank carried forward
44003	53/F/Idiopathic PAH/S [Visit 2]	Discontinued for severe sickness- not worsening of disease	Adverse event	Last rank carried forward
49002	39/F/Anorexigens [Visit 2]	Died	Death	Worst rank
53001	67/F//CVD/B [Visit 3]	Had mild fatigue that resolved with decrease in walk distance from 430-390 with no change in Borg dyspnea score	Withdrew consent	Last rank carried forward

The process of imputing the worst values may be somewhat harsh. The analysis per sponsor indicates that with the above imputations, the six week walk distance is still significant ($p=0.013$); the week 12 metric, however, no longer demonstrated a significant drug effect ($p=0.6$), but there remains an overall effect of approximately 14.5 m. The fact that the week 6 data still demonstrates a drug effect suggests that treprostinil by the inhalation route is active. The lack of effect at week 12 probably is related to the number of subjects with imputed worse outcome values.

With respect to the trough drug effect (visit 5), this metric was placed lower in the hierarchy of secondary endpoints, after a metric that was no different between treatments. As such, the walk distance can only be considered as descriptive without a statistical interpretation.

With respect to secondary endpoints, these are fully described in the analysis of this study under "REFERENCES".

Review of Safety:

A full review of safety is included with the complete description of the study under "REFERENCES". With respect to the

Deaths, Dropouts and Discontinuations for the 12-week double-blind study:

There was one death in the study. Patient #49002 died a sudden death on day 5 of treatment. She was a 39 year-old female with the origin of her PAH due to use of anorexigens. Concomitant PAH medication included bosentan. Her baseline walk distance was 402 meters with a Borg dyspnea score of 3.

Serious Adverse events:

There were 10 treprostinil-treated patients and 15 placebo-treated patients who had serious adverse events during the double blind phase of the study. The number of subjects with serious events suggestive of worsening status was denoted by a √. The numbers of patients with serious events that may reflect worsening of the disease process were similar in the two treatments. 6/115 in the treprostinil group (5.2%) and 7/120 (5.8%) in the placebo group.

Table 10: Serious Adverse Events in the TRIUMPH 001 study

Pt ID	Demographics Age/sex/etiology	Event
Treprostinil		
13008√	64/F/primary	Patient had multiple (4) syncopal episodes over a six week period.
15008√	58/F/primary	She had a syncopal episode that was not associated with a dose of medication.
19003	74/F/Primary	She had abdominal pain, black tarry stools and a decrease in hemoglobin from 12 to 9 g/dL.
19011	52/F/primary	Patient was hospitalized with diarrhea, abdominal pain and recurrent *C. difficile.*
22002√	65/F/Collagen	Had syncopal episode at home; she was admitted for worsening disease.
35006√	46/M/Primary	Had decrease exercise capacity, increase in fatigue and dizziness. Hospitalized for worsening disease.
38009√	40/F/Other-hereditary telangiaectasia	Had right heart decompensation; edema of the extremities.
39002	74/F/CVD	Hospitalized with new onset diabetic ketoacidosis.
47001√	59/F/CVD	Hospitalized for anemia hemoglobin of 8.9 g/dL; She was also hospitalized for worsening disease-details not submitted.
Placebo		
10005	50/F/Primary	Hospitalized for bronchitis and discharged with antibiotics.
10006√	56/F/CVD	Hospitalized twice for worsening cor pulmonale; Flolan was started. She also had headaches that were defined as serious adverse event.
11010	43/F/anorexigens	Hospitalized for gallstones.
17004√	74/F/Primary	Had worsening congestive heart failure. Sponsor is awaiting additional information.
19001√	35/F/Anorexigens	She was hospitalized for chest pain diagnosed as anxiety attack. She was also hospitalized for GI bleed coffee-ground emesis and dark tarry stools. She was also hospitalized for volume overload and UTI.
19002√	60/F/Primary	She was hospitalized four times for fluid overload. Symptoms were increase in weight and extremity edema. On the first hospitalization she was noted to be hypokalemic. On the second hospitalization for fluid overload she had shortness of breath requiring oxygen treatment. On this hospitalization she was noted to be hyperkalemic. She also had an endoscopy for dark stools.
19009√	65/F/Primary	She was hospitalized for worsening pulmonary hypertension. No details given.
19010	36/M/Primary	He was admitted to ER for a near syncopal episode after working in the sun. This episode occurred about two weeks after discontinuation of therapy but during the observation period of the double blind study.
23005	65/F/CVD	During double blind phase she had musculoskeletal chest pain.
36001	54/M/CVD	She was hospitalized for small cell lung cancer.
38004√	46/M/Primary	Had worse PAH, also hospitalized for atrial flutter.
40002	63/F/CVD	She was admitted to the hospital for back pain and hematuria. She was also admitted for hyperkalemia (K+= 6.2) Spironolactone dose was decreased.
49002√	39/F/Anorexigens	She had a sudden death.
61001	43/F/CVD	She had increased fatigue and dyspnea, admitted for anemia and received two units of PRBC. She had candida esophagitis based on endoscopy.

The √ is my interpretation of worsening disease.

Overall adverse events

The sponsor supplies a list of adverse events > 3% and more frequent in the Treprostinil than placebo group.

Table 11: Adverse Events TRIUMPH 001 > 3% of those enrolled

Adverse event	Treprostinil (N=115)	Placebo (N=120)	Difference in %
Patient with any event*	101 (88%)	100 (83%)	5
Cough	62 (54%)	35 (29%)	25
Headache	47 (41%)	27 (23%)	18
Nausea	22 (19%)	13 (11%)	8
Dizziness	20 (17%)	18 (15%)	2
Flushing	17 (15%)	1 (< 1%)	15
Throat irritation	16 (14%)	10 (8%)	6
Pharyngeal pain	13 (11%)	7 (6%)	5
Diarrhea	11 (10%)	9 (8%)	3
Chest discomfort	7 (6%)	4 (3%)	3
Syncope	7 (6%)	1 (<1%)	6
Epistaxis	6 (5%)	2 (2%)	3
Jaw pain	6 (5%)	5 (4%)	1
Extremity pain	5 (4%)	4 (3%)	1
Lower respiratory tract infection	5 (4%)	1 (< 1%)	4
Urinary tract infection	5 (4%)	1 (< 1%)	4
Chest pain	4 (3%)	3 (3%)	0
Pulmonary hypertension	3 (3%)	2 (2%)	1
Chills	3 (3%)	1 (< 1%)	3
Hemoptysis	3 (3%)	0	3
Stomatitis	3 (3%)	0	3
Wheezing	3 (3%)	0	3

*Sum of adverse events greater than this number

The main adverse events during the double blind study reflect adverse events that suggest local irritation (cough, throat irritation); prostacyclin related vasodilatation (e.g. headache and flushing); muscle/bone pain (jaw pain) and disease related adverse events (e.g., syncope).

Labeling Recommendations:

Full labeling assessments are contained at the end of this document.

Advisory Committee Meeting

None scheduled.

INDIVIDUAL STUDIES:

TRIUMPH I study: Double Blind Placebo Controlled Clinical Investigation into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Arterial Hypertension.

Important dates of this study:

The amendments are changes to the protocol. The Versions incorporate the changes included in one or more amendments.

Original Protocol submitted 11 January 2005.
Version #2: Used in European Union (EU) sites. Amendments 1-4 were approved.
Version #3: 31 January 2006- includes amendments 1-3.
Version #4: 26 February 2007- includes amendments 1-5 as used in the USA.

Amendment #1 dated 9 March 2005 included:

- Increased the entry criteria for 6-minute baseline walk distance to a maximum of 450 M.
- Reduces the initial dosing for inhaled treprostinil from nine to six breaths.
- Allowed for decreasing the bosentan dose for liver toxicity.
- Excluded patients whose PAH is due to chronic thromboembolic events or congenital heart disease.
- Adds a pregnancy test.

Amendment # 2-dated 12 May 2005 (USA); Amendment # 2-16 May 2005 (EU)

- Allows for an open label extension study and defines eligibility criteria for enrollment.
- Remove pregnancy test requirement during therapy.
- Removes the requirement to collect supine blood pressure.
- Added new investigators.

Amendment #3- dated 2 October 2005 (USA); Amendment # 3- 18 October 2005 (EU).

- Allows that the right heart catheterization that defines eligibility could be done up to 13 months prior to enrollment.
- Changes dosing procedure and requires monitoring of blood pressure for 15-30 minutes after the initial inhalation.
- Entry procedures for open label study.

Amendment # 4- dated 16 June 2006 (USA); Amendment# 4- dated 28 June 2006 (EU).

- Allows background therapy of stable sildenafil as an option to the use of bosentan.
- Altered the power calculations for this study. Allowed for an interim analysis. Added a data safety monitoring board.
- Altered some aspects of the open-label study

Amendment #5: dated 15 February 2007; Amendment #5- 17 December 2007 (EU); Amendment # 5- 18 April 2008 (Israel).

- Removed interim analysis,
- Added optional pharmaco-genetic analysis;
- Addition of NT- Pro-BNP at 12 and 24 months.

Amendment #6- 20 March 2007

- Removed the 13 month requirement prior to enrollment to have had a catheterization.

First patient enrolled: 7 June 2005.
Last patient enrolled: 13 July 2007.
Last patient completed: 12 October 2007.
Statistical methods dated: 26 September 2007.

Note: The statistical method section was completed shortly before the last subject completed.

The most current version of the protocol as implemented in the USA is version 4.0, the most current version of the protocol implemented in the EU was Version 2.0; in Israel it is Version 3.0. This version (3.0) includes the five amendments. The sixth amendment remains a stand alone document.

Formulation:

The appropriate study medication (treprostinil sodium or placebo) was provided to the investigational sites directly by Catalent Pharma Solutions. One kit supplied each subject with study medication for the entire double-blind portion of the study.

Inclusion criteria:

Patients are eligible for enrollment if they:

- Sign an informed consent. In the USA, HIPPA authorization is required.
- Are males and non-child bearing females (unless on acceptable birth control) of 18-75 years inclusive.
- Have PAH with the origin as either idiopathic/familial, anorexigens, secondary to collagen vascular disease or due to HIV.
- Have an un-encouraged 6-minute walk test of between 200 and 450 m.
- Have stable disease (NYHA class III-IV).
- Have a history (within 13 months) of a cardiac catheterization consistent with PAH; PAPm $\geq$ 25 mmHg, PCWP or LVEDP of $\leq$ 15 mm Hg and a PVR of > 3 mm Hg/L/min. Also a chest-X-ray consistent with PAH.
- Are on stable doses of bosentan or sildenafil for > 3 months.

Exclusion criteria:

Patients are ineligible for enrollment if they:

- Are considering pregnancy.

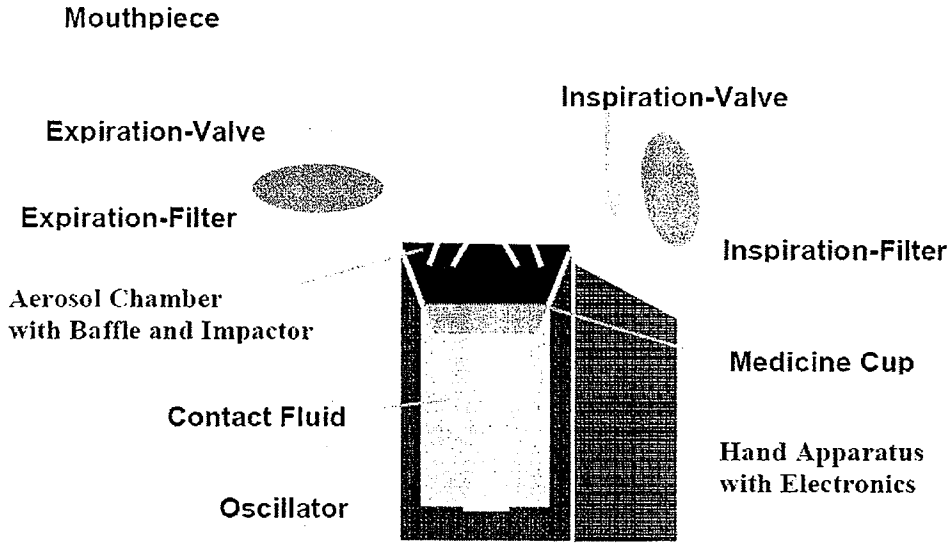
- Had recent investigational treatment, or demonstrated sensitivity to any of the potential drugs, or has received any prostanoids within 30 days.
- Have conditions not related to PAH that would limit exercise. These include: pulmonary venous hypertension, peripheral vascular disease, COPD, pulmonary capillary hemangiomatosis or musculoskeletal disease.
- Had a recent change in PAH medications including calcium channel blockers, endothelin blockers or PDE5 inhibitors other than sildenafil, this excludes anticoagulants which is not a reason for exclusion.
- Have other causes of pulmonary hypertension such as: parasitic disease, sickle cell disease, mitral stenosis or portal hypertension.
- Have confounding other diseases.
- Are unlikely to cooperate.

Doses and Formulations:

The test substance (treprostinil sodium) or placebo is to be administered by inhalation via the OptiNeb inhalation device (an ultrasonic nebulizer). The dose is to be administered QID (0, 4, 8 and 12 hours) during waking hours, without nighttime administration. The initial dose would be 3 breaths four times daily. If the initial dose is tolerated (i.e., stable BP and no flushing symptoms), the dose will be subsequently increased to a target dose or 9 breaths four times daily during waking hours. Each breath should deliver 6 μg (a total dose of 54 μg). Bosentan or sildenafil are commercially available products. The dose of bosentan is 125 mg BID; that of sildenafil is the dose currently taken by the subject.

The OptiNeb nebulizer is shown below. The oscillator vibrates a contact fluid, which vaporizes the treprostinil in the medication cup. The size of the particles is determined by the oscillator's properties. The volume (and dose) is dependent on the concentration of drug in the medicine cup as well as the volume contained between the inspiration valve and mouthpiece.

Figure 4: OptiNeb ultrasonic nebulizer.



Procedures:

The double-blind portion of the study is 12 weeks in duration. The study planned to enroll at total of 220 subjects who were currently being treated with stable doses of bosentan or sildenafil. Approximately half of these subjects are to be randomized to placebo and half to treprostinil. A listing of the procedures during the study is shown below:

Figure 5: Procedure during the Double-Blind Phase of TRIUMPH 001

Week→	Screening/ Baseline	1	2/4	6	8/10	~11.9	12
Visit # →	1	2		3		4	5
Procedures↓							
Informed consent/history	x						
Inclusion/Exclusion, Physical exam, NYHA class, laboratory tests, bosentan or sildenafil	x			x			x
Pharmacokinetic blood samples, pulmonary function tests, heart failure questionnaire, chest x-ray	x						x
Concomitant meds	x		x	x	x		x
Vital signs, six minute walk test, Borg dyspnea scale	x	x		x		x	x
Tolerance to drug			x	x	x	x	
Telephone call			x			x	
Device training	x			x			
Inhalation of study drug at site		x		x		x	
Pregnancy test	x						
Adverse events assessments	x	x		x		x	x

The peak measurements will be performed between 10 and 60 minutes post inhalation. These will be carried out at visits 2, 3 and 4. A trough test (performed at least 4 hours post

inhaled dose) will be done at visits 1 and 5. All walk-tests are to be performed at 3-5 hours post bosentan or 30-120 minutes after a sildenafil dose.

Randomization and blinding:

Stratification will be by center (not background therapy). Randomization is in blocks of four.

Primary endpoint:

The primary endpoint is the peak six-minute walk distance (6MWD) compared to baseline for the two treatments at peak (visit 5).

Secondary end points are:

- Time to worsening[5].
- The Borg Dyspnea score[6].
- Change in NYHA functional class as assessed by the investigator.
- Change in walk distance walked at the week 12 trough walking distance.
- Change in distance walked at the week 6 peak walking distance.
- QOL as of week 12 (Minnesota Living with Heart Failure; [MLWHF] questionnaire)[7].
- Signs and symptoms of PAH[8]

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[5] Time to death, transplantation, hospitalization for PAH or transition to IV or SC prostacyclin therapy.

[6] Dyspnea during the 6-minute walk test is assessed by the Borg dyspnea scale. The scale spans values of 0 (no dyspnea) to 10 (the worst shortness of breath ever experienced.). The scale contains markers to define to the patient representative values thus for example, 0= Nothing at all; 2= Slight; 4= Somewhat severe; 7 Very severe; 9= Very, very severe. 10= Maximum. Lower values imply less dyspnea.

[7] The QOL questionnaire consists of 21 questions that assess various dimensions of heart failure's impact on the patient. Each question is rated from 0 to 5 with 0=no effect and 5= very much. The specific questions are :

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by-		
Causing swelling in your ankles or legs?	Making your working to earn a living difficult?	Costing you money for medical care?
Making you sit down to rest during the day?	Making your recreational pastimes, sports or hobbies difficult?	Giving you side effects from treatments?
Making your walking about or climbing stairs difficult?	Making your sexual activity difficult?	Making you feel you are a burden to your family or friends?
Making your working around the house or yard difficult?	Making you eat less of the foods you like?	Making you feel a loss of self-control in your life?
Making your going places away from home difficult?	Making you short of breath?	Making you worry?
Making your sleeping well at night difficult?	Making you tired, fatigued or low on energy?	Making it difficult for you to concentrate or remember things?
Making your relating to or doing things with your friends or family difficult?	Making you stay in a hospital?	Making you feel depressed?

- Troponin T and proBNP levels
- Change in walk distance at day 2 (peak walking distance after the initial dose)
- The PK of treprostinil.

There was no alpha allocation to any of these endpoints. The statistical plan (submitted late) indicates that the alpha testing would cease when in the hierarchy a single secondary endpoint above no longer demonstrates significance.

Statistics:

The study was powered assuming a difference in peak between the two treatments of 35 meters at peak with a standard deviation of 75 meters. The sponsor assumes a 10% dropout rate. With a two-sided t-test at a level of 0.05 the trial would require 110 patients per group to have a 90% power to detect the assumed difference.

The primary populations are those who are randomized and received at least one dose of medication (the modified intent to treat population (mITT).

For missing values the following algorithm was employed:

Table 12: Imputation Algorithm for TRIUMPH 001 Study

	Non-parametric imputation	Parametric imputation
• Death or • Clinical deterioration or • Too ill to walk or • Addition of new PAH medications	Lowest rank	Value corresponding to poorest change among randomized subjects[1]
• Adverse event or • Lost to follow up or • Protocol violation or • Consent withdrawn or • Other reasons or missing data	Last rank carried forward	Last observation carried forward[4]
• Lack of efficacy	Mean matched placebo rank[2]	Geometric means corresponding to geometric mean matched placebo change[3]

[1] To impute a walk distance value corresponding to the poorest change:
Value (for that subject) = Baseline for that subject multiplied by the minimum value for all subjects defined as the walk value/baseline for the worst measured subject.
[2] to impute a mean matched placebo rank:
Take the mean rank for all 12-week placebo patients with the same etiology of disease and same overall baseline walk quartile.
[3] To impute the geometric mean matched placebo change value for an individual subject:
The value for that subject is the baseline value for that subject multiplied by the geometric mean for all 12-week values for placebo subjects who have the same etiology of their PAH and overall walk distance quartiles.
[4] Excluding week 12 trough assessments

Sign→	Loud P2 sound	Right Vent S3 sound	Right Vent S4 sound	Right ventricular heave	Murmur of tricuspid insufficiency	Murmur of pulmonary valve insufficiency	Hepatomegaly	Jugular venous distension	Edema
Symptoms→	Ascites	Dyspnea	Orthopnea	Dizziness	Syncope	Chest Pain	Palpitations	Fatigue	

Method of primary endpoint assessment:

For the primary endpoint, the method of analysis of the peak 6MWD was a non-parametric analysis of covariance (ANCOVA). The median difference between treatments will be estimated by the Hodges-Lehmann (H-L) estimator.

The particular covariates used in the analysis were: a variable related to disease category (one of five options; idiopathic/familial; collagen vascular disease; HIV-associated PAH; PAH-associated with anorexigens; or other), baseline walk-distance and treatment. No interaction term is included in the model. Of note, there was no term for the corresponding therapy (bosentan or sildenafil).

Several additional sensitivity analyses were planned, which appear to be minor variants of the primary analysis. One additional analysis appears to employ all data assessed at peak during the study by the general estimating equation approach. The test will assess whether there is an overall difference comparing placebo-treated to treprostinil treated subjects.

For the secondary metrics

Time to clinical worsening will be assessed by a log-rank statistic. A Cox proportional hazards model stratified by disease etiology will be applied to the data.

Borg Dyspnea Score: The change in baseline for the two groups is to be assessed by a Wilcoxon rank sum test. For those with no data, the imputation rules are as follows: If they died, worsened clinically, required additional PAH therapy or were too ill to perform the 6MWT, the change will be 10. Patients who withdrew for adverse event or were lost to follow up will have their last value carried forward.

NYHA functional classification: The change will be assessed by a Wilcoxon rank sum test. The LOCF method will be applied to those who discontinued for adverse events or were lost to follow. Those who discontinued due to obvious worsening will be classified as NYHA IV.

Trough 6MWT: Will be assessed as was the peak 6MWT.

QOL: The change will be assessed by a Wilcoxon rank sum test. Imputation will be as listed in Table 12.

Signs and symptoms score: The change in the presence or absence of a particular heart failure sign or symptom will be assessed. Missing information is coded as unknown. A Fisher's exact Test will be employed. An overall change of score will be assessed with a -1 assigned for present at baseline and no longer present, and 0 for absent sign and symptom. Conversely a +1 is assigned for a newly observed sign or symptom not present at baseline. In order to be assessed data must be available for at least 8 or the assessed signs/symptoms.

First dose peak 6-MWT: This will be assessed by a non-parametric analysis of covariance with the response variable equal to the rank of the change in walk distance. The covariates will include terms for: treatment group, baseline walk distance and disease etiology. Since the assessment is to be done early no missing values are anticipated.

Safety metrics: In addition to the usual safety metrics, the sponsor plans to assess changes in lung function as assessed by TLC and FEV. Vital signs will be measured after the first inhalation.

Results:

Investigators and sites and number randomized for each treatment is shown below.

Table 13: Investigators Sites and Number Enrolled for Each Treatment

Site	Investigators and sites	enrolled #UT-15/#PBO = total
10	Raymond Benza, M.D., University of Alabama at Birmingham; Birmingham, AB.	10/9 =19
11	Richard Channick, M.D., USCD Medical Center; La Jolla, CA.	8/10=18
12	David Badesch, M.D., University of Colorado Health Science Center; Denver, CO.	3/2= 5
13	Vallerie McLaughlin, M.D., University of Michigan; Ann Arbor, MI.	15/14=29
14	Ivan Robbins, M.D., Vanderbilt University Medical Center; Nashville, TN.	6/6 =12
15	Victor Tapson, M.D., Duke University Medical Center; Durham, NC.	5/7= 12
16	Ronald Oudiz, M.D., Harbor-UCLA Medical Center; Torrence, CA.	5/5=10
17	Nicholas Hill, M.D., Tufts New England Medical Center; Boston, MA.	3/2=5
18	Srinivas Murali, M.D., Allegheny General Hospital; Pittsburgh, PA.	1/1=2
19	Fernando Torres, M.D., UTSW Medical Center Dallas/St Paul University Hospital; Dallas, TX.	5/6=11
22	Steven Knoper, M.D., University of Arizona Medical Center; Tucson, AZ.	2/2=4
23	Reda Girgis, M.D., Johns Hopkins University; Baltimore, MD.	4/4=8
25	Timothy Williamson, M.D., Kansas University Medical Center; Kansas City, KS.	2/2=4
30	Horst Olschewski, M.D., Medical University of Graz; Graz, Austria.	1/1=2
31	Gerald Simonneau, M.D., Hospital Antoine Beclere; Clamert, France.	3/3=6
32	Werner Seeger, M.D., Justus-Liebig University; Giessen, Germany.	7/8=15
33	Nazzareno Galie, M.D., University of Bologna; Bologna, Italy.	2/2=4
34	Joanna Pepke-Zaba, M.D., Papworth Hospital; Cambridge, England.	3/5=8
35	Sean Gaine, M.D., Mater Misericordiae University Hospital; Dublin, Ireland.	5/1=6
36	Rober Naeije, M.D., Erasme Hospital. Free University of Brussels; Brussels, Belgium.	2/6=8
37	Marion Delcroix, M.D., University Hospital Gasthuisberg; Leuven, Belgium.	1/3=4
38	Irene Lang, M.D., Medical University of Vienna; Vienna, Austria.	4/5=9
39	Andrew Peacock, M.D., Scottish Pulmonary Vascular Unit, Western Infirmary; Glascow, Scotland.	3/0=3
40	John Gerard Coughlan, M.D., Royal Free Hospital; London, England.	6/5=11
43	Simon Gibbs, M.D., Hammersmith Hospital; London, England.	1/0=1
44	Joan Albert Barbera, M.D., Hospital Clinic of Barcelona; Barcelona, Spain.	1 / 2 =3
47	Mordechai Kramer, M.D., Rabin Medical Center; Petach Tikvah, Israel.	5/5=10
49	Neville Berkman, M.D., Hadassah Ein Kerem Medical Center; Jerusalem, Israel.	1/1=2
53	Mordechai Yigla, M.D., Rambam Medical Center; Haifa, Israel.	0/1=1
61	James Tarver, M.D., Orlando Heart Care; Orlando, Fl.	0/1=1
62	Roxana Sulica, M.D., Beth Israel Medical Center; New York, NY.	1/1=2

There were 235 subjects enrolled. The majority were enrolled through USA sites (N=142). The other patients were derived from sites in Western Europe or Israel (N=93)

Demographics:

The demographic characteristics of the two treatment groups were balanced.

Table 14: Demographics of Those Enrolled into TRIUMPH 001

Characteristic	Treprostinil (N=115)	Placebo (N=120)
Age Mean ± SD	55 ± 12	52 ± 14
Male/Female (% female)	22/93 (81%)	22/98 (82%)
Etiology of PAH (%)		
Idiopathic	64 (56%)	67 (56%)
Collagen Vascular disease	40 (35%)	37 (31%)
Other	11 (10%)	16 (13%)
Background therapy		
Bosentan	77 (67%)	88 (74%)
Median Bosentan dose	125 mg	125 mg
Sildenafil	38 (33%)	32 (27%)
Mean Sildenafil dose	37.5 mg	37.8 mg
NYHA status III/IV	112/3	118/2

The treatment groups were reasonably balanced. There were, however, somewhat more patients treated with sildenafil in the treprostinil group than in the placebo group. There were very few patients with NYHA class IV enrolled into this study.

Formulations:

The kit numbers for each of the treatments is shown below.

Table 15: Kit numbers for TRIUMPH 001

Kit number	Active	Placebo
001-180	02704B	02704A
0201-220; 680-691	02704C	02704A
269-316; 400-447; 470-481; 500-535; 628-659	02704D	02704A
700-783	03306C	00607A
Missing in sequence	181-200;221-268; 317-399; 448-469; 482-499; 536-627; 660-679; 692-699	

Doses:

The dose that patients were taking (and % of patients) at various points during the study is shown below.

Table 16: Doses at Various Times during TRIUMP 001

	# of breaths	Treprostinil	Placebo
Week 6	3	6 (5%)	4 (3%)
	6	14 (13%)	15 (13%)
	9	72 (65%)	88 (76%)
	12	2 (2%)	0 (0%)
Week 12	3	4 (4%)	2 (2%)
	6	16 (15%)	8 (7%)
	9	75 (72%)	96 (87%)
	12	2 (2%)	1 (<1%)

The fraction of patients at weeks 6 and 12 who were at or above the proposed target of 9 breaths was higher in the placebo group than Treprostinil group.

Of note, the first dose, the dose for which the initial peak values for 6MWD were carried out (not pivotal peak values), was only 3 breaths of inhaled drug at the time of the walk-test.

Protocol deviations;

Per sponsor, there were 10 protocol deviations.

- Five subjects did not have cardiac catheterizations within the 13 month specified time prior to randomization or they had results outside of allowed range.
- Two patients did not have three months of stable concomitant therapies.
- One subject was > 75 years old.
- One subject had NYHA Class II at baseline.
- One subject had an atrial septal defect closure.

Other deviations:

- Five patient allocation numbers were missing (#s 10002, 14008, 38005, 40003, 400008)
- There were five patients who were randomized out of sequence (#s: 13002, 13009, 13020, 34001, and 38007).

The disposition of subjects during this study is shown below.

Table 17: Disposition of patients TRIUMPH 001

	Treprostinil	Placebo
N	115	120
Completed	102 (89%)	110 (92%)
Did not complete	13 (11%)	10 (8%)
Death	0	1 (<1%)
Worsening PAH	3 (3%)	0
Adverse event	7 (6%)	4 (3%)
Withdrawal of consent	3 (3%)	5 (4%)

There were slightly more individuals who discontinued from their treprostinil treatment compared to placebo group (11 versus 8%).

Primary outcome:

The sponsor's analysis of the primary endpoint is a non-parametric analysis with the imputation rules as noted in Table 18. The analysis adjusted the primary effect for baseline walk distance and disease etiology.

The primary analysis for chronic (week 12 peak walking time) is shown below:

Table 18: Primary Analysis for TRIUMPH 001

Baseline (median)	359	361
Change at Week 12	+ 21.6	+3.0
Treatment effect (Hodges-Lehmann estimate) (95%CI)	+ 20.0 (8.0, 32.8)	

The results show a modest benefit in walk distance in the treprostinil group relative to placebo. The initial power calculations, however, assumed a much greater effect.

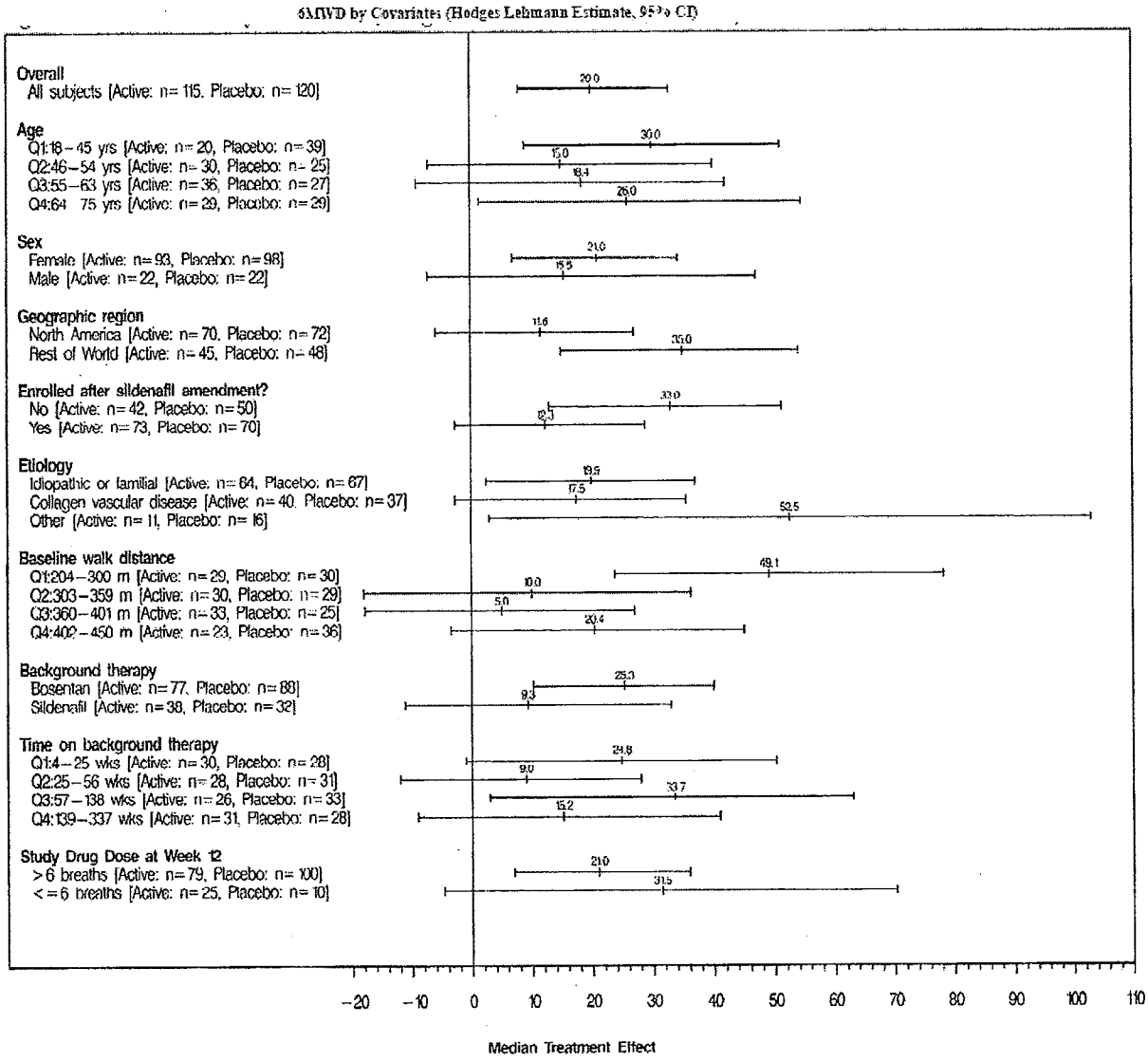
Other analyses which were performed by the sponsor imputing using worst rank for all patients did not have substantially different outcomes. The median treatment difference was 18.3 meters favoring treprostinil.

With respect to subgroup analysis the sponsor performed several analyses as shown below as the Forest plot. Key subgroups suggest:

- Patients within the USA had a lesser effect than those in the rest of the world.
- Patients who were treated with sildenafil had a lesser effect than those on concomitant bosentan.
- The largest effect was observed in the lowest quartile, subjects with walk distance at baseline of between 200 and 300 meters at baseline.

Since the point estimate for each subgroup is positive, none of the subgroups deserve comments in labeling.

Figure 6: Forest Plot for Primary Endpoint TRIUMPH 001



Reviewer's analysis:

Those subjects who discontinued were not followed during the entire duration of therapy. It is therefore, not possible to determine if these subjects suffered worsening of disease, died or were started on rescue therapy. I have gone through the CRFs for those who discontinued and my assessment is shown below. The orange highlighted lines reflect patients whose assessment by this reviewer differs from the categorized imputed values. Patients who

died or who were categorized as worst outcome by the sponsor and whose imputed value would agree with that already assigned were not high-lighted.

Table 19: Discontinued Patients in TRIUMPH 001 and the Sponsor's and this reviewer's Imputations

Pt ID	Demographics Age/gender/etiology/PAH baseline med B=Bosentan; S= Sildenafil [Last Visit with walk test]	Description	Sponsor's assessment	Reviewer's assessment
Active				
10013	49/F/CVD/S [Visit 3]	Stopped for severe fatigue	Adv event	Worst value
12004	52/F/CVD/B [Visit 2]	Stopped for severe fatigue	Adv event	Worst value
13008	64/F/idiopathic PAH/B [Visit 2]	Hospitalized for worsening PAH	New PAH med-	Worst value
13010	55/M/idiopathic PAH/B [Visit 6]	No evidence of worsening disease- Withdrew consent – no deterioration in last walk- No adverse event consistent with deterioration	Withdrew consent	LOCF
13018	59/F/idiopathic PAH/B [Visit 2]	Had increased dyspnea –not yet recovered	Withdrew consent	Worst value
17003	55/F/idiopathic PAH/S [Visit 3]	Last walk distance decreased from 362 M to 244 M supposedly discontinued due to wheezing	Adverse event	Worst value
17005	51/F/idiopathic PAH/S [Visit 2]	Adverse events consisted of decrease saturation, excessively tired, increased shortness of breath	Adverse event	Worst value
18002	58/F/idiopathic PAH/B [Visit 4]	No evidence of adverse events suggesting worsening of disease or walk distance deterioration	Adverse event	Last rank carried forth
19007	44/F/CVD/B [Visit 3]	No deterioration in walk at week 6 but had stopped meds previously. Fatigue was noted prior to D/C and continued through discontinuation.	Withdrew consent	Worst value
22002	64/F/CVD/S Completed [visit5]	Patient hospitalized for PAH	New PAH med-	Worst
31002	60/F/Anorexigens/B [Visit2]	Only adverse event listed is hemoptysis, but this was not listed as reason for discontinuation (only interrupted)	Adverse event	?Worst value
32015	54/F/Idiopathic PAH/S [Visit 3]	Adverse events suggest reason for discontinuation was due to burning in pharynx. No evidence of decreased walk distance at week 6. Says not able to perform walk test due to lumboischialalgia	Adverse event	Last rank carried forward
35006	56/M/Idiopathic PAH/S [Visit 3]	Disease progression	Disease progression	Worst value
39001	72/M/Idiopathic PAH/B [Visit 5]	Protocol violation-entered open label phase. Can't tell why subject discontinued	Protocol violation	Last rank carried forward
40012	60/F/CVD/B [Visit 2]	No walk tests after first dose study. Adverse events are chest tightness and sore throat	Adverse event	Last rank carried forward
47001	60/F/CVD/B [Visit 3]	Disease progression, patient hospitalized, can't tell if patient survived.	Disease progression	Worst value
Placebo				
13004	60/F/Idiopathic PAH/B [Visit 2]	No adverse events suggestive of decompensation. No follow-up 6MWD.	Withdrew consent	Last rank carried forward

15009	54/M/CVD/B [Visit 5]	Minimal change in walk distance but a decrease in Borg-dyspnea score (from 9 at baseline to 5 at 6 weeks). Last dose was approximately 35 days previously.	Withdrew consent	Last rank carried forward.
15012	46/F/CVD/B [Visit 3]	Discontinued due to worsening cough, but had hypoxia that began 3 days after enrollment. Walk distance decreased from 290 to 235 M but dyspnea assessment was less from Borg sale 7 at baseline to 5 at week 6.	Adverse event	Worst value
19010	36/M/Idiopathic PAH/S [Visit 2]	Hospitalized for syncope	Withdrew consent	Worst value
23001	61/F/CVD/B [Visit 2]	Had worsening fatigue and dyspnea	Adverse event	Worst value
31006	29/F/CVD/B [Visit 3]	No evidence of worsening of disease	Withdrew consent	Last rank carried forward
38003	56/F/Idiopathic PAH/B [Visit 2]	Discontinued for burning sensation of the throat	Adverse event	Last rank carried forward
44003	53/F/Idiopathic PAH/S [Visit 2]	Discontinued for severe sickness- not worsening of disease	Adverse event	Last rank carried forward
49002	39/F/Anorexigens [Visit 2]	Died	Death	Worst rank
53001	67/F//CVD/B [Visit 3]	Had mild fatigue that resolved with decrease in walk distance from 430-390 with no change in Borg dyspnea score	Withdrew consent	Last rank carried forward

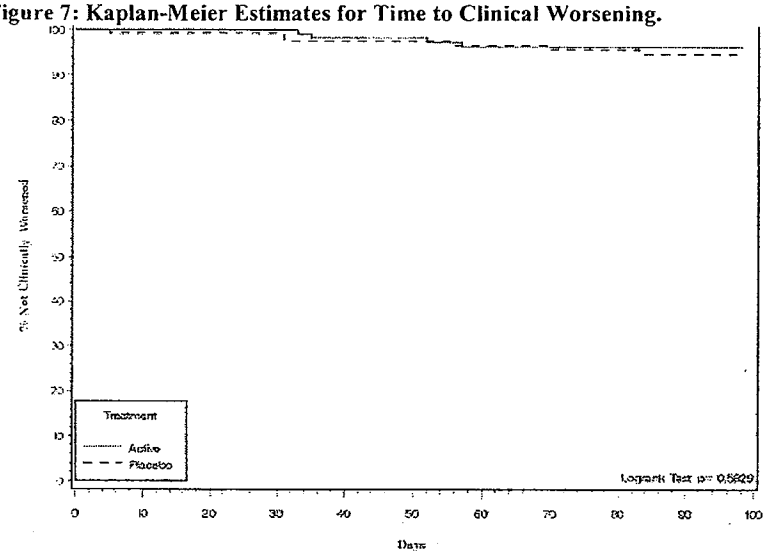
The values as imputed above alter the outcome of the study particularly at week 12. At week 6 peak, the treatment effect is still significant (nominal p =0.013). At the pivotal week 12 peak 6 MWD, however, the treatment effect was no longer significant (p=0.6). The median change from baseline however, was 16.5 M in the treatment group and 2.0 M in the placebo group. Based on the totality of the assessment, despite the loss of a significance by the ANCOVA model, there is adequate information that there is an effect of treprostinil at week 12 on walk distance.

Secondary outcomes:

- Time to clinical worsening:

The sponsor's analysis of clinical worsening indicates no difference between the treprostinil inhaled and placebo treated subjects. Slightly more placebo subjects completed the study, compared to treprostinil patients 92% versus 89%, respectively. The Kaplan-Meier estimates of time to clinical worsening are shown below. The log rank test p-value was 0.59.

Figure 7: Kaplan-Meier Estimates for Time to Clinical Worsening.



Since the hierarchy of endpoints, as described in the statistical plan, required previous endpoints to be significant to apply a meaningful α-value to subsequent parameters, and since this last metric was not different between treatments, any subsequent parameter which is analyzed lacks a statistically meaningful interpretation.

- Change in Borg Dyspnea Score.

The Borg dyspnea scale is performed immediately after the 6-minute walk test. The metric assessed the degree of shortness of breath during the immediately preceding walk assessment. The scale ranges from 0 (no shortness of breath to 10 (worst shortness of breath). There were no differences either at baseline or at peak measurements on day 1, week 6 or week 12. The analyses are predicated on employing the sponsor's imputed values and did not include this reviewer's assessment of patient outcome.

- NYHA classification

There was no difference is the shift of patients NYHA status comparing treprostinil to placebo. Again the analysis below is the sponsor's assessment of outcome.

NYHA class	Treprostinil (N=115) Baseline=N/Week 12=n	Placebo (N=120) Baseline=N/Week 12=n
I	0/0	0/0
II	0/22	0/22
III	112/88	118/93
IV	3/5	2/5

- Change in 6-minute walk test at interdosing interval.

The sponsor's analysis of the walk difference at the trough time is shown below. Note that the number of subjects with trough data is substantially lower than those who enrolled. The corresponding means are markedly different when the imputed values are ignored.

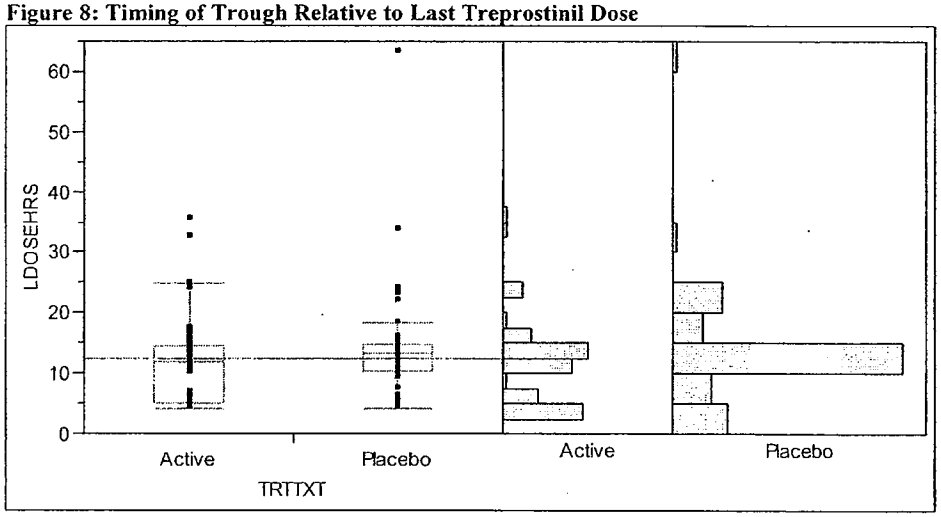
It should be noted that the baseline value is the single baseline measurement, not corresponding necessarily to the time of day at which this measurement was performed. The consequence of not corrected for the different times during the day when the trough values could have been measured relative to baseline is unclear.

Table 20: 6MWD at Trough with and Without Imputation Rules TRIUMPH 001

	Inhaled treprostinil	Placebo
Change based on pre-specified analysis		
N=	N=115	N=120
Baseline	359	361
Change	+12.4	+0.8
	13.7 (4.0 , 24.8) nominal p=0.007	
Change without imputation		
N=	N=71	N=73
Baseline	347	343
Change	+36.8	0.0
	29.0 (13.0, 44) nominal p <0.001	

There are two different possible interdosing intervals; a short interval which occurs during daytime dosing (i.e. prior to hour 4, 8 and 12) and a longer interdosing interval, approximately 12 hours which occurs overnight. I counted 92 subjects who had trough measurements had these measurements between 10-16 hours after active dose and an additional 42 patients had their measurements between 4- 6 hours post last dose.

Figure 8: Timing of Trough Relative to Last Treprostinil Dose



With respect to the walk distance at trough, for the treated group the walk distance for those whose trough was 4-6 hour after the last dose was (mean ± SD) 35 ± 41 m (N=26); for placebo it was 22 ± 42 (N=18). For those whose trough test was performed at 10-16 hours post dose the effect was 35 ± 46 (N=42) for UT-15 and 5.0 ± 50 (N=50) for placebo. Since these results to don't include any imputations, the overall effect is less than for each category of trough measurements.

- Change in 6 minute walk-distance at peak at week 6. The change from baseline at week 6 peak are shown below as per sponsor:

Table 21: Peak 6MWD at week 6 TRIUMPH 001

	Inhaled treprostinil	Placebo
N	N=115	N=120
Baseline	359	361
Change	+21.6	+3.0
Mean change (H-L treatment effect)	+ 18.5	

- Quality of Life

The sponsor's analysis of the Minnesota Living with Heart Failure Questionnaire data is shown below:

Table 22: Categories of the MLWHF Questionnaire

	Median Placebo Corrected change in QOL assessments from baseline (95% CI)
Global	-4.0 (-8.0 to 0.0)
Physical	-2.0 (-3/0 to 0.0)
Emotional	-1.0 (-2.0 to 0.0)

This reviewer would have imputed values somewhat different based on the assessments as noted in Table 22. Since there are more treated patients who were treated with treprostinil than placebo who had worse outcome (see Table 19), the lower CI of each of the realms of the QOL questionnaire now would have spanned 0 and would not therefore, be significantly different comparing treatments. It should be further noted that this questionnaire has not been validated in a PAH population.

- PAH signs and symptoms

The status of each sign and symptoms was assigned a categorical value of absent or present at the three visits (baseline, Week 6 and week 12) during which it was assessed. A change of 0 was assigned for no change. A + 1 was assigned for a sign that was present at baseline and no longer present. A change of -1 was assigned for a sign, which was absent at baseline and was evident at end of treatment.

The sponsor's analysis is shown below.

Table 23: Changes in Signs and Symptoms TRIUMPH 001

Sign/Symptom	Treprostinil			Placebo		
	New	No change	Resolved	New	No change	Resolved
Loud P2	5	92	5	5	97	9
Right Ventricular S3 sound	2	94	6	4	104	3
Right Ventricular S4 sound	4	93	5	3	96	12
Right ventricular heave	9	80	13	5	90	16
Murmur of tricuspid insufficiency	**14**	**80**	**8**	**9**	**86**	**16**
Murmur of pulmonic insufficiency	0	98	4	2	108	1
Hepatomegaly	1	100	1	6	99	6
Jugular venous Dist at 45 degrees	7	78	17	14	82	15
Edema	**11**	**79**	**12**	**13**	**93**	**5**
Ascites	1	100	1	1	109	1
Dyspnea	4	97	1	1	107	3
Orthopnea	4	91	7	7	93	11
Dizziness	16	67	19	15	76	20
Syncope	1	97	4	1	108	2
Chest pain	**8**	**83**	**11**	**12**	**86**	**13**
Palpitations	6	75	21	8	84	19
Fatigue	**17**	**71**	**14**	**6**	**87**	**8**

There was overall no change in the distribution of the symptoms. Fatigue and tricuspid insufficiency murmur were better in the placebo treated patients. Edema improvement seems to have been slightly better for treprostinil.

- First dose 6 minute walk change

The sponsor assessed the effect of walk distance after the first dose. It should be noted that the initial dose for subjects was three breaths and not the final dose of 9 breaths. The analysis per sponsor is shown below. It seems unlikely that at the 3 breath dose gives a full accounting of the potential effect of inhaled treprostinil as a "when-needed" therapy.

Table 24: First Dose Effect TRIUMPH 001

	N	Baseline	Change	Estimated difference
Treprostinil	115	359	+6.6	6.0 (-1.2 to 14).
Placebo	120	361	+3.0	

- NT Pro-BNP

NT Pro-BNP is a measure of left ventricular dysfunction. NT Pro-BNP was measured at baseline, 6 weeks and 12 weeks of therapy. The sponsor's analysis (which excludes those who deteriorated) is shown below.

Table 25: Pro-BNP changes TRIUMPH 001

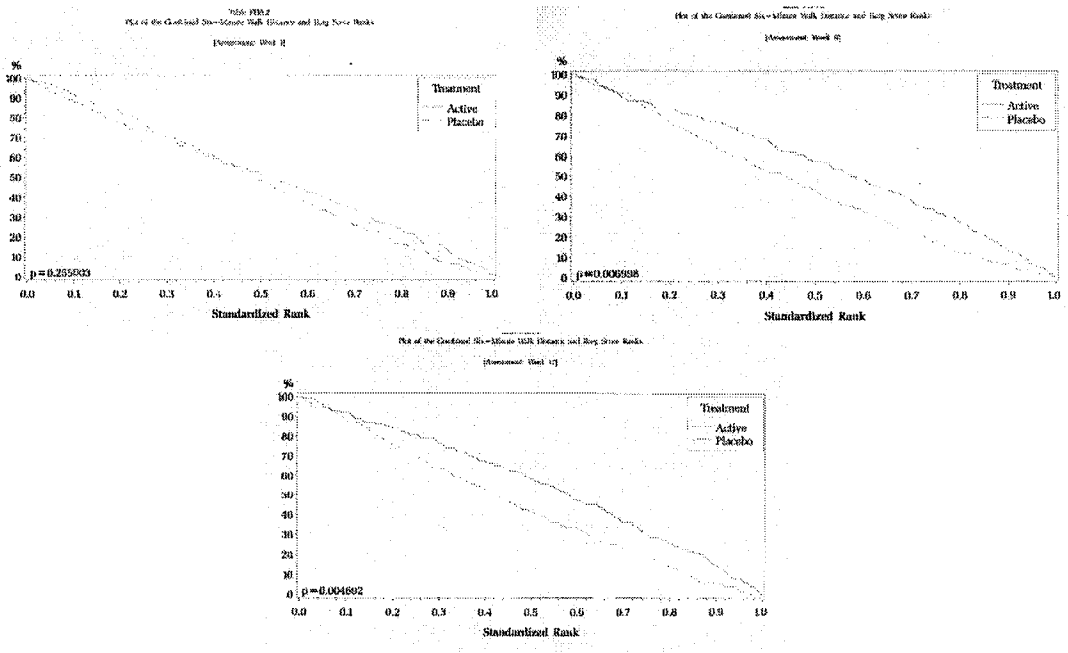
	Treprostinil			Placebo			
	n	Baseline	value	n	Baseline	value	Change*
Week 6	86	602	382	87	690	729	-159
Week 12	73	593	377	82	670	757	-187

* H-L placebo-corrected change from baseline.

Additional analysis:

The sponsor performed a combined assessment of the ranks of the walk distance and the Borg dyspnea scale. This analysis was equivalent to the analysis employed to assert efficacy of the SC route of treprostinil administration. The analysis ranks patients by the 6MWD and the change in Borg dyspnea scale, and then sums the ranks and renormalized ranks for the sum of the ranks. At week 12, there is a decided difference favoring inhaled treprostinil.

Figure 9: Combined 6MWD and Borg Dyspnea TRIUMPH 001.



Safety:

Duration of exposure and dosing information:

The study was a 12-week long study. The mean duration of observation for the placebo group was 81.5 ± 14 days and for active treatment it was 80.0 ± 14 for active treatment. The maximum dose (assuming 6 µg/breath) for those receiving inhaled treprostinil averaged 50 ± 10 µg/treatment (goal dose was 54 µg/treatment). For the active treatment the mean dose was 7.6 breaths at end of double-blind study. For placebo patient the mean dose was 8.5 breaths. The numbers of patients with dosing at the end of the double-blind portion for the study is shown below.

Table 26: Dose at Week 12 Visit or Last Visit - TRIUMPH 001

	Active	Placebo
≤ 3	19	12
4-6	17	8
7-8	2	3
≥ 9	77	97
Total	115	120

Deaths, Dropouts and Discontinuations:

There was one death in the study. Patient #49002 died a sudden death on day 5 of treatment. This was a 39 year-old female with the origin of her PAH due to use of anorexigens. Concomitant PAH medication included bosentan. Her baseline walk distance was 402 meters with a Borg dyspnea score of 3.

Serious Adverse events:

There were 10 treated patients and 15 placebo patients who had serious adverse events during the double blind phase of the study. The number of subjects with serious events suggestive of worsening status was denoted by a √. The numbers of patients with serious events that may reflect worsening of the disease process were similar in the two treatments. 6/115 in the treprostinil group (5.2%) and 7/120 (5.8%) in the placebo group.

Table 27: Serious Adverse Events TRIUMPH 001

Pt ID	Demographics Age/sex/etiology	Event
Treprostinil		
13008√	64/F/primary	She had multiple (4) syncopal episodes over a six week period.
15008√	58/F/primary	She had a syncopal episode that was not associated with a dose of medication.
19003	74/F/Primary	She had abdominal pain, black tarry stools and a decrease in hemoglobin from 12 to 9 g/dL.
19011	52/F/primary	She was hospitalized with diarrhea, abdominal pain and recurrent *C. difficile.*
22002√	65/F/Collagen	She had a syncopal episode at home; admitted for worsening disease.
35006√	46/M/Primary	He had a decrease exercise capacity, increase in fatigue and dizziness. Hospitalized for worsening disease.
38009√	40/F/Other-hereditary telangiaectasia	She had right heart decompensation and edema of the extremities.
39002	74/F/CVD	She was hospitalized with new onset diabetic ketoacidosis.
47001√	59/F/CVD	She was hospitalized for anemia hemoglobin of 8.9 g/dL; She was also hospitalized for worsening disease-details not submitted.
Placebo		
10005	50/F/Primary	She was hospitalized for bronchitis and discharged with antibiotics.
10006√	56/F/CVD	She was hospitalized twice for worsening cor pulmonale; Flolan was started. She also had headaches that were defined as serious adverse event.
11010	43/F/anorexigens	She was hospitalized for gallstones.

17004√	74/F/Primary	Had worsening congestive heart failure. Sponsor is awaiting additional information.
19001√	35/F/Anorexigens	She was hospitalized for chest pain diagnosed as anxiety attack. She was also hospitalized for GI bleed coffee-ground emesis and dark tarry stools. She was also hospitalized for volume overload and UTI.
19002√	60/F/Primary	She was hospitalized four times for fluid overload. Symptoms were increase in weight and extremity edema. On the first hospitalization she was noted to be hypokalemic. On the second hospitalization for fluid overload, she had shortness of breath requiring oxygen treatment. On this hospitalization she was also noted to be hyperkalemic. She also had an endoscopy for dark stools.
19009√	65/F/Primary	She was hospitalized for worsening pulmonary hypertension. No details given.
19010	36/M/Primary	He was admitted to ER for a near syncopal episode after working in the sun. This episode occurred about two weeks after discontinuation of therapy but during the observation period of the double blind study.
23005	65/F/CVD	During double blind phase she had musculoskeletal chest pain
36001	54/M/CVD	She was hospitalized for small cell lung cancer.
38004√	46/M/Primary	Had worse PAH, also hospitalized for atrial flutter.
40002	63/F/CVD	She was admitted to the hospital for back pain and hematuria. She was also admitted for hyperkalemia (K+= 6.2) Spironolactone dose was decreased.
49002√	39/F/Anorexigens	She sustained a sudden death
61001	43/F/CVD	Patient had increased fatigue and dyspnea, admitted for anemia and received two units of PRBC. Endoscopy showed candida esophagitis.

The √ is my interpretation of worsening disease.

Overall adverse events:

The sponsor supplies a list of adverse events > 3% and more frequent in the treprostinil than placebo group. The submitted data files mixed in those events during the double-blind portion of the study with those occurring during open label treatment.

Table 28: Adverse events and (%) occurring during the Double-blind portion of TRIUMPH 001

Adverse event	Treprostinil (N=115)	Placebo (N=120)	Difference in %
Patient with any event*	101 (88%)	100 (83%)	5
Cough	62 (54%)	35 (29%)	25
Headache	47 (41%)	27 (23%)	18
Nausea	22 (19%)	13 (11%)	8
Dizziness	20 (17%)	18 (15%)	2
Flushing	17 (15%)	1 (< 1%)	15
Throat irritation	16 (14%)	10 (8%)	6
Pharyngeal pain	13 (11%)	7 (6%)	5
Diarrhea	11 (10%)	9 (8%)	3
Chest discomfort	7 (6%)	4 (3%)	3
Syncope	7 (6%)	1 (<1%)	6
Epistaxis	6 (5%)	2 (2%)	3
Jaw pain	6 (5%)	5 (4%)	1
Extremity pain	5 (4%)	4 (3%)	1
Lower respiratory tract infection	5 (4%)	1 (< 1%)	4
Urinary tract infection	5 (4%)	1 (< 1%)	4
Chest pain	4 (3%)	3 (3%)	0
Pulmonary hypertension	3 (3%)	2 (2%)	1
Chills	3 (3%)	1 (< 1%)	3
Hemoptysis	3 (3%)	0	3
Stomatitis	3 (3%)	0	3
Wheezing	3 (3%)	0	3

*Sum of adverse events greater than this number

The adverse events appear to fall into three main categories, there are those adverse events related to the route of delivery. These events include cough, throat irritation, pharyngeal (pain as well as hemoptysis). There are those adverse events that seem to relate to the adverse events commonly attributable to prostacyclin use (e.g., headache, dizziness, flushing and gastrointestinal symptoms). Lastly, there are those events related to the underlying disease process (e.g. syncope, pulmonary hypertension). Of note, the sponsor was to assess further whether the irritative effect of treprostinil was of significance. I did not see any follow up ENT assessment on these subjects.

Adverse events attributable to the pulmonary system and cardiovascular system:

There were four patients in the active treatment group with cardiovascular adverse events. There were 14 placebo patients with similar cardiovascular adverse events. Only one placebo patient discontinued due to adverse event of palpitation. The cardiac events in the treatment group were palpitations (N=2), right heart failure (N=1) and angina pectoris (N=1). For the placebo group the adverse events were palpitation (N=6) cor pulmonale (N=2), chest pain (N=2), tachycardia (N=1), atrial fibrillation or fibrillation with tachycardia (N=1).

With respect to the pulmonary system, other events aside from worsening of disease included three subjects in the active treatment group who had hemoptysis and one patient who had throat edema. In the placebo subjects, one patient had a pleural effusion.

Labs:

Laboratory values were assessed at baseline, visit 3 (week 6) and visit 5 (week 12) during the double blind phase of the study.

Laboratory measurements reported as adverse events were hypokalemia (N= 3); hepatic enzymes increased, leucopenia, LDH increased, neutrophilia, hyperkalemia, blood glucose increased, potassium decreased, anemia, iron deficiency (N=1, each).

Table 29: Change in Laboratory Values at Week 12.

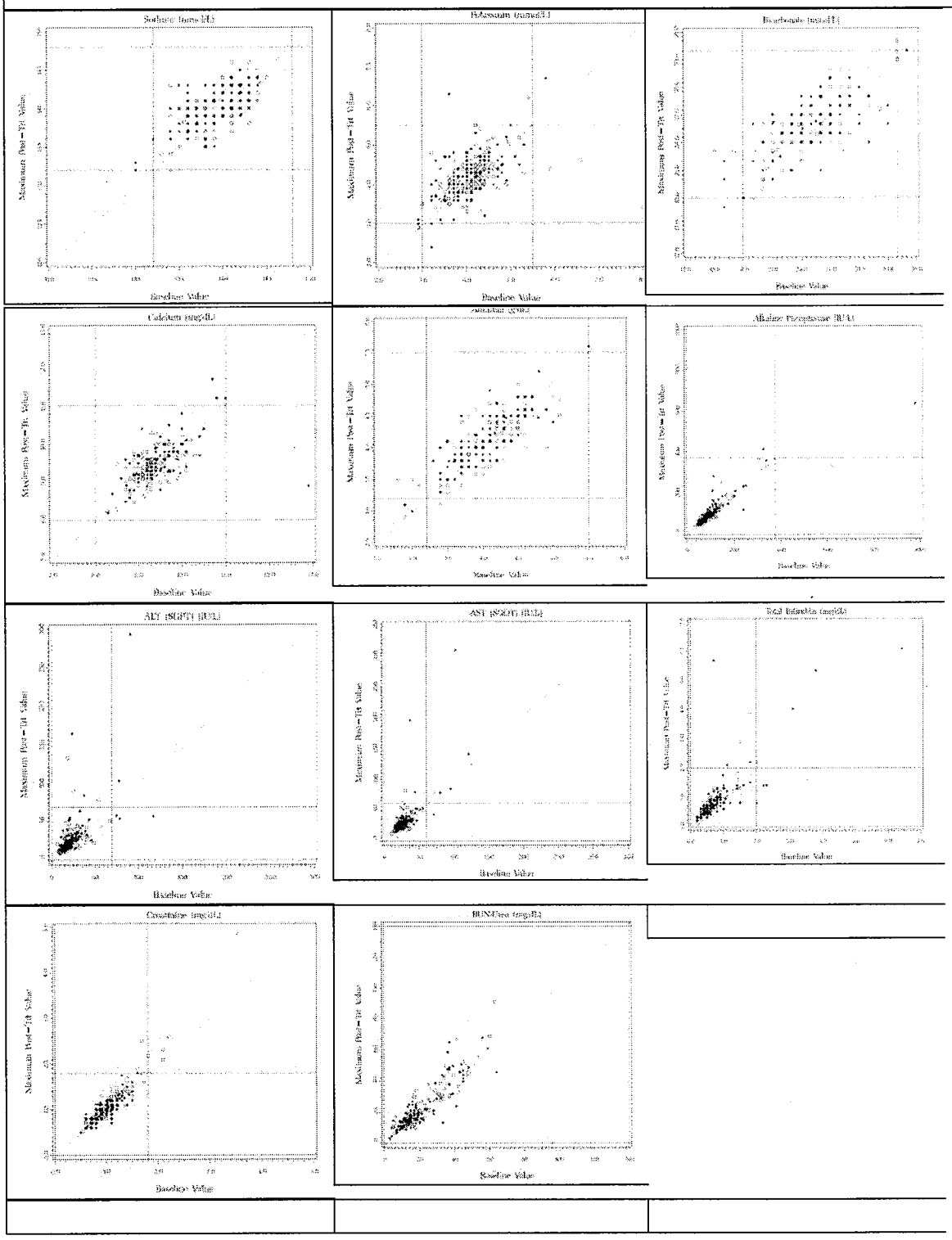
Parameter		Active	Placebo
Hematology			
Hemoglobin	N Change: mean ± SE [range]	97 -0.03 ± 0.07 [-4.8 to 0]	104 -0.07 ± 0.04 [-1.8 to 0.8]
Hematocrit	N Change: mean ± SE [range]	99 -0.2 ± 0.3 [-8 to 8]	107 -0.3 ± 0.3 [-11 to 9]
Platelet count	N Change: mean ± SE [range]	98 -1.5 ± 4.5 [-256 to 120]	104 -1.2 ± 6.3 [-298 to 234]
Chemistry			
Sodium	N Change: mean ± SE [range]	102 -0.1 ± 0.3 [-10 to 8]	109 -0.3 ± 0.3 [-11 to 9]
Potassium	N Change: mean ± SE [range]	101 -0.09 ± 0.05 [-1.2 to 1.3]	109 -0.11 ± 0.07 [-4.6 to 1.3]
Bicarbonate	N Change: mean ± SE [range]	72 -0.19 ± 0.37 [-9.0 to 6.0]	83 0.14 ± 0.32 [-8.3 to 8.0]
Calcium	N Change: mean ± SE [range]	83 -0.10 ± 0.06 [-4 to 1.0]	97 -0.07 ± 0.05 [-1.2 to 1.0]
Albumin	N Change: mean ± SE [range]	80 0.01 ± 0.05 [-0.6 to 0.8]	88 -0.08 ± 0.04 [-1.0 to 0.7]
Alkaline Phosphatase	N Change: mean ± SE [range]	88 -4.4 ± 6.8 [-533 to 173]	93 1.1 ± 1.9 [-38 to 105]
Lactate dehydrogenase	N Change: mean ± SE [range]	41 2.4 ± 6.4 [-87 to 888]	49 17.6 ± 6.8 [-760 to 160]
ALT (SGPT)	N Change: mean ± SE [range]	89 3.7 ± 2.8 [-76 to 167]	95 2.7 ± 1.7 [-27 to 114]
AST (SGOT)	N Change: mean ± SE [range]	86 4.2 ± 2.7 [-43 to ±158]	92 1.6 ± 1.0 [-19 to 51]
Creatinine	N Change: mean ± SE [range]	101 -0.01 ± 0.01 [-0.4 to 0.3]	108 0.02 ±0.01 [-0.3 to 0.8]
BUN	N Change: mean ± SE [range]	98 -0.2 ± 0.7 [-29 to 28]	100 1.1 ± 0.8 [-16 to 33]

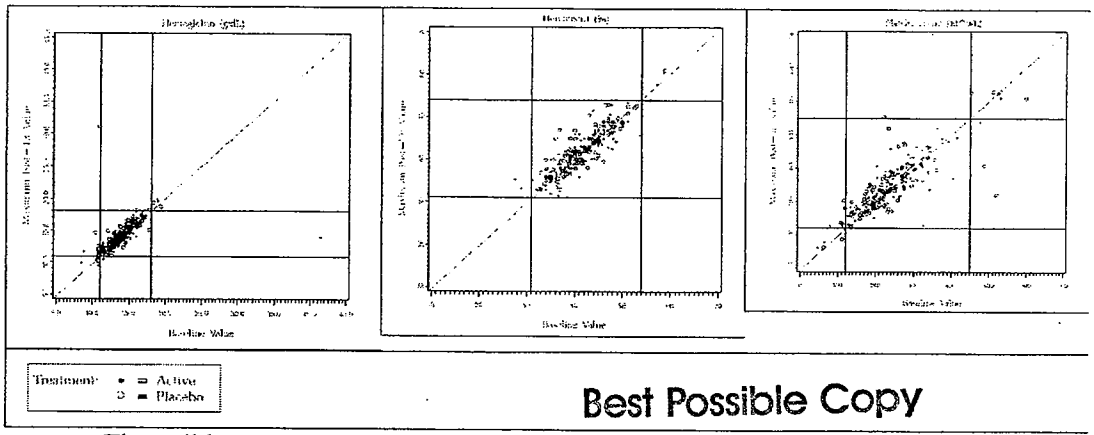
There did not appear to be a strong signal that laboratory values were substantially altered in this study. Changes in the liver function tests are confounded by the concomitant use of bosentan by approximately 70% of those enrolled.

Shifts

The sponsor supplies scatter plots for baseline versus maximum or minimum on-treatment value. The reason for the two plots was the two on-treatment assessments of lab values. Below is the representation with the maximal value on treatment.

Figure 10: Scatter Plot of All Laboratory Values.





There did not appear to be a strong signal that laboratory values were substantially altered. Changes in liver function studies are particularly difficult to assess given the large fraction of subjects treated with bosentan.

Special labs:

Subjects had pulmonary function tests performed at baseline and at some unspecified time on Week 12. There were no differences between the active and placebo groups with the decline numerically greater in the active treatment groups. Neither group post 12 weeks differed from baseline for the FVC and FEV1.

Table 30: Pulmonary Function Studies at Week 12 of TRIUMPH 001

	Active	Placebo
FEV1 (liters/sec) or % normal?		
N=	101	104
Change ± SE [25-75%]	-2.2 ± 1.4 [-5.0 to 3.0]	-0.9± 1.3[-4.0 to 3.0]
FVC (liters or % normal)		
N=	101	104
Change ± SE [25-75%]	-2.3± 1.8 [-5.0 to 3.0]	-0.8 ± 1.7 [-4.0 to 4.0]

CXR/ECGs: Chest X-rays were performed at baseline and at end of double-blind phase. There were 12 chest X-rays that were changed from baseline; six in each of the treatment groups. Changes in more than one patient were cardiomegaly (2 treprostinil and 2 placebo patients); new pleural effusion (one treprostinil and one placebo).

Vital signs: Vital signs were measured at baseline at Day1* (Visit 2), Week 6* (visit 3), visit 4 (week 12)* and Visit 5 (week 12 trough). For the visits with an *, the measurements were done 15-30 minutes after treatment.

Table 31; Change in vital signs from immediately prior to inhalation to after inhalation.

	Visit 2		Visit 3		Visit 4		Visit 5	
	UT-15	PBO	UT-15	PBO	UT-15	PBO	UT-15	PBO
SBP	-2.8 ± 1.0	-2.3 ± 1.0	-2.1 ± 1.1	-1.2 ± 0.9	-3.0 ± 1.2	-1.8 ± 1.1	-1.1 ± 1.6	-1.7 ± 1.4
DBP	-1.5 ± 0.7	0.8 ± 0.7	0.6 ± 1.0	1.5 ± 1.0	-2.7 ± 0.7	-0.3 ± 1.4	-1.6 ± 0.9	-0.5 ± 0.9
HR	-2.6 ± 0.7	-0.9 ± 0.7	-1.2 ± 0.9	-1.1 ± 1.0	-1.2 ± 0.8	-0.4 ± 0.8	-0.6 ± 1.4	-1.2 ± 1.1

There was a modest trend to a decrease in SBP and DBP in the treprostinil treated group compared to placebo. No orthostatic measurements were performed. Heart rate was minimally changed.

Study number: LRX-TRIUMPH 0001

Title of Study" An Open-Label Study to Investigate the Efficacy and Safety of Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Hypertension.

Enrollment criteria: Patients who complete the Triumph I study are eligible for enrollment as long as they still fulfill the inclusion/exclusion criteria of that study. The cutoff for data lock was January 1, 2008.

Doses: The initial dose during the open-label (OL) study is 3 breaths QID. The dose is increased as tolerated to 6 and 9 breaths as tolerated.

Procedures: The following procedures were to be performed at baseline and every three months. Vital signs, pregnancy test, clinical laboratory, 6MWT, Borg dyspnea score, NYHA classification, PAH signs and symptoms, adverse event assessment, Minnesota Living with Heart Failure Questionnaire.

Results:

Disposition:

Because of the open-label nature of the study, the primary interest to this reviewer is safety. With respect to the efficacy data, individuals who died, decompensated and required rescue therapy were censored. The values of their efficacy parameters were ignored. Efficacy assessments were therefore skewed. Patients who discontinued were not subsequently followed for eventual outcome.

The disposition of the study subjects at the reporting period (1/1/08) is shown below:

Table 32: Disposition of Subjects TRIUMPH-OL

Completed double blind study	212	
Enrolled in open-label study	206	
Ongoing	179 (72%)	
Discontinued	57 (28%)	
Adverse event		26 (13%)
Disease progression		11 (5%)
Withdrawal of consent		10 (5%)
Death		5 (2%)
Lack of efficacy-other		5 (2%)
Mean duration of exposure	53 weeks	
Patient-weeks of exposure	53 x 206= 10918 patient-week or	
Patient-years of exposure	209 patient-years.	

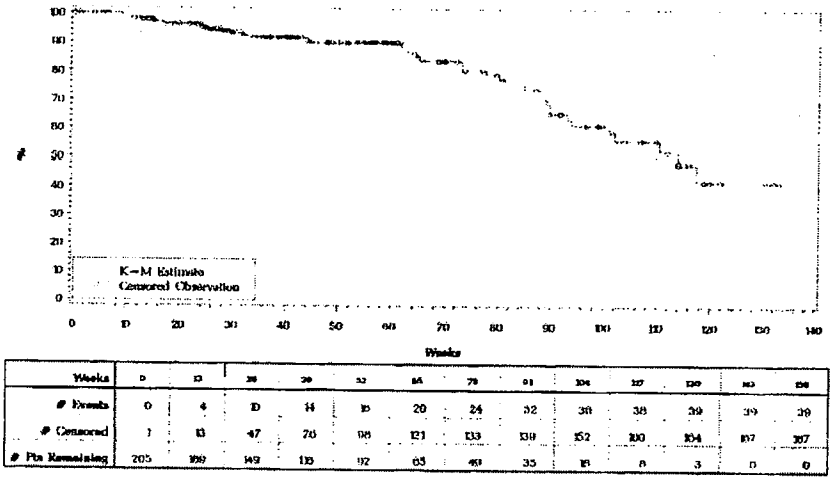
The demographics among those entering the open-label study were approximately the same as those entering the double-blind portion of the study.

The study allowed up to a total dose of 12 breaths per treatment. Among those enrolled a small number of subjects at any of the assessed time point were on doses of greater than 9 breaths. At any time point the maximum number of subjects at 12 breaths was N=18.

There were seven deaths during the course of the open label phase among those who did not prematurely discontinue. There was one additional death that was reported to have died more than one month after discontinuing drug. There were 17 subjects who died, had disease progression or received a lung transplant. There were 39 individuals who died, discontinued due to disease progression or had an additional PAH medication added. The Kaplan-Meier curve for the latter is shown below.

Figure 11: Kaplan-Meier Curve Analysis of Death, Discontinuation Due to Disease Progression or Addition of Approved PAH Therapy

Figure 11.4.1-4 Kaplan-Meier Analysis of Death, Discontinuation due to Disease Progression or Addition of Approved PAH Therapy



Weeks	0	12	24	36	48	60	72	84	96	108	120	132	144
# Events	0	4	10	14	16	20	24	32	36	38	39	39	39
# Censored	1	13	47	70	98	121	133	139	152	160	164	167	167
# Pts Remaining	205	188	148	120	92	65	48	35	15	8	3	0	0

Deaths:

Patient 11006 was a 62 year-old female with idiopathic pulmonary arterial hypertension. She had a history of breast cancer diagnosed in August, 2002. She was enrolled in the double blind phase on August 2005. She was diagnosed with pneumonia on [redacted]. She was found blue two days later and died on the way to the hospital [redacted]. b(6)

Patient 13015 was a 75 year-old female with PAH as a consequence of collagen vascular disease. She died on [redacted] due to esophageal carcinoma (day 457). The last dose of medication was June 23, 2007. Hospitalizations during the study included right flank pain [redacted] Tachycardia [redacted] lower back pain [redacted], broken hip [redacted] and esophageal carcinoma diagnosed during the course of the broken hip hospitalization, b(6)

Patient 15003 was a 36 year-old female at the time of her death with familial pulmonary artery hypertension died of worsening disease. The specifics are not supplied. She died on day 199 of treatment

Patient 19009 was a 68 year-old female with familial or idiopathic pulmonary arterial hypertension. She was treated with placebo during the double-blind portion of the study. She died on day 68 of the open-label portion of the study from worsening disease.

Patient 25001 was a 68 year-old female with pulmonary arterial hypertension secondary to collagen vascular disease. The patient died on day 121 of the OL phase due to pulmonary parenchymal bleed. The patient was hospitalized for the last 3 weeks of her life with community acquired pneumonia, bacteremia and sepsis that apparently resolved after 5 days of the hospitalization. The patient had a GI bleed but apparently died from hypoxia secondary to a pulmonary parenchymal bleed. The last dose of treprostinil was at 11 PM prior to the day of death. The patient receive placebo during the double-blind phase.

Patient 36001 was a 64 year-old male that died of small cell lung cancer on day 75 of the open label phase. The subject had pulmonary artery hypertension secondary to collagen vascular disease.

Patient 36003 was a 70 year-old female with idiopathic or primary pulmonary arterial hypertension. She died approximately 50 days after her last dose of medication. Since she died well after discontinuing therapy (the reason she discontinued therapy is not clear). There were no AE reports for the terminal event. The sponsor sites an acute pulmonary embolism as the cause of death. The subjects had worsening PAH episode requiring hospitalization at approximately day 120 of the open label phase.

Patient 44001 was a 55 year-old male with a history of familial/primary pulmonary arterial hypertension. The patient died on day 119 of the open-label portion of the study. The cause of death, cited by the sponsor, was pulmonary embolism. An autopsy was performed but it is unclear if the autopsy confirmed or was the source of the sponsor's conclusion.

There were two additional deaths which occurred after the Jan 1, 2008 cutoff.
Patient 10015 was a 42 year-old male with PAH as a consequence of HIV died of septic shock after approximately 13 months in the open-label study.

Patient 36008 was a 47 year-old female with PAH as a consequence of idiopathic or familial disease. The subject was found drowned after 17 months of treatment in the open-label study.

Serious adverse events:

There were 59 patients with 109 events listed by the sponsor as serious. Among these events were 26 patients with events, which suggest worsening of their underlying disease. The verbatim terms included (pulmonary hypertension, dyspnea, syncope, fluid overload, right heart failure, congestive heart failure, hypoxia, ascites and cor pulmonale). There were 26 individuals with serious adverse events that might be referred to the pulmonary/respiratory system. These events include some already included under worsening of disease such as dyspnea and worsening pulmonary hypertension. There were also eight subjects with pneumonia defined as serious adverse events. There were four patients with hemoptysis or pulmonary hemorrhage (only three were considered serious, see below). There were 17 patients who had adverse events that appeared cardiac in nature. Many of these events are already accounted for by worsening of

disease. Additional serious cardiac events included; chest pain, atrial fibrillation, tachycardia, palpitations, AV block, heart failure or angina.

Hemoptysis:
Patient #13017 was a 49 year-old male with PAH as a consequence of idiopathic or familial disease. He reported bright red hemoptysis and was admitted to an outside hospital where he had bronchoscopy performed and the irritated vessel was cauterized. No further bleeding was noted. He also had several episodes of syncope (see below) associated with worsening of aortic stenosis.

Patient 14001 was a 52 year-old female with idiopathic or familial PAH. She had an episode of hemoptysis classified as mild in intensity.

Patient 14012 was a 22 year-old male with idiopathic or familial pulmonary arterial hypertension. He complained of blood in sputum when coughing. He was sent to the emergency room and was admitted. The patient had a bronchial arteriogram with embolization with good effect.

Patient 25001 was a 69 year-old female with PAH secondary to collagen vascular disease. She was admitted to the hospital with pneumonia, bacteremia, sepsis, renal failure and hypoxia. The bacteremia and sepsis resolved on . The patient's course during the hospitalization included hematemesis. The patient died during that hospitalization with the cause of death listed as parenchymal pulmonary bleed. The last dose of medication was the date prior to the bleed late at night. b(6)

Reviewer's comments: It is unclear if the severe events of "hemoptysis" are idiosyncratic to the inhalation route of delivery of treprostinil, related to treprostinil by any route, related to the inhaled route of any drug or related to the underlying disease process. Below I've summarized the experience with several treatments for PAH. The information includes

- The OL experience by SC administered treprostinil.

Data is available for the long-term use of SC treprostinil. The information included data for 860 patients who were followed for a mean duration of 78 weeks. There were 7 subjects with an adverse event of hemoptysis labeled as "severe" in intensity. There were an additional 13 hemoptysis events classified as "moderate" in intensity and 13 additional subjects with hemoptysis classified as "mild" in intensity. Among those who had events with available case report forms (there were three such subjects) and with hemoptysis labeled as "severe" in intensity. These hemoptysis events led to hospitalization and in at least in one case, to death. One patient required bronchoscopy and embolization of the bleeding site.

- The experience with inhaled Iloprost:

The database for Iloprost for PAH consisted of a 12-week placebo-controlled study in which there were 203 subjects were enrolled and randomized in equal numbers to placebo or Iloprost. There was also a long term extension study that enrolled 63 subjects. During the 12-week study there were 7 episodes of hemoptysis, five in the Iloprost treated patients and 2 in the placebo

patients. With the exception of one placebo subject with the intensity labeled as "moderate", all other events were of intensity "mild".

- The experience with sildenafil-

The development program for treprostinil by inhalation mirrors that of oral sildenafil. In that application there was one major placebo controlled study with a long-term extension. The placebo controlled study enrolled 277 subjects; the long term extension had data on 255 subjects. One subject #10333, enrolled in the long-term extension study developed hemoptysis and was hospitalized. About two months later she died from an episode of hemoptysis.

There were 3 additional cases of hemoptysis that resulted in hospitalization but did not apparently require invasive methods to stop the bleeding.

One additional subject died of hemoptysis and exsanguinations in a study of the use of sildenafil on top of epoprostenol.

Syncope:

There were eight subjects with at least one episode of syncope during the study.

Patient 10007, a 47 year-old female, with familial or idiopathic PAH had a syncopal episode but discontinued therapy about 1 month later for worsening headache and chest pain.

Patient 11003 was 50 year-old female with her PAH due to previous use of anorexigens. She passed out at home. Hospitalization work up was negative. The CRF indicates that the episode was due to dehydration and the lasix dose was decreased from 80 mg BID to 40 mg QD. She had a presyncopal episode approximately 2 weeks later during exercise.

Patient 13017 was a 49-year-old male with idiopathic or familial PAH had two episodes of syncope. The sponsor attributes these events to worsening aortic stenosis. At baseline, the physical exam indicated that the patient had mild aortic stenosis and a bicuspid aortic valve. He received a valve replacement in March, 2007.

Patient 14001 was a 53 year-old female with idiopathic or familial PAH had two episodes of syncope. At least one resulted in hospitalization. Other adverse events include worsening of PAH and hemoptysis.

Patient 15003 was a 35 year-old female with idiopathic or familial PAH. She had one episode of syncope. Around the time of the syncope she had worsening of her PAH symptoms and was hospitalized for worsening PAH.

Patient 32001 was a 55 year-old female with idiopathic or familial PAH. She had an episode of syncope. Other notable adverse events include worsening of general condition. The last visit was at the time of the data cut off. The syncopal episode occurred approximately 2 months prior to that date.

Patient 32001 was a 26 year-old female with idiopathic or familial PAH. She had an episode of syncope but apparently still continued on therapy. She had previous episodes of dizziness at least one associated with exercise. The dose of inhaled treprostinil was then decreased.

Patient 32014was a 27 year-old female with PAH as a consequence of idiopathic or familial disease

Overall adverse events:

Adverse events occurring in > 5% of those enrolled in the open-label study are shown below.

Table 33: Adverse Events during TRIUMPH OL study (> 5%)

Event	N=206
Any	176 (85%)
Cough	67 (33%)
Headache	40 (19%)
Nausea	26 (13%)
Pulmonary hypertension	19 (9%)
Chest pain	18 (9%)
Pharyngolaryngeal pain	17 (8%)
Dizziness	15 (7%)
Throat irritation	15 (7%)
Sinusitis	14 (7%)
Fatigue	13 (6%)
Upper respiratory tract infection	13 (6%)
Vomiting	13 9%)
Chest discomfort	12 (6%)
Dyspnea	12 (6%)
Pneumonia	12 (6%)
Nasopharyngitis	11 (5%)
Dyspnea exacerbated	10 (5%)

Given the open-label nature of the study and the absence of a control group, these adverse events add only minimal information to the information obtained during the double-blind study.

Laboratory:

Several laboratory measurements were listed as adverse events. The adverse laboratory events with > 3 individuals were anemia (N=4), hypothyroidism (N=3), elevated LFTs (N =10), elevated blood sugar (N=5), increased potassium (N=6), decreased potassium (N=9), increased cholesterol (N=5). Of these events, only six were defined as "severe" in intensity. Only hyperkalemia had more than one laboratory adverse event with this intensity. The only subject with the LFT abnormality with intensity as "severe" was on Bosentan and did not discontinue therapy with treprostinil.

For the laboratory values baseline was defined differently for those treated with UT-15 during the double blind phase and those treated with placebo. For those treated with placebo, the baseline value used was the last measurement during the double-blind study. There were some values up to 27 months but the numbers of available subjects were < 20 at both the 24 and 27 month time point.

Table 34: Change in Mean ± SE Laboratory Values TRIUMPH-OL

		Months						
Hematology		3	6	9	12	15	18	21
Hematology								
Hemoglobin g/dL	N value	190 -0.21 ± 0.16	148 -0.19 ± 0.16	115 -0.36 ± 0.14	90 -0.02 ± 0.51	66 -0.12 ± 0.19	47 -0.14 ± 0.19	32 -0.18 ± 0.27
Hematocrit %	N value	190 -0.3 ± 0.2	148 -0.6 ± 0.3	115 -1.2 ± 0.4	90 -0.3 ± 0.4	66 -0.5 ± 0.5	47 -0.3 = 0.6	32 -0.5 ± 0.8
Platelet count 10^9	N value	189 3.4 ± 3.2	146 -0.6 ± 3.8	114 -1.6 ± 5.4	88 -2.5 ± 5.6	64 6.2 ± 5.8	46 7.5 ± 6.8	32 10 ± 9.6
Chemistry								
Sodium mmol/L	N value	189 -0.1 ± 0.2	150 0.4 ± 0.2	117 0.3 ± 0.2	91 0.2 ± 0.3	68 0.5 ± 0.5	49 0.5 + 0.4	33 0.9 + 0.6
Potassium mmol/L	N value	197 0.01 ± 0.00	148 0.02 ± 0.04	116 0.01 ± 0.05	90 0.00 ± 0.06	67 -0.01 ± 0.06	49 -0.04 + 0.06	33 -0.10 + 0.08
Chloride Mmol/L	N value	154 0 ± 0.3	118 0 ± 0.4	96 1.0 ± 0.4	80 0 ± 0.4	64 0.5 ± 0.5	46 0.1 + 0.5	28 0.4 + 0.6
Bicarbonate Mmol/L	N value	144 -0.22 ± 0.25	110 0.36 ± 0.26	87 0.06 ± 0.33	70 0.65 ± 0.38	58 -0.03 ± 0.37	41 0.20 + 0.5	26 -0.28 + 0.72
Calcium Mg/dL	N value	163 -0.05 ± 0.16	130 0.15 = 0.11	107 0.18 ± 0.13	81 -0.09 ± 0.20	63 -0.05 ± 0.05	46 0.07 + 0.07	31 -0.07 + 0.09
Albumin g/dL	N value	157 0.03 ± 0.03	122 -0.01 ± 0	96 -0.02 ± 0.03	75 0.05 ± 0.04	59 0.01 ± 0.05	42 0.05 + 0.06	29 0.03 + 0.07
Alkaline Phos IU/L	N value	169 -3.1 ± 3.7	134 1.1 ± 5.9	106 -7.8 ± 5.2	85 -4.0 ± 5.7	61 -12 ± 5	43 -14 + 9.4	30 -2.8 + 3.5
LDH IU/L	N value	89 -11.8 ± 6.2	59 -0.3 ± 13.6	51 -14 ± 8.6	39 -18 ± 7.9	26 -5.7 ± 11.4		
Creatinine Mg/dL	N value	188 -0.02 ± 0.01	149 -0.03 ± 0.01	115 -0.03 ± 0.01	90 -0.03 ± 0.02	67 -0.01 ± 0.02	47 -0.02 + 0.02	33 -0.03 + 0.03
BUN Mg/dL	N value	185 -0.3 ± 0.6	144 -0.4 ± 0.6	115 0.1± 0.7	87 1.5 ± 0.7	66 2.1 ± 0.8	48 2.1 ± 1.6	33 1.8 ± 1.4

For Liver function tests the table below lists the greatest change from baseline.

Table 35: Maximum change in LFTS during TRIUMPH OL

		Month						
Parameter		3	6	9	12	15	18	21
ALT (SGPT) IU/L	N Max increase	168 225	133 311	106 99	84 62	60 146	43 203	30 203
AST (SGOT) IU/L	N Max increase	162 158	126 349	98 24	79 50	55 18	37 29	24 26

Of the subjects with SGOT > 80 at any one measurement only two subjects #11004 and 11014 had their last measurement at > this value. For SGPT values > 80 IU/L, there were 5 subjects whose last value was still above this value at final measurements.

Vital signs:

Below are the changes in vital signs, from baseline to time point of treatment, prior to the administration of study drug. In addition, the acute change from pre- to post- dose is also showed. Over the course of the open-label study BP rose from baseline (this is only among those who have not discontinued). There was however a consistent drop in SBP and DBP from

pre to post dose. Heart rate was variable and slightly increased from baseline. There was a small decrease in heart rate from pre-dose to post dose.

Table 36: Change in Vital Signs during TRIUMPH-OL

	Month					
	3	6	9	12	15	18
SBP						
Change from baseline	0.1 ± 0.8	4.6 ± 1.2	4.8 ± 1.4	4.3 = 1.7	4.4 ± 1.8	2.3 ± 2.3
Change from pre-dose	-1.2 ± 0.8	-4.3 ± 0.9	-2.6 ± 0.9	-1.2 ± 1.1	-3.1 ± 1.5	-2.3 ± 1.8
DBP						
Change from baseline	0.6 ± 0.6	0.9 ± 0.8	1.2 ± 1.0	0.3 ± 1.2	2.8 ± 1.3	3.2 ± 1.5
Change from pre-dose	-2.1 ± 0.6	-3.0 ± 0.7	-1.6 ± 0.7	-0.5 ± 1.0	-2.3 ± 1.2	-3.1 ± 1.3
HR						
Change from baseline	0.2 ± 0.6	0.8 ± 0.9	0.6 ± 1.1	-1.0 ± 1.3	2.0 ± 1.5	1.0 ± 1.8
Change from pre-dose	-0.4 ± 0.7	-1.3 ± 0.7	-0.8 ± 0.8	0.4 ± 1.0	-2.1 ± 0.9	0.6 ± 1.1

Pulmonary function studies:

Pulmonary function studies were not performed during the open-label study.

ECGs:

No ECGs were planned.

CXR:

Chest X- Rays were not planned.

Study: RIV-PH-408

Title of study: REVIVE: Intravenous Remodulin (Treprostinil Sodium) As Adjunctive Therapy to Subjects Currently Receiving Sildenafil (Revatio®), Bosentan (Tracleer®) or the combination of Sildenafil and Bosentan for the Treatment of Pulmonary Artery Hypertension.

Summary:

This was an open-label uncontrolled study on the use of treprostinil by the intravenous route on top of sildenafil or bosentan. Twenty subjects were enrolled of which 17 completed.

This study does not add information to the decision to approve treprostinil by the inhalation route.

Study: P01:11

Title of study: A Multicenter, Uncontrolled, Open-Study in Patients with Pulmonary Arterial Hypertension, Transitioning for Chronic Intravenous Flolan Therapy to Chronic Subcutaneous Uniprost (UT-15) Therapy.

Summary:

The study was reviewed previously (see review dated March 20, 2001; NDA 21,272). The study employed UT-15 by a route other than the inhalation route and therefore, has minimal relevance to the decision regarding inhaled treprostinil.

Study P01:06

Title: An international Multicenter, Uncontrolled, Open Evaluation of Chronic UT-15 plus Conventional Therapy in Patients with Pulmonary Hypertension: A continuation Study:

Study Summary:

This study was an open-label continuation study on the use of subcutaneous UT-15 in patients with PAH. Since the route of administration is not by the inhalation route, the results do

not add to the decision to approve inhaled treprostinil. The study was previously reviewed (NDA 21,272; dated March 20, 2007).

Study: P01:02

Title: A Dose-Range-Finding Study Comparing Intravenous and Subcutaneous I5AU8I (UT-I5) in NYHA Class III/IV Patients with Primary Pulmonary Hypertension.

Study Summary:

This was a multicenter open label study that explored the dose effect of subcutaneous or intravenous treprostinil on pulmonary hemodynamics.

Since this was a single dose intravenous followed by a single dose SC dose study that did not employ inhaled treprostinil, its results have little bearing on the assessment of safety or efficacy of treprostinil by the inhaled route. This study was previously reviewed (NDA 21,272, dated March 20, 2001).

Study: P0I:01

Title: A Dose-Range-Finding Study of Intravenous 15AU81 (UT-I5) In Patients with Primary Pulmonary Hypertension.

Summary:

This is a hemodynamic study when treprostinil is administered by the intravenous route. The results bear little on the defining the safety and efficacy of treprostinil by the inhaled route. The study was previously reviewed (NDA 21,272, dated March 20, 2001).

Umber LRX-TRE-INH-007

Title of study:

Investigation into efficacy, haemodynamic Effects and Safety of Inhaled Treprostinil Sodium and Sildenafil in Patients with Pulmonary Arterial Hypertension.

Principal Investigator: Prof. Dr. W. Seeger
Justus-Liebig University Giessen, Germany

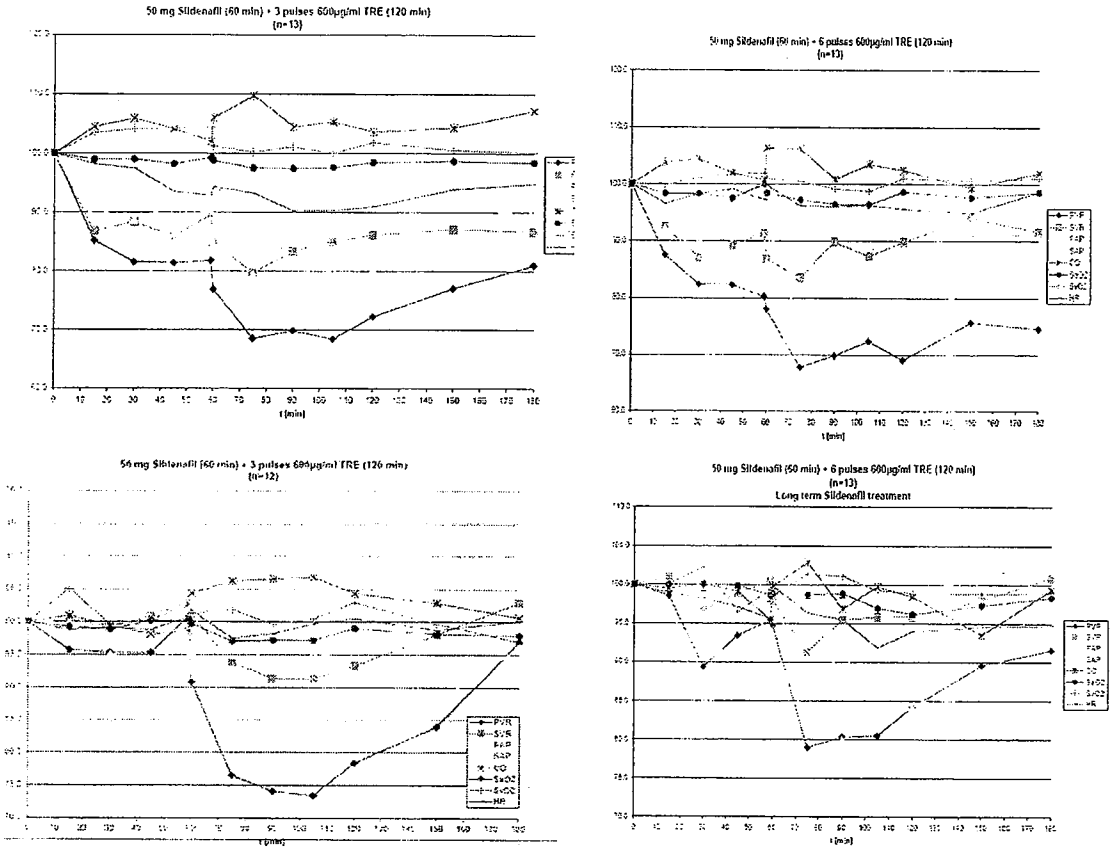
This was a single, site single blinded (patient) study. Neither the protocol nor individual line listings from the enrolled subjects were submitted. The drug used was treprostinil for subcutaneous administration that was administered by an OptiNebN™ device. Subjects were invasively monitored with a Swan-Ganz pulmonary artery catheter. The timing of insertion and the measurements are not stated. Subjects are patients with PAH either due to idiopathic/primary disease, collagen vascular disease, congenital heart disease, HIV or chronic thromboembolic disease.

There are four dose groups.

- Group 1 had 600 μg/ml of treprostinil (3 pulses, breaths).
- Group 2 had 600 μg/ml of treprostinil (6 pulses, breaths).
- Group 3- was to be on 50 mg TID of sildenafil for three months and had treprostinil 600 μg/ml (for 3 pulses, breaths).
- Group 4- was to be on 50 mg TID of sildenafil for three months and had treprostinil 600 μg/ml for (for 6 pulses, breaths).

The results are shown below. Assuming that the effect is unrelated to the instrumentation, the results suggest that there is an effect of single inhalation treatment that peaks at about 90 minutes post inhalation. (I believe that the captions are mislabeled). The upper two probably reflect the effect without sildenafil and the lower two are treprostinil on top of sildenafil. (Without line listings, I can't however be sure).

Figure 12: hemodynamic Effects Study LRX-TRE-007



Conclusion: The study is unreliable given the lack of a protocol and line listings. There is no information with regards to patient safety submitted. There is no conclusion regarding the dose-response of treprostinil with this study.

Study number LRX-TRE-INH 004

Title of Study: Investigation into efficacy, hemodynamic effects and safety of a metacresol-free formulation of inhaled treprostinil sodium in patients with pulmonary arterial hypertension.

Investigator: Pr Dr. W. Seeger
Justus-Liebig University Giessen, Germany

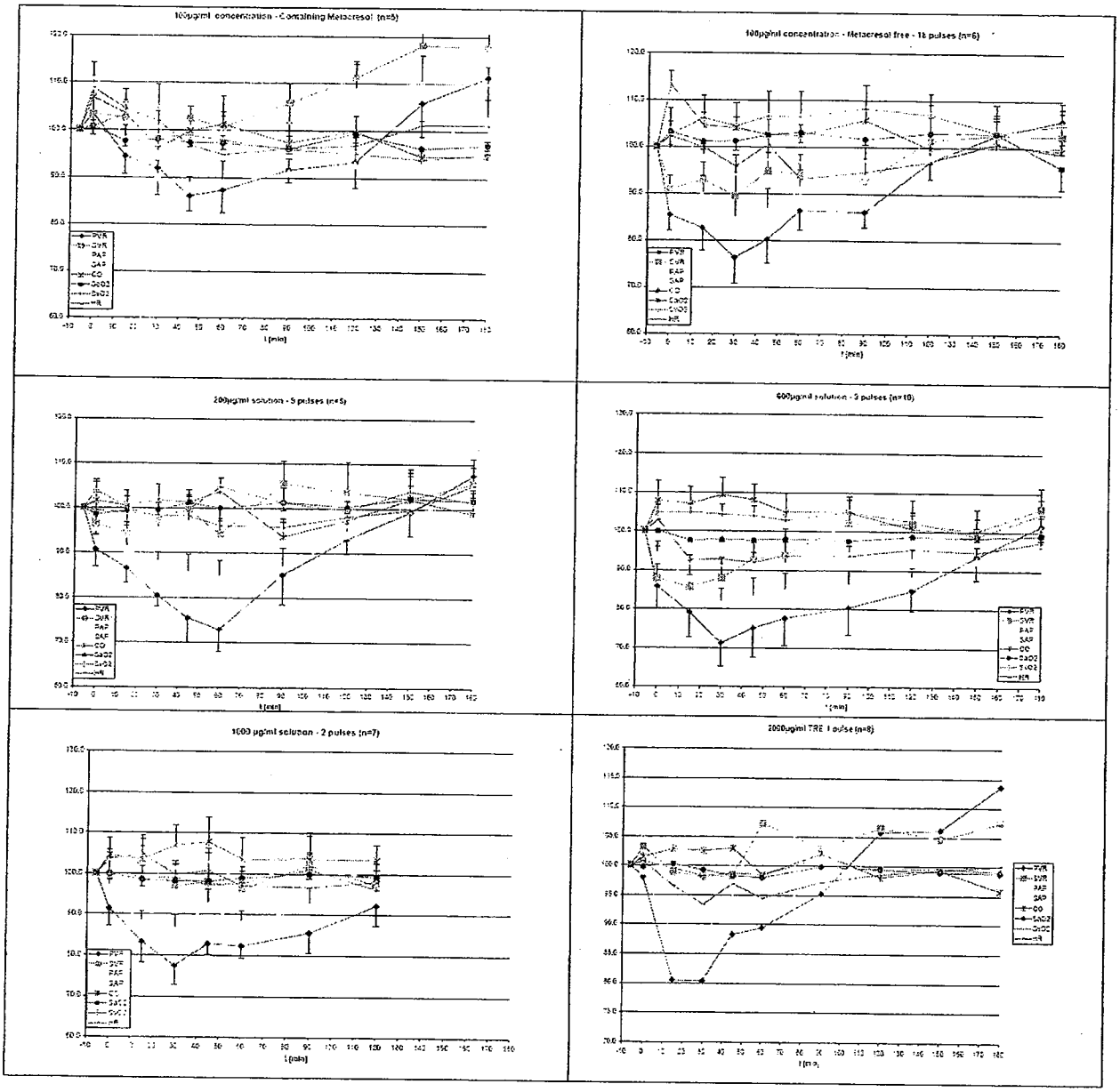
Study summary:

This was a single site, single blinded (patient) study. Neither the protocol nor the individual data listings were submitted. The drug used was treprostinil for subcutaneous administration or treprostinil without metacresol. The drug was administered by a OptiNebN™ device. Subjects were invasively monitored with a Swan-Ganz pulmonary artery catheter. The timing of insertion and the measurements are not stated. Subjects are patients with PAH either due to idiopathic/primary disease, collagen vascular disease, congenital heart disease, HIV or chronic thromboembolic disease. The various treatments are as shown below.

- Group 1: Treprostinil 100 µg/ml with metacresol -18 pulses inhaled
- Group 2 Treprostinil 100 µg/ml without metacresol 18 pulses inhaled
- Group 3 Treprostinil 200 µg/ml; without metacresol 9 pulses inhaled
- Group 4: Treprostinil 600 µg/ml without metacresol 3 pulses inhaled
- Group 5 Treprostinil 1000 µg/ml without metacresol 2 pulses inhaled
- Group 6: Treprostinil 2000 µg/ml without metacresol 1 pulses inhaled

The results are shown below.

Figure 13: Hemodynamics for Study LRX-TRE-INH 004



All groups received about the same total dose. The results here suggest that there is a decrease in pulmonary vascular resistance last about 30 minutes post inhalation. There was a trend to overshoot at the end of the 3-hour measurement period.

Conclusion:

The study is not consistent with study 007. Furthermore, in the absence of some internal control (either placebo or lower dose), the study does not support that inhaled treprostinil has activity in altering pulmonary hemodynamics. There was no safety information supplied.

Study number LRX-TRE-INH-003

Title of study: Investigation into efficacy, hemodynamic effects and safety of inhaled treprostinil sodium administered for different inhalation times in patients with pulmonary arterial hypertension

Investigator Prof D. W Seeger.
Justus-Liebig University Giessen, Germany

This was a single site study with the principal investigator the same as in study 007 and 004. The study was a single blinded (patient) study. Neither the protocol nor the individual data from subjects were submitted. The drug used was treprostinil for subcutaneous administration or treprostinil without metacresol. The drug was administered by a OptiNebN™ device. Subjects were invasively monitored with a Swan-Ganz pulmonary artery catheter. The timing of insertion and the measurements are not stated. Subjects are patients with PAH either due to idiopathic/primary disease, collagen vascular disease, congenital heart disease, HIV or chronic thromboembolic disease. The various treatments are as shown below.

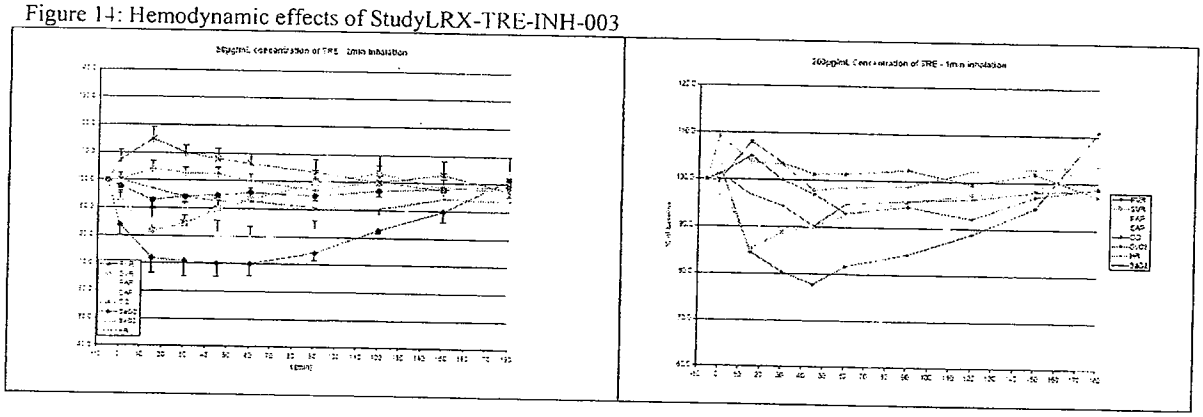
The doses used were

- 96 µg/ml over 2 minute

Or

- 200 µg/ml over 1 minute.

Figure 14: Hemodynamic effects of StudyLRX-TRE-INH-003



Conclusion:

There is too little data to assess this study.

Study number LRX-TRE-INH-0002

Title of study: Investigation into efficacy, hemodynamic effects and safety of inhaled treprostinil sodium and placebo in patients with pulmonary arterial hypertension.

Investigator Prof D. W Seeger.
Justus-Liebig University Giessen, Germany

This is a single site study. Neither the protocol, the line-listings nor adverse events were supplied. The study planned to enroll 8 patients to be treated with treprostinil or placebo. Six additional patients were treated with two higher doses of treprostinil.

Patients were of either gender with PAH due either to idiopathic/primary, collagen vascular disease, congenital heart disease, HIV or chronic thromboembolic disease or patients with pulmonary fibrosis. There were eight subjects who were treated with either treprostinil or placebo in the main part of study. An additional six patients per group were later added.

The study was divided into three parts (parts D, E and F).

- Study part D the comparison was treprostinil 16 µg/ml inhaled for 6 minutes compared to placebo inhaled for 6 minutes.
- Study part E the dose of treprostinil was 48 µg/ml for 6 min there was no concurrent placebo
- Study part F the dose of treprostinil was 96 µg/ml for 2 min there was no concurrent placebo.

(Reviewer's comments: The duration of inhalation for 6 minutes does not seem to be consistent with the way the OptiNeb™ device works. The duration of inhalation far exceeds the 9 inhalations proposed for the use of inhaled treprostinil.)

The results are shown below. Compared to placebo there were effects on PVR and PAP that were observed by 20 minutes after inhalation and persisted for about 2 hours. There also appears to be an effect on SBP and heart rate whose time course is less clear.

Figure 15: hemodynamic Effects for Study LRX-TRE-INH-0002

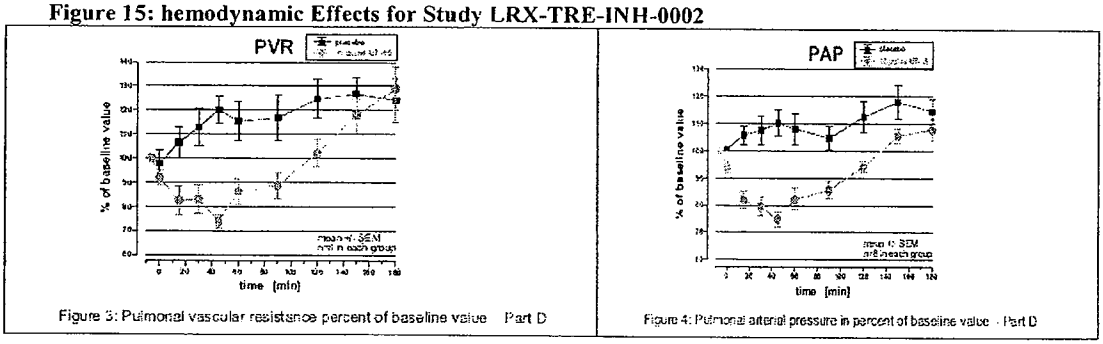


Figure 3: Pulmonal vascular resistance percent of baseline value - Part D

Figure 4: Pulmonal arterial pressure in percent of baseline value - Part D

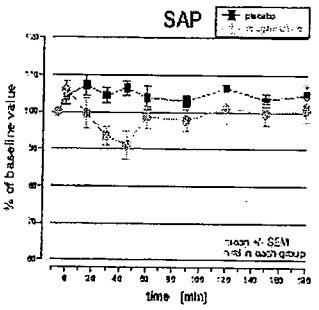


Figure 6: Systemic arterial pressure in percent of baseline value – Part D

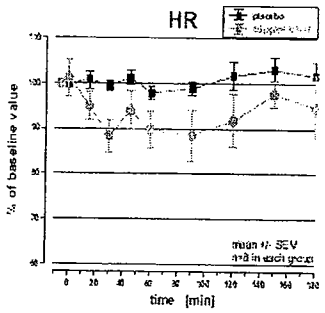


Figure 7: Heart rate in percent of baseline value – Part D

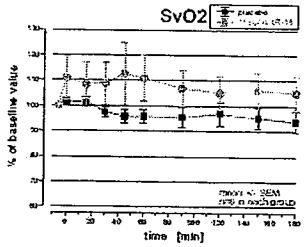


Figure 9: Systemic venous oxygen saturation in percent of baseline value – Part D

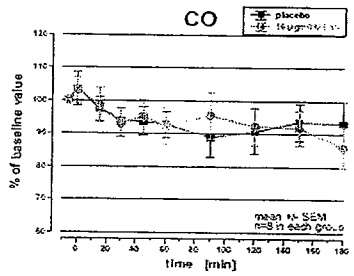


Figure 5: Cardiac output in percent of baseline value – Part D

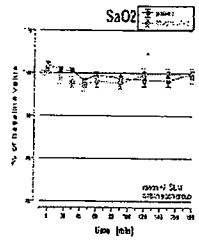


Figure 8: Systemic arterial oxygen saturation in percent of baseline value – Part D

The results below are uncontrolled.

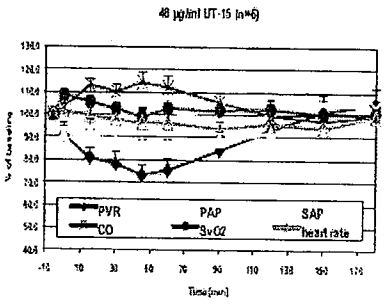


Figure 20: Haemodynamic effects following inhalation of 48 µg/ml of TRE – Part E

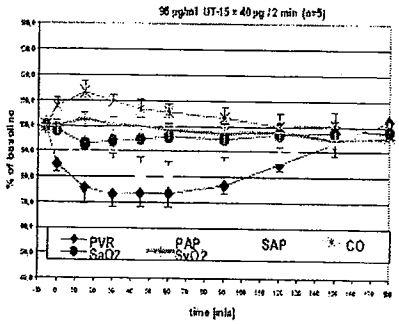


Figure 19: Haemodynamic effects following inhalation of 96 µg/ml of TRE – Part F

Study number LRX-TRE-INH-0005

Title of Study: Long term treatment with inhaled treprostinil for pulmonary hypertension:

Investigators:

Richard Channick, Horst Olschewski, Werner Seeger [redacted] b(4)

Study summary:

Twenty four subjects with PAH secondary to either idiopathic pulmonary hypertension (N=12); collagen vascular disease associated PAH (N=12) and non-operable chronic thromboembolic disease (N=3) were treated long-term in an open-label fashion. Patients were followed for between 125 and 211 weeks. During the observation period seven subjects died. The sponsor attributed the deaths as follows PE (N=1), ischemic bowel disease and multi-organ failure related to scleroderma (N=2), sudden death (N=1), liver failure due to cirrhosis (N=1), and worsening PAH (N=2).

Comments:

The study contains walk distance data that are difficult to interpret in an open-label study with substantial numbers of patients who discontinued.

Study LRX-TRE-INH-0001

Title: Investigation into efficacy, hemodynamic effects and safety of inhaled treprostinil sodium and Iloprost in patients with pulmonary arterial hypertension

Investigator: Prof D. W Seeger.
Justus-Liebig University Giessen, Germany

Neither the protocol nor the data was supplied. This was a three-period cross over study comparing different doses of treprostinil 4 µg/ml (6 minutes), 8 µg/ml (6 minutes) or 16 µg/ml (3 minutes) to a 4 µg dose of Iloprost. In the first period subjects appeared to have received treprostinil and the hemodynamics were assessed for 1 hour. After a 1 hour washout period, the

subject then received a 4 µg dose of Iloprost (note that the dose of Iloprost is lower than the currently listed maintenance dose of Iloprost and the nebulizer approved for administering iloprost is not the nebulizer used in this study).

The results of the study are shown below:

Figure 16: Hemodynamic Effects Study LRX-TRE-INH-0001

Treprostinil 4 µg/ml 6 min	Treprostinil 8 µg/ml 6 min	Treprostinil 16 µg/ml 3 min

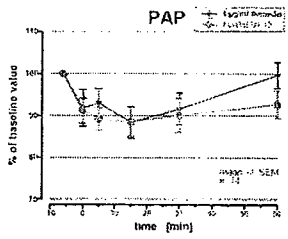
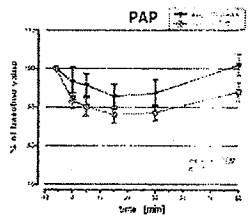
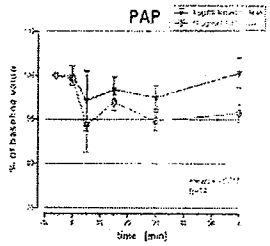

		

Figure 3: Pulmonal arterial pressure in percent of baseline value –	Figure 10: Pulmonal arterial pressure in percent of baseline	Figure 17: Pulmonal arterial pressure in percent of baseline value –

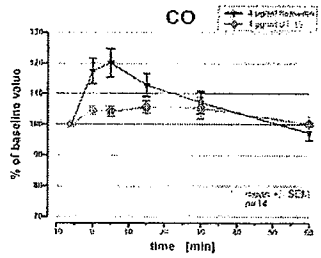
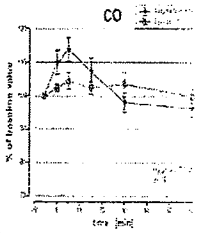
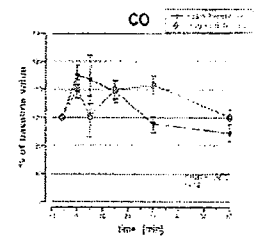

		

Figure 4: Cardiac output in percent of baseline value – Pe	Figure 11: Cardiac output in percent of baseline value – Period B	Figure 18: Cardiac output in percent of baseline value – Period C

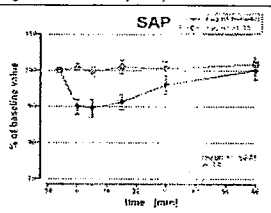
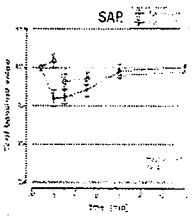
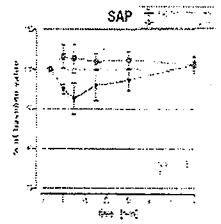

		

Figure 5: Systemic arterial pressure in percent of baseline value –	Figure 12: Systemic arterial pressure in percent of baseline value – Period	Figure 19: Systemic arterial pressure in percent of baseline value – Period C

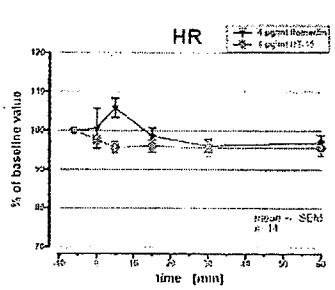
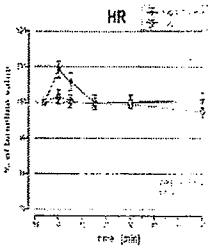
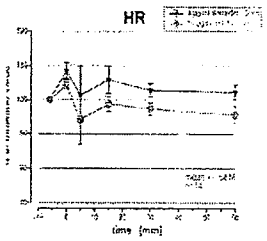
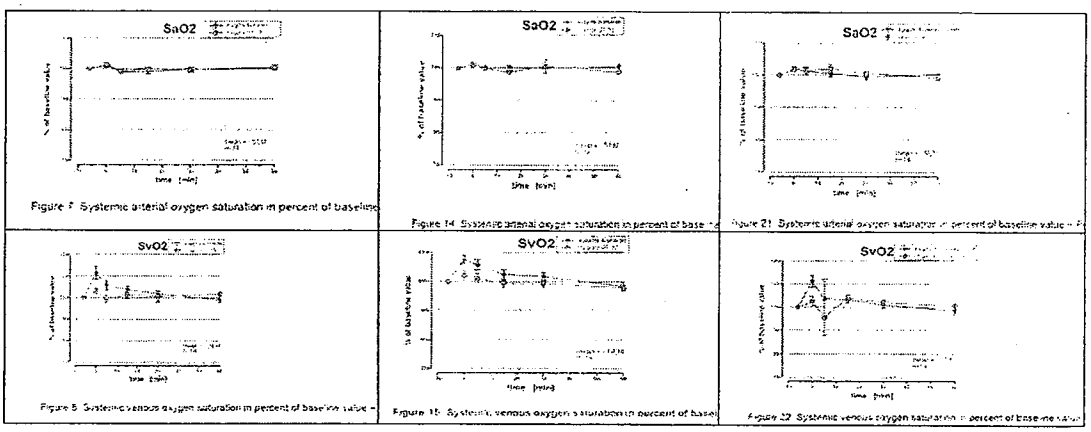

		

Figure 6: Heart rate in percent of baseline value – Period	Figure 13: Heart rate in percent of baseline value – Period B	gure 20: Heart rate in percent of baseline value – Period C



The results of this study are difficult to interpret. There appears to be an effect on PAP and SAP with treprostinil. There are difficulties, however, with any further interpretation of the studies. It is unclear if the individuals are unique for each cross-over treatment. It is also unclear whether there was any carryover of whatever effect the initial treatment after only a single hour washout. It is also unclear how much dose was administered. The protocol only stipulates a solution strength and a duration of exposure.

Study Number: RIV-PH-407

Study Title: A 12-Week, Multi-Center Evaluation of the Medtronic MiniMed 407C Infusion

Pump for Delivery of Intravenous Remodulin in Pediatric Subjects with

Pulmonary Arterial Hypertension.

Principal Investigators: Robyn Barst, MD: Columbia University Medical Center
D. Dunbar Ivy, MD: The Children's Hospital, Denver, CO.

Study summary.

This was a small study in pediatric patients to assess the utility of a new pump. Only nine pediatric patents with PAH were enrolled and only five completed the 12-week study. The route of

treprostinil administration was subcutaneous. The study adds little to assessing ether the safety or efficacy of inhaled treprostinil.

Study Number: RIV-PH-406

Title: Delivery of Intravenous Treprostinil at Low Infusion Rates Using a Miniaturized Infusion

Pump in Patients with Pulmonary Arterial Hypertension

Study Drug: Intravenous Remodulin (treprostinil sodium)
Indication: Pulmonary Arterial Hypertension

This study does not impact on the decision related to the current application.

Study number LRX-TRE-INH-0006

Title of Publication:

"Safety and Efficacy of Inhaled Treprostinil as Add-On therapy to Bosentan in Pulmonary Arterial Hypertension". Chabbick RN, Olschewski H, Wegner S, Staub T, Voswinckel R, and Rubin LJ.; J Am Coll Cardiol 2006:48: 1433-7.

Summary:

The publication consists of an open-label uncontrolled cohort with information available for 11 patients who were treated with inhaled treprostinil (solution did not contain metacresol). The solution was administered via an Opti-Neb ultrasonic nebulizer. Subjects either received 30 or 45 µg/treatment four times daily. The study enrolled 12 subjects with PAH (5 with primary/idiopathic, 3 with scleroderma, 2 with anorexigens and 1 with hereditary hemorrhagic telangiectasias). Data for 11 of the 12 were analyzed. There was an increase in six-minute walk distance compared to baseline at 12 weeks of 67 meters (at peak).

Comments;

An open-label baseline controlled is unconvincing in the demonstration of efficacy. .

Study Number LRX-TRIUMPH BA-001

An Open-Label, Randomized, Three-Period, Crossover, Comparative Pharmacokinetics and Steady-State Absolute Bioavailability Study of Treprostinil Sodium for Inhalation and Administration of Remodulin® By Continuous Intravenous Infusion to Normal Healthy Volunteers

Study summary:

This was a three period cross-over study comparing treprostinil as administered by the IV route (15 ng/kg/min) for 1 hour (900 ng/kg). The weight of those enrolled averaged 69.5 Kg. The total dose therefore averaged 62.6 µg compared to inhaled treprostinil 3 breaths (18 µg) as well as 6 breaths (36 µg). The first PK sample was collected at 5 minutes (0.083 hours).

The curves for the different treatments and the constants are shown in Figure and table below.

Figure 17: Pharmacokinetic Profile Comparing IV Treprostinil to Inhaled Treprostinil Study LRX-TRIUMPH BA-001

Figure 11.4.3.1: Mean Treprostinil Concentration-Time Profiles for Remodulin IV (Treatment A), 3 Breaths Inhaled Treprostinil (Treatment B), and 6 Breaths Inhaled Treprostinil (Treatment C) on Linear and Semi-Logarithmic Scales

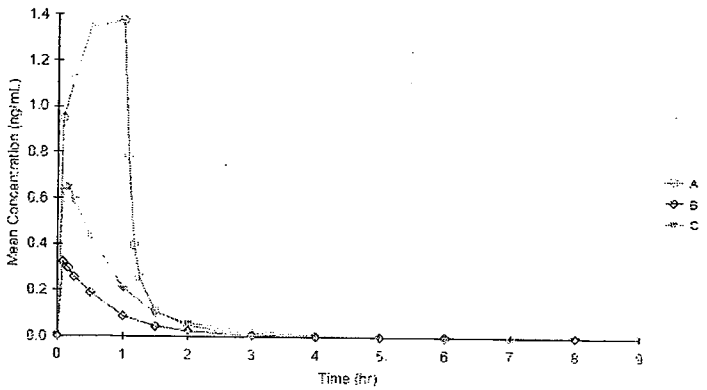


Table 37: Pharmacokinetic Parameters for IV and Inhaled Treprostinil LRX-TRIUMPH BA-001

Parameter	Treatment A IV	Treatment B	Treatment C
AUC_{0-inf}(mg*hr/ml)	1.43 ± 0.24	0.26 ± 0.08	0.61 ± 0.17
C_{max} (mg/ml)	1.46 ± 0.28	0.35 ± 0.14	0.70 ± 0.14
T_{max} (hr)	0.81 ± 0.26	0.15 ± 0.11	0.15 ± 0.07
$T_{1/2}$ (hr)	0.70 ± 0.43	0.53 ± 0.14	0.76 ± 0.34
Absolute bioavailability	100%	64%	71%

Absolute bioavailability by the inhaled route is between 64-71%. The peak concentration for the inhaled drug occurs at 0.15 hours (approximately 9 minutes). This suggests that some individuals did not have peak concentrations immediately after the inhaled dose.

Study number: stf-p02-01

A pharmacokinetic study of subcutaneous UT-15 in patients with secondary pulmonary hypertension: A study in patients with porto-pulmonary hypertension

Study summary:

This study describes the PK effect of subcutaneously administered treprostinil in patients with mild (N=5) and moderate (N=4) hepatic dysfunction. Mild or moderate hepatic dysfunction was defined based on Pugh classifications. The dose of treprostinil was 10 ng/kg/min for150 minutes.

The PK comparisons are shown below compared to a non-concurrent healthy population that was dosed with a 15 ng/kg/min infusion. The results were normalized for different doses.

The results are shown below. There were increases in C_{max} and AUC as the degree of hepatic dysfunction progressed.

Parameter	Healthy	Mild	Moderate
C_{max} (ng/ml) mean ± SD	0.98	2.2 ± 0.43	4.3 + 1.5
T_{max} (hr) range	2.0-2.8	2.6 (1.4-2.7)	2.5 (2.0-2.8)
$AUC_{0-\infty}$ (ng.hr/ml) mean ± SD	2.7	6.9 ± 1.8	13.6 ± 4.2

No safety is supplied.

The results are only tangentially pertinent to the current application.

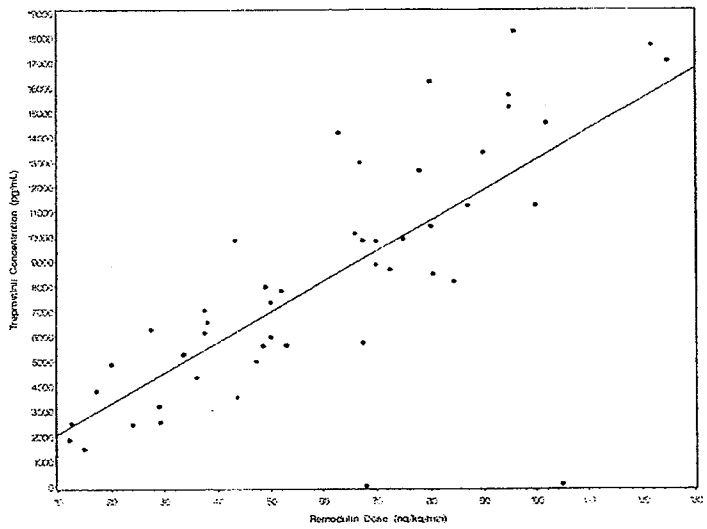
Study number RIV-PH-409:

Title of study: A Dose Proportionality Pharmacokinetic Study in Pulmonary Arterial Hypertension Patients Receiving Remodulin (treprostinil sodium) by Intravenous or Subcutaneous Infusion.

The study was a pharmacokinetic study of PAH patients who had been receiving treprostinil either administered subcutaneously or intravenously. Single steady state measurements were performed. The sponsor suggests that concentration was linearly related to dose.

Figure 18: Single Steady State Pharmacokinetics for Those receiving SC treprostinil

Figure 11.2: Plot of treprostinil plasma level versus Remodulin® dose for analysis of raw data for All 49 subjects



y = 857.4 + 122.20x and has an R^2 value of 0.56

The results are only tangentially relevant to the current application.

Study number: RIV-PH-402:

TRUST-1: Treprostinil for Untreated Symptomatic PAH Trial: A 12-Week Multicenter Randomized Double-Blind Placebo-Controlled Trial of the Safety and Efficacy of Intravenous Remodulin® in Patients in India with Pulmonary Arterial Hypertension (PAH)

Study summary:

This study was a comparison of intravenous treprostinil versus placebo in patients with PAH in India. The study was prematurely discontinued due to concerns regarding overall safety. A review of this study was previously included in my review (NDA 21,272; dated March 20, 2007). Since the route of administration of treprostinil did not correspond to the proposed route in this NDA the study has minimal relevance.

Study P01:13
Title of study: A Multicenter, Randomized, Parallel Placebo-Controlled Study Of The Safety And Efficacy Of Subcutaneous Remodulin® Therapy After Transition From Flolan® In Patients with Pulmonary Arterial Hypertension

Study summary: this study was previously reviewed in conjunction with the fulfillment of the sponsor's subpart H requirement (see review NDA 21,272 dated October 27, 2007). The route of administration in that study did not correspond to the proposed current route of administration. The results of that study are only tangentially relevant to this application.

Study number P01:04-05

***Title of study:** An International, Multicenter, Double-Blind, Randomized, Parallel Placebo-Controlled Comparison of the Safety and Efficacy of Chronic Subcutaneous UT-15 Plus Conventional Therapy to Conventional Therapy in Patients with Pulmonary Hypertension: A 12-Week Study.*

Study summary:

This study was the pivotal study (actually the results are derived from pooling two prospectively performed studies). The study was reviewed as part of the original NDA and reflects the systemic effect of subcutaneously administered treprostinil. Since the route of administration of treprostinil in these pooled studies differed from the current application, the results from that study bear limited relevance to this application. The study was originally reviewed (NDA 21,272, dated March 20, 2001).

Study #: P01:03

Title: A Multicenter, Double-Blind, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic Subcutaneous UT-15 Plus Conventional Therapy to Conventional Therapy in Patients with Severe Primary Pulmonary Hypertension: An 8-Week Study

Study summary:

This study was submitted and previously reviewed during the original NDA process for subcutaneously administered treprostinil. The route of administration was subcutaneously. The results of this study have little relevance to the current application. (See review in NDA 21,272, dated March 20, 2001).

Study number: RIN-INH-102

Title of study: 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.

Study summary:

This was a single dose (by inhalation) study in normal individuals. The intent of this study was to define a maximum tolerated dose of inhaled treprostinil to carry forth into the QTc study. Pharmacokinetic evaluations were also planned in conjunction with the single inhaled dose. Those enrolled were normal individuals. Forty subjects were to be enrolled, distributed into some number of cohorts. Each cohort was to consist of 8 patients. Within each cohort 1 placebo and 3 active dose patients will be male and an equal number of patients female. The study was to dose escalate until the investigator determined that further increase would be unsafe.

There were two amendments submitted for this protocol, unfortunately the original protocol was not included in this submission.

Subjects eligible to enroll were of either gender, between the ages of 18-45 years, have a BMI within 18-32 kg/m^2, are otherwise normal and if female, are on appropriate contraception methods. Volunteers were otherwise excluded for underlying illnesses or histories that might confound the interpretation of the study, including a history of hypotension. Foods (e.g. grapefruit juice and caffeine), OTC medications and prescription medications were proscribed at least for 48 hours pre-dosing.

Subjects received a specified dose administered by the OptiNeb device. The initial dose was 9 breaths. The second cohort was to receive 12 breaths, the third cohort 15 breaths. With that cohort the sponsor decided that the maximum tolerated dose was attained and the last two cohorts received 14 puffs and 13 puffs, respectively.

Pharmacokinetic samples were collected prior to dose administration (0 hour), at the end of the dose administration interval, and at the following time points from the completion of dose administration: 0.083, 0.167, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours. Blood pressure and heart rate were recorded prior to dose administration and at 1, 2, 3, 4, 6, and 8 hours after dose administration. Subjects were queried for adverse events prior to dose administration and at 4, 8, 12, and 24 hours after dose administration.

Results:

Demographics there were 21 and 19 females enrolled with a mean ± SD age of 36 ± 7 years.

Pharmacokinetics:

Figure 19: Mean Plasma Concentration (0-8 Hours) Semi-logarithmic Scale: N=6/Cohort Study RIN-INH-102

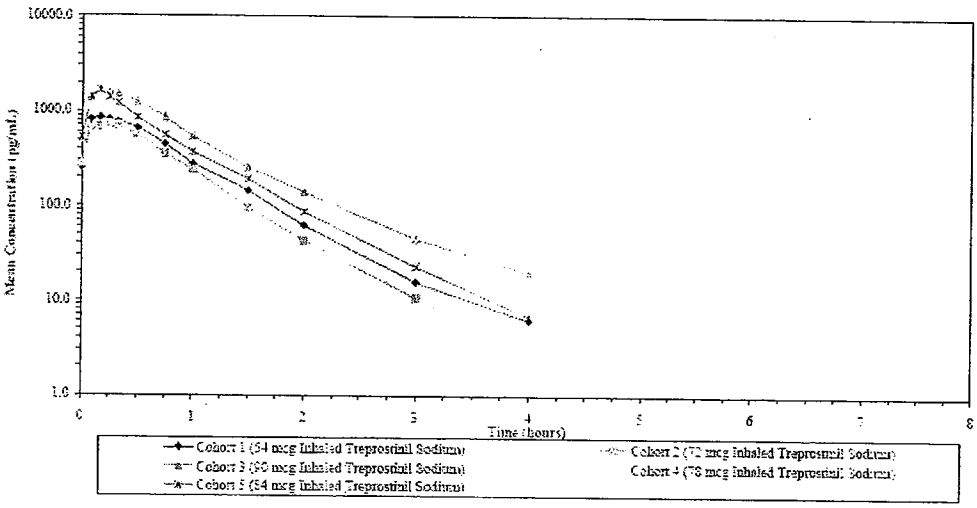


Table 38: Pharmacokinetic Parameters mean ± SD Study RIN-INH-102

Dose	AUC $_{0-\infty}$ pg-hr/ml	C_{max} pg/ml	T_{max} (hr)	$T_{1/2}$ (hr)	Cl/F L/hr/kg
9 puffs	812 ± 472	915 ± 416	0.25 ± 0.15	0.55 ± 0.18	1.45 ± 1.4
12 puffs	660 ± 444	787 ± 479	0.18 ± 0.11	0.46 ± 0.08	3.4 ± 3.5
15 puffs	1579 ± 816	1708 ± 1055	0.21 ± 0.05	0.57 ± 0.11	1.4 ± 1.9
14 puffs	1206 ± 534	1284 ± 872	0.18 ± 0.06	0.58 ± 0.15	1.19 ± 0.75
13 puffs	1181 ± 239	1582 ± 836	0.19 ± 0.10	0.54 ± 0.14	1.01 ± 0.27

There was large variability in the numerical values with substantial overlap in AUC and C_{max} across doses. Peak concentrations were not observed at the first measurement but at the second time-point, suggesting that there was no extremely rapid distribution phase. The results are not convincingly dose proportional but the large variability makes any conclusion very tentative.

Table 39 : Adverse Events Study RIN-INH-102

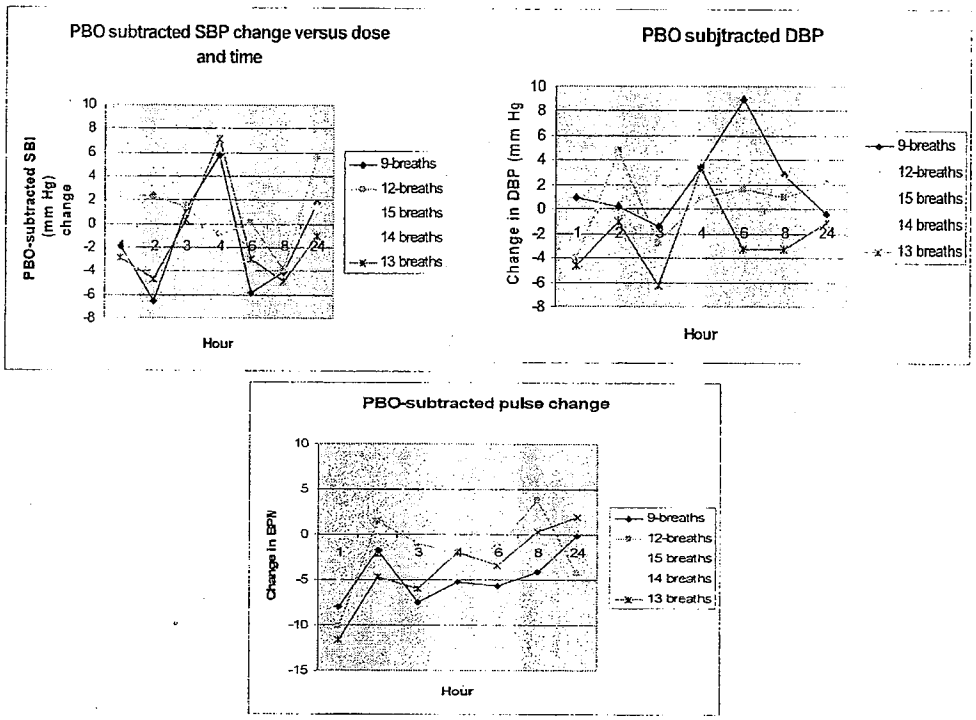
		Number of breaths				
	PBO	9	12	18	13	14
N=	10	6	6	6	6	6
# with ADR	2	2	4	5	2	4
# of ADRs	2	5	10	18	3	9
# of events with intensity greater than mild	1	2	0	2	1	1

Of those with moderate events the following were reported:
Patient # 4 treated with 9 breaths adverse event was dizziness
Patient # 5 treated with 9 breaths also had dizziness
Patient # 22 treated with 15 puffs had vomiting and also had difficulty inhaling
Patient # 26 treated with placebo had a syncopal episode
Patient # 32 treated with 13 breaths had lightheadedness
Patient # 33 treated with 14 breaths had menstrual cramps.

Of those with adverse events greater than "mild" in intensity only 2 had serum C_{max} values > 2000 pg/ml (one was adverse cramps; there were a total of 5 subjects with C_{max} > 2000 pg/ml).

Blood pressure and heart rate were recorded prior to dose administration and at 1, 2, 3, 4, 6, and 8 hours after dose administration. The timing of the blood pressures missed peak concentrations of treprostinil. From the measured values and the small numbers of patients per treatment group, it is difficult to make any conclusions. Of note, there is no convincing dose-response to the relationships that are observed.

Figure 20: Vital Signs Study RIN-INH-102



Neither the adverse event profile nor the vital sign information suggests that tolerability in dose has been reached.

Study number RIN-PH-103 (PRACS R06-028)

Title of Study A Double-blind Randomized Parallel Group Trial To define the ECG Effects of Inhaled Treprostinil, Sodium Using A Clinical and Supratherapeutic Dose Compare to Placebo And Moxifloxacin (A Positive Control) in Healthy Men and Women: A thorough ECG trial.

Overview summary:

The study is being reviewed by the thorough QT group.

The doses as used in this study, although above the proposed dose, do not seem to be the maximum tolerated dose. The tolerability study (# RIN-INH-102) was not convincing that 14 breaths were the maximum tolerated dose. In addition, sampling of ECGs did not begin till the five minute time point after the end of inhalation. The effect captured did not, therefore, capture the maximal effect of treprostinil by inhalation.

Background:

In *in vitro* studies, the sponsor asserts that treprostinil had no measurable effect on hERG channels at concentrations in excess of several thousand fold that attained by SC and IV dosing and approximately 20–fold higher than the C_{max} for inhaled treprostinil (See study RIN-INH-102). Treprostinil at concentrations of 300 μM did not prolong the APD_{60} or APD_{90} at both 1 and 0.5 times basic cycle length. There was shortening of the APD_{60} or APD_{90} parameter at concentrations of treprostinil greater than 30 μM at cycle lengths of either 1 or 0.5 seconds or both, In beagle dogs, intravenous doses of ob between 2- 200 μg/kg did not PR or QT intervals.

Inclusion Criteria:

The study planned to enroll 240 subjects. Subjects are to be of either gender between the ages of 18-45 years with BMI between 18-32 kg/m^2 and weigh at least 110 lbs. If female, the subject must be on adequate birth control methods.

Exclusion criteria:

Subjects were excluded if they have a history of cardiovascular, respiratory, renal, hepatic, gastrointestinal, immunologic, hematologic, endocrine, neurologic or psychiatric disease. Subjects with a history or evidence of blood pressure, heart rate, ECG, laboratory or chronic viral disease, allergies to medication or who are taking medications are excluded.

Doses:

There will be 4 treatment groups. The drugs were administered to subjects in a double dummy design consisting of inhaled treprostinil or oral moxifloxacin. The formulation of treprostinil that was inhaled was:

Table 40 : Doses for the QT study

Group	Treprostinil	Moxifloxacin
PBO	Placebo 14 puffs	Placebo
Moxifloxacin	PBO 14 puffs	400 mg
9 puffs	9 pulses	PBO
14 puffs	14 pulses	PBO

(Note: it is pretty obvious that patients who receive 9 puffs of drug are in the treprostinil inhaled group).

Procedure:

The procedures are shown below:

Figure 21: Procedures definitive QT study

TRIAL PHASE (EACH TREATMENT PERIOD)	Screening Day -28 to Day -2 (Performed Once)	CONFINEMENT AT CLINICAL RESEARCH UNIT			Early Discontinuation or End of Study/ Discharge
		Check-in Day -2	Baseline Day -1	Treatment Day 1	
Informed Consent	X				
Eligibility (Inclusion/Exclusion)	X	X[a]			
Prior Medication Assessment	X	X[a]			
Medical History	X	X[a]			
Vital Signs	X	X		X[d]	X
Physical Exam	X	X			X
Clinical Laboratory Tests ▫ CBC with differential ▫ Clinical Chemistry ▫ Urinalysis	X	X			X
Clinical Laboratory Screens ▫ HIV Antibody Screen ▫ Hepatitis B Screen ▫ Hepatitis C Screen	X				
Pregnancy Screen (females only)	X	X			X
FSH (if necessary to document postmenopausal status)	X				
Urine Drug/Alcohol Screen	X	X			
12 lead ECG from H-12			X[c]	X[c]	
Safety 12-lead ECG	X	X		X[d]	X
Study Drug Administration				X	
Pharmacokinetic Sampling				X[b]	
Adverse Events				X[e]	X
Concomitant Medication				X	X

[a] Updated and/or reviewed

[b] Pharmacokinetic samples will be collected at predose (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*.

[c] ECGs will be obtained on Day -1 and Day 1 at the following times: after planned (Day -1) or actual (Day 1) dose administration: *0.083*, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 23.5 hours after dose administration.

[d] Vital signs (HR, RR, blood pressure) and 12-Lead safety ECG will be collected 2-3 hours after dose administration on Day 1.

[e] Adverse events will be queried at approximately 2-3 hours after the dose of study medication on Day 1. Adverse events will also be recorded when spontaneously reported throughout the course of the study.

Baseline ECGs are time matched on day 1 to those after intervention (treatment day 1)

Note: some of the safety assessments such as vital signs were not timed to capture peak effects. ECGs were not timed to the start of the inhalation, with the first ECG performed at 0.083 hrs (5 minutes) after dose administration. Pharmacokinetic samples also did not necessarily capture peak effects.

The ECGs, in digital format were collected using a [redacted] continuous ECG recorder. ECGs are recorded at 10-second intervals. The ECGs were extracted for the same time point at baseline ± 5 minutes. b(4)

(It is unclear to me how a specific ECG was defined as the prototype for each time point. In theory, for earlier measurements, the QTc could be chosen to under-read for time points around 2-4 hours, the T_{max} for moxifloxacin, they could be over-read.)

Results:

Demographics:

The demographic characteristics of those enrolled are shown below.

Table 41: Demographics for Those in the Definitive QT study, Mean ± SE

Parameter	Placebo N=61	Moxifloxacin N=60	Treprostinil 9 puffs N=60	Treprostinil 14 puffs N=60
Age	25.1 ± 0.8	23.6 ± 0.7	24.8 ± 0.9	26.5 ± 0.9
BMI	25.5 ± 0.4	24.6 ± 0.3	25.7 ± 0.5	25.3 ± 0.5

Pharmacokinetics:

The pharmacokinetic curves for the 9 and 14 puff group are shown below. There is a rapid decay of concentrations after the inhalation time. It is unclear if peak concentrations were captured.

Figure 22: Mean Plasma Concentration for Those Enrolled in the Definitive QT Study

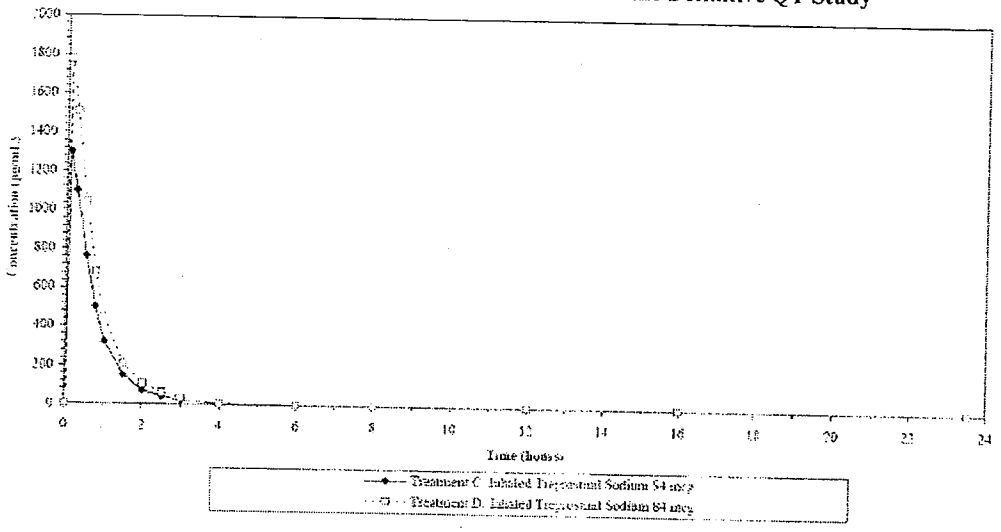


Table 42: Pharmacokinetic parameters mean± SD

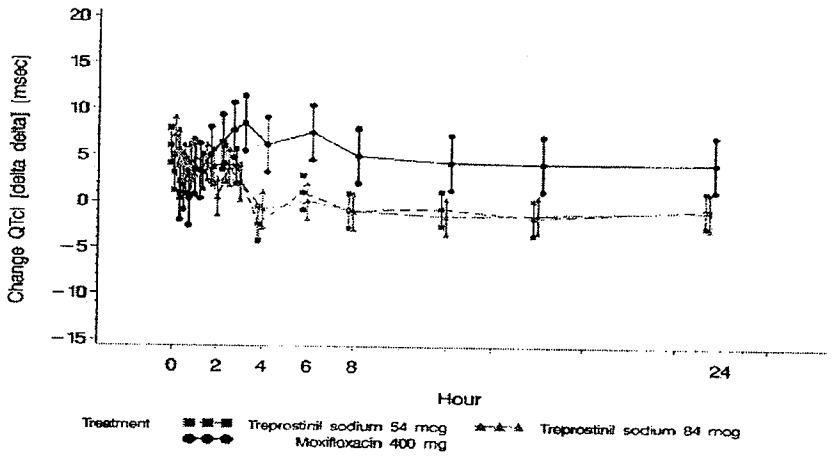
	Treprostinil 9 puffs	Treprostinil 14 purrs
C_{max} (pg/ml)	1316 ± 430	1796 ± 635
$AUC_{0-\infty}$ (pg*hr/ml)	975 ± 281	1352 ± 356
T_{max} (hr)	0.12 ± 0.07	0.12 ± 0.07
$t_{1/2}$ (hr)	0.54 ± 0.1	0.62 ± 0.3

Peak concentration generally occurred at or near the first measurement of concentrations. There was a substantial amount of concentration overlap between those who were treated with 9 puffs and those treated with 14 puffs.

The QT effects

The sponsor analyzed the data based on the double delta effect (baseline and placebo) the results as per sponsor is shown below.

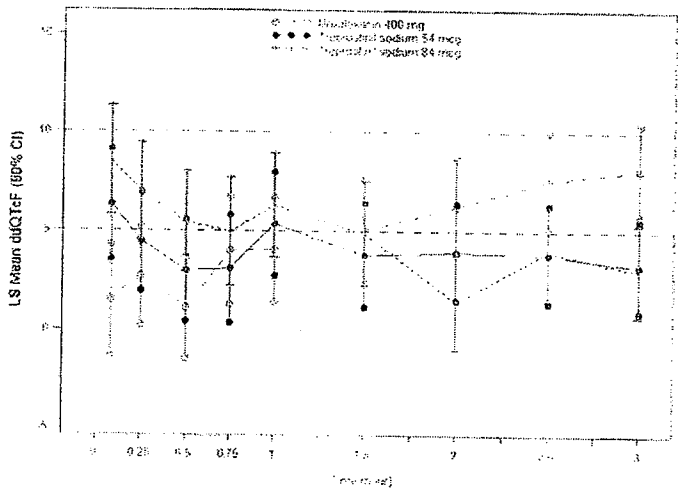
Figure 23: QTc Change over Time Mean ± SE



The effect during the first several measurements is amplified and shown below. Note that the y-axis is different in the two representations of repolarization metrics. Here it is QTcF, above it is the QTcI. There is a strong trend for the two treprostinil regimens to approach an increase in QTc placebo and baseline subtracted) of approximately 10 msec. The effects decay rapidly consistent with the rapid decrease in plasma concentrations. The effects of moxifloxacin begin to rise at the end of the displayed time points. The question is, whether earlier time points of QTc had they been measured captured greater increases in QTc.

The time course for moxifloxacin increases is not until hours later.

Figure 24: Early QT_cI Effects 0-3 hours Mena ± SE



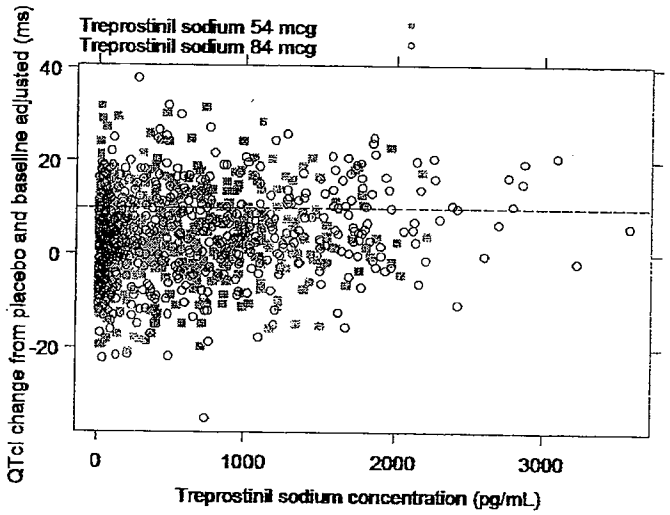
There appears to be an elevated and rapidly decreasing QTc measurement during the initial measurements.

The effect for the fraction of patients in the 14 puff cohort whose Cmax exceeded the Cmax for the 9 puff dose is shown below.

The scatter plot of

Figure 25: Scatter plot of concentration Versus QT effects.

Placebo-Corrected Change from Baseline versus Treprostinil Plasma Concentration – Estimates from Linear Mixed Model [1] QTc Individual, QTc Fridericia, QTc Bazett and QT Interval (msec) – Safety Analysis Set



Quantitative assessment:

Table 43: Concentration-related Parameters

QT Parameter	Slope of Plasma Concentration	Standard Error of Plasma Concentration	p-value	Predicted QTc at Average C_{max}	One-sided Upper 95% Confidence Bound of Predicted QTc	Overall Model Fit
QTcI	0.0040	0.0004	0.0000	6.8977	8.0418	<.0001
QTcF	0.0040	0.0004	0.0000	7.3455	8.4696	<.0001
QTcB	0.0065	0.0006	0.0000	13.3221	14.7745	<.0001

[1] Linear Mixed Model if fit for change from baseline (not placebo-corrected) versus the plasma concentration as a fixed effect with subject included in the model as a random effect.
[2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

Other ECG parameters:

There appears to be no significant effect on PR or QRS intervals.

Safety:

The safety of single inhaled doses in a normal population is unlikely to add to the overall description of the safety profile of this route of administration.

There were 82 subjects who had a total of 131 adverse events.

It is unclear if the earlier time points of QTc had they been measured captured greater increases in QTc. The rapid dissipation of any QTc effects makes it unlikely that these effects would provoke cardiovascular adverse events.

15 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Abraham Karkowsky
4/3/2009 01:13:23 PM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22-387
Brand Name	TYVASO™
Generic Name	Treprostinil sodium
Sponsor	United Therapeutics
Indication	Treatment of Pulmonary Arterial Hypertension in Patients with NYHA Class 3 — Severity of Disease
Dosage Form	Inhalation
Drug Class	Chemically stable tricyclic benzindene analogue of prostacyclin
Therapeutic Dosing Regimen	The most common dose in patients is — — 9 inhalations) four times daily with some patients receiving doses of — — 12 inhalations) four times daily.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	84 mcg when administered via inhalation
Submission Number and Date	N 000; 30 June 2008
Review Division	DCRP / HFD 110

b(4)

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The study failed to exclude a 10 ms increase in the QTc interval. The largest upper bound of the 2-sided 90% CI for the mean ΔΔQTcF difference between Treprostinil sodium (54 and 84 mcg) and placebo were 9.4 ms and 11.2 ms, respectively. This is unlikely to be of clinical relevance since the upper bound was only 11.3 ms for the supra-therapeutic dose, occurred only at 5 minutes post-dose and may be related to the heart rate increase secondary to vasodilatation associated with treprostinil (see Figure 3 for heart rate changes). In addition, the patient population for the proposed indication will be monitored periodically for ECG and electrolyte abnormalities.

The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was higher than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating assay sensitivity was established.

In this randomized, blinded, parallel study, 240 healthy subjects was randomized to receive treprostinil sodium 54 mcg, treprostinil sodium 84 mcg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Treprostinil sodium (54 mcg and 84 mcg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Treprostinil sodium 54 mcg	0.083	6.4	(3.5, 9.4)
Treprostinil sodium 84 mcg	0.083	8.5	(5.8, 11.3)
Moxifloxacin 400 mg*	3	8.2	(5.8, 10.7)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 5.1 ms.

The maximum tolerated single-dose of inhaled treprostinil in healthy volunteers is 84 μg. In Study RIN-PH-102, AEs occurring in the 90-μg cohort included chest pain, chest discomfort, nausea and vomiting. These AEs were determined to be intolerable thus prohibiting dose escalation above 90 μg.

The supratherapeutic dose (84 mcg) produces mean C_{max} and $AUC_{(0-\infty)}$ values 1.4-fold higher than the mean C_{max}, $AUC_{(0-\infty)}$ for the therapeutic dose (54 mcg). The supratherapeutic dose reflects the scenario where a 54-mcg dose is given to a patient with hepatic impairment which will result in a 2-fold increase in AUC.

1.2 Responses to Questions Posed by Review Division

1. What is the risk for QT prolongation in patients who have C_{max} more than mean+2 times the standard deviation?

   The mean C_{max} after 54-mcg dose is 1315 pg/ml with an SD of 430 pg/ml; hence, the mean + 2•SD is 2175 pg/ml. The mean C_{max} after 84-mcg dose is 1795 pg/ml with an SD of 634 pg/ml. Hence the mean + 2•SD is 3063 pg/ml.

   As shown in Figure 5, there are too few observations over 3000 pg/ml to draw any meaningful conclusions about magnitude of QTc prolongation at these high concentrations using the observed data.

   There were no subjects with a change from baseline in QTc greater than 30 ms (Table 11).

2. What is the risk for QT prolongation immediately after administration of treprostinil?

   Figure 4 shows the time course of mean ΔΔQTcF after administration of treprostinil sodium (84, 54 mcg) and moxifloxacin. The sponsor did not obtain an ECG immediately after dosing; however, at 5 minutes post-dosing, the upper bound of the 90% CI is slightly above 10 ms for the supratherapeutic dose (84 mcg). By 15 minutes the QTc prolonging effects is below 10 ms and remains below this threshold for the remainder of the day.

2 PROPOSED LABEL

2.1 SPONSORS PROPOSED LABEL

b(4)

[redacted]

3 BACKGROUND

3.1 PRODUCT INFORMATION

TYVASO™ (UT-15, treprostinil sodium), a prostacyclin analogue is being developed by United Therapeutics as an aqueous solution for inhalation, for the proposed indication of treatment of pulmonary arterial hypertension(WHO Group I) in patients with NYHA Class III [redacted]. TYVASO (strength of 0.6 mg/ml) is intended for oral inhalation using the Optineb-ir, an ultrasonic, pulsed delivery nebulizer. b(4)

3.2 MARKET APPROVAL STATUS

Treprostinil sodium for infusion (Remodulin® Injection) is currently approved in the USA and in other countries for s.c and IV administration

3.3 PRECLINICAL INFORMATION

Source: Pharmacology Written Summary-CTD 2.6.2

> "Treprostinil did not inhibit hERG-mediated current at concentrations of up to 39,052 ng/ml and did not prolong action potential duration in rabbit Purkinje fibers at concentrations of up to 117,156 ng/ml, which were the highest concentrations tested in each assay. These concentrations greatly exceed peak systemic exposure (1.8 ng/ml) and estimated peak cardiac exposure (<100 ng/ml) in patients using Tyvaso at the maximum recommended dose.
>
> "In the cardiovascular safety pharmacology study, dogs were given IV bolus doses of treprostinil sodium at dose levels of 0, 2, 20, and 200 mcg/kg. As expected, treprostinil caused an initial drop in arterial blood pressure and compensatory increase of heart rate at all dose levels, which reflected the drug's primary pharmacodynamic activity and were not considered adverse. The initial drop in arterial blood pressure was followed by a period (up to 6 hours) of elevated blood pressure. At 200 mcg/kg, increased diastolic blood pressure was considered excessive and thus adverse. Transient atrioventricular blocks that may have been drug-related were observed in one dog at 2 mcg/kg and another dog at

200 mcg/kg; however, these events were unrelated to dose level and PR interval was unaffected. Treprostinil did not affect QT interval (actual or corrected for heart rate) at any dose level. Based on these results, the NOAEL was 20 mcg/kg. Systemic exposure was not measured in this study, but peak exposure at the NOAEL can be conservatively estimated at 250 ng/ml by assuming that the drug rapidly distributed within the bloodstream and that dogs had a total blood volume of 80 ml/kg (8% of body weight). Thus, peak systemic and cardiac exposure at the NOAEL in dogs exceeded peak systemic exposure (1.8 ng/ml) and estimated cardiac exposure (<100 ng/ml) in patients using Tyvaso at the maximum recommended dose.

"The only clinical signs of altered CV function noted in repeat-dose inhalation toxicity studies were secondary to treprostinil-induced vasodilatation, such as reddening or flushing of skin, weakness, and reflex tachycardia. In the 7-day inhalation toxicity study in dogs, no clinically significant effects on ECG or blood pressure were noted after the 1st and 7th doses at any dose level. The only treprostinil-related effect was increased heart rate at 2 hours post dose at estimated dose levels ≥860 mcg/kg/day, which was considered secondary to treprostinil related vasodilatation. In the 13-week inhalation toxicity study in dogs, no clinically significant effects on ECG or blood pressure were noted after the 1st, 30th, and 80th doses at any dose level. The only treprostinil-related effect was sinus tachycardia during the early weeks of the study at estimated dose levels ≥322 mcg/kg/day, which was considered secondary to treprostinil-related vasodilatation. By the end of the dosing period, sinus tachycardia was observed only at an estimated dose level of 1558 mcg/kg/day. This pattern suggested that dogs may have adapted to the vasodilatory effects of treprostinil, leading to a reduction in reflex tachycardia. In both of the repeat-dose toxicity studies, systemic treprostinil exposures associated with tachycardia in dogs (Cmax >140 ng/ml and AUCinf >59 h*ng/ml) far exceeded exposures in patients at the recommended therapeutic dose.

Reviewer's Comment: In vitro and in vivo studies suggest no effect on the QT interval although there is vasodilatation and reflex tachycardia consistent with pharmacodynamic effects.

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety-CTD-2.7.4

"Safety information is summarized for 590 patients who participated in clinical studies; 58 subjects who participated in normal volunteer studies; 48 patients with PAH who participated in acute dose studies; and 484 (Studies P01:03/04/05/06) patients with PAH who participated in chronic, continuous dose studies.

"To date, well over 3,000 subjects have been exposed to Remodulin from single administration to subjects receiving continuous infusion of Remodulin for greater than 8 years.

"In chronic studies in patients with PAH, the most common adverse events included local infusion site pain, infusion site reaction, and infusion site

bleeding/bruising. While infusion site pain and reaction were clearly drug-related, infusion site bleeding/bruising was more common in the placebo group. Systemic adverse events known to be associated with vasodilators, and prostacyclin in particular, were also common and included diarrhoea, headache, nausea, jaw pain, body pain, and vasodilatation. The majority of these events were considered drug-related.

"Serious adverse events in these patients were relatively common, but very few of these events were judged to be drug-related. The most common serious adverse events that are drug-related are what would be expected of prostaglandin-type drugs.

"RIN-PH-102 was a single-dose, dose-escalating exploration of the maximum tolerated single dose of inhaled treprostinil. The study enrolled 40 healthy volunteers (19 male, 21 female), aged 18-44 years, and was conducted in order to inform dose selection for the subsequent thorough QTc study.

"The first three dosing groups were 54mcg, 72mcg, and 90mcg. Among the 6 subjects receiving active drug in the 90mcg dosing group, 2 developed chest pain/discomfort. Upon physical examination, the chest pain was attributed to bronchoconstriction in one of the subjects. Based on this finding, no further dose escalation was attempted, and two subsequent dosing groups (78mcg and 84mcg) were added to further explore the tolerability of doses between 72mcg and 90mcg."

Reviewer's Comments: It is difficult to come to any conclusions regarding the deaths in the clinical trials and post-marketing reports due to cardiac arrest since they are confounded due to disease progression and co-morbidities. Convulsion and hypotension/vasovagal syncope have been reported but not associated with QT prolongation. There are no reports of TdP. An MGPS data mining analysis of the AERS database for AEs related to QT prolongation with treprostinil indicates incidence was similar to the background rate in the general population (see section 5.4.4).

The maximum tolerated single-dose of inhaled treprostinil in healthy volunteers was determined to be 84 μg. AEs occurring in the 90-μg cohort (chest pain, chest discomfort, nausea and vomiting) were determined to be intolerable thus prohibiting dose escalation above 90 μg.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of treprostinil's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study. The sponsor submitted the study report for treprostinil sodium including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

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

4.2.2 Protocol Number

RIN-PH-103 (PRACS R06-0288)

4.2.3 Study Dates

February 11, 2008 – March 28, 2008

4.2.4 Objectives

The primary objective of this trial was 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).

4.2.5 Study Description

4.2.5.1 Design

The study was a randomized, double-blind, single-site, single-dose, four-arm parallel design conducted using healthy male and female subjects (18-45 years of age, inclusive).

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin and its placebo tablets were overencapsulated.

Reviewer's Comment: It is not clear how administration was double-blinded when treprostinil 54 mcg was delivered in 9 breaths whereas all other treatments were delivered in 14 breaths.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Two hundred forty-one (241) healthy, normal, male and female subjects were randomly assigned to receive one of the following four treatment regimens on study 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.

4.2.6.2 Sponsor's Justification for Doses

"The clinical dose of inhaled treprostinil sodium is 54 mcg delivered as 9 pulses. The supratherapeutic dose is 84 mcg delivered as 14 pulses as determined by a preceding maximum tolerated dose study in healthy volunteers."

Reviewer's Comment: Based on the tolerability data as per study RIN-PH-102, the choice of 84 mcg as the supratherapeutic dose is appropriate. Although, liver impairment could increase the exposure to treprostinil by 2-fold, tolerability issues did not allow for testing of higher doses.

4.2.6.3 Instructions with Regard to Meals

No food was administered for at least 8 hours prior to dosing through at least 4 hours after dosing.

Reviewer's Comment: Since treprostinil sodium would be administered via inhalation route, the effect of food would be of no significance.

4.2.6.4 ECG and PK Assessments

Three 12-lead ECGs were obtained at baseline (day -1) and on day 1 at the following time points from dosing in all four parallel groups: 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 initiation of dose administration. A total number of 45 ECGs were analyzed at baseline. A total of 45 ECGs were also analyzed at day 1 resulting in a total of 90 ECGs for each of 240 completed subjects.

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.

Reviewer's Comment: Based on the terminal half-life of <1 hour, the sampling schedules for ECG's and PK are adequate.

4.2.6.5 Baseline

Baseline value is defined as the time-matched ECG measurements one day before dose.

4.2.7 ECG Collection

Digital ECGs were obtained using a [redacted] continuous recorder, which captured ECGs on Day -1 and on Day 1 at the time points specified above. Subjects were required to lie down approximately 10 minutes prior to the scheduled ECG collection time point through 10 minutes after the scheduled time point. b(4)

The ECGs were stored on a flashcard about every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed. Three

ECGs were extracted at each time point at baseline and on treatment (+/- 5 minutes of the schedule time).

ECG readers were blinded to subject identifiers, treatment and visit. All ECGs for a given subject were analyzed by the same reader.

The ECG analysis was conducted in Lead II and when not analyzable in Lead V5, or most appropriate lead. Interval duration measurements were first obtained by trained analysts using the proprietary validated electronic caliper system applied on a computer screen. A cardiologist then verified the interval durations and performed the morphology analysis, noting any T-U wave complex that suggested an abnormal form compatible with an effect on cardiac repolarization.

Quality Assurance reports for inter- and intra-observer variability were produced by eResearch and provided to the Sponsor.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 241 healthy adult (119 males; 122 females) subjects, 18-45 years of age with a normal baseline ECG and BMI between 18-32 kg/m^2 participated in this study. Of all randomized subjects (N = 241), 240 subjects completed the study. Subject 207 was discontinued by the sponsor prior to Day 1, study hour 6 activities due to dosing error (no drug in nebulizer). Subject 707 was added to replace Subject 207 in Treatment A.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor used QTcI as the primary outcome. The largest upper bounds of the 2-sided 90% CI for ΔΔQTcI between treprostinil sodium (54 and 84 mcg) and placebo were 8.0 ms and 9.1 ms. The analysis results were presented in Table 2.

The sponsor also performed the same analysis for QTcF. The largest upper bounds of the 2-sided 90% CI for ΔΔQTcF between treprostinil sodium (54 and 84 mcg) and placebo were 8.3 ms and 9.8 ms, respectively. The analysis results were presented in Table 3.

Table 2: ANOVA treatment comparisons based on LS-mean changes in QTcI

Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Individual (msec)

	Treprostinil sodium 54 mcg		Treprostinil sodium 84 mcg		Moxifloxacin 400 mg	
Time	Estimate [1]	Upper Bound [2]	Estimate [1]	Upper Bound [2]	Estimate [1]	Upper Bound [2]
End-Inhal	6.1	8.0	7.9	9.1	1.0	3.9
15 min	3.1	5.0	5.8	7.7	2.1	5.0
30 min	2.2	4.1	4.3	6.2	0.4	3.3
45 min	2.7	4.6	4.2	6.1	3.7	6.7
1 hr	4.2	6.1	4.8	6.6	3.3	6.3
1.5 hr	3.2	5.1	4.3	6.2	5.1	8.1
2 hr	3.7	5.6	0.5	2.4	6.5	9.4
2.5 hr	4.1	6.0	3.7	5.6	7.7	10.7
3 hr	3.8	5.7	2.1	4.0	8.5	11.5
4 hr	-2.4	-0.5	-0.8	1.1	6.2	9.2
6 hr	1.0	2.9	0.1	2.0	7.5	10.5

Source: sponsor's table 14.2.3.16

Table 3: ANOVA treatment comparisons based on LS-mean changes in QTcF

Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Fridericia (msec)

	Treprostinil sodium 54 mcg		Treprostinil sodium 84 mcg		Moxifloxacin 400 mg	
Time	Estimate [1]	Upper Bound [2]	Estimate [1]	Upper Bound [2]	Estimate [1]	Upper Bound [2]
End-Inhal	6.4	8.2	7.9	9.8	1.5	4.5
15 min	4.5	6.5	6.2	8.2	2.8	5.8
30 min	2.7	4.6	4.6	6.5	0.5	3.9
45 min	3.0	4.9	4.1	6.0	4.0	7.0
1 hr	5.3	7.2	5.5	7.5	3.8	6.8
1.5 hr	3.7	5.6	4.4	6.4	5.0	8.0
2 hr	4.0	5.9	0.6	2.6	6.2	9.2
2.5 hr	3.8	5.7	3.4	5.3	7.3	10.3
3 hr	3.6	5.5	2.4	4.4	8.2	11.2
4 hr	-1.9	0.0	0.1	2.0	6.4	9.5
6 hr	1.1	3.0	0.2	2.1	7.8	10.8

Source: sponsor's table 14.2.3.17

4.2.8.2.2 Assay Sensitivity

The time matched analysis for the QTcI endpoint revealed that the moxifloxacin group met the assay sensitivity criteria outlined in the statistical plan with six time points mean >5ms and three time points with upper confidence intervals >10 ms.

Reviewer's Comments: After evaluating different correction methods in Section 5.1, this reviewer chose QTcF as the primary outcome and computed the raw means as well as model predicted LS means for all three groups in section 0. The largest 90% upper C.I. for both ΔΔQTcF and ΔΔQTcI are slightly above 10 ms.

4.2.8.2.3 Categorical Analysis

The specific outlier criteria were a new abnormal u wave, new > 500 ms absolute QTc duration and a > 60 ms change from baseline. There were no subjects on treprostinil that met any of these criteria. The nonspecific outlier criterion was a 30- to 60-ms change from baseline. One subject in the supratherapeutic treprostinil dose group met this criterion. This was likely a spurious finding due to the high rate of background QT variability.

4.2.8.3 Safety Analysis

No deaths, other serious adverse events, or other significant adverse events occurred over the course of the study.

The results of this ECG trial showed no signal of any effect on AV conduction or cardiac depolarization as measured by the PR and QRS interval durations. There were no new clinically relevant morphological changes.

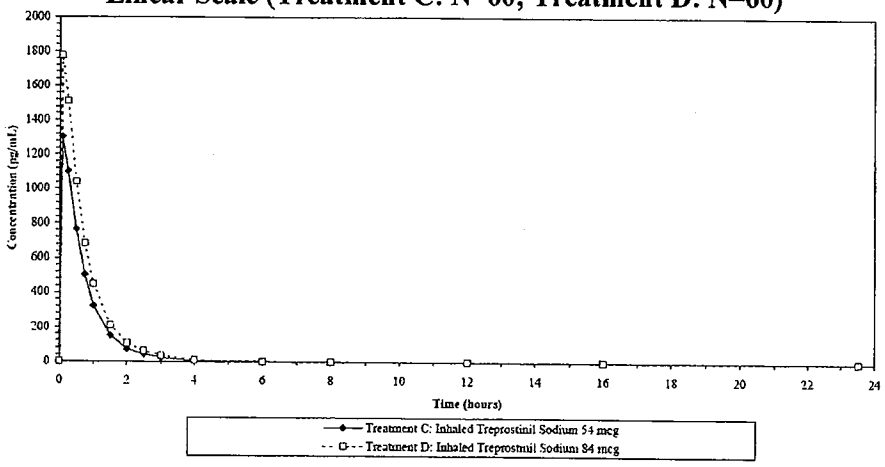
There was a 5-6 bpm increase in heart rate placebo corrected for the inhaled treprostinil sodium dose groups just at the end of inhalation with the time averaged heart rate change being 3 bpm. Due to the pharmacological properties of treprostinil (vasodilator), a slight increase in heart rate was not unexpected.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Figure 1 shows the mean plasma concentration of Treprostinil sodium from time 0 to 23.5 hours after dosing on linear for Treatments C and D.

Figure 1: Mean Plasma Concentration of Treprostinil sodium (0 - 23.5 hours) Linear Scale (Treatment C: N=60; Treatment D: N=60)



Source: Figure 11.1 from Page 43 of 726 (report-body.pdf)

The PK results of Treprostinil sodium are presented in Table 4. The Cmax and AUC values in the thorough QT study were 1.36-fold higher following administration of 84 mcg Treprostinil sodium compared with 54 mcg Treprostinil sodium, the intended clinical dose.

Table 4: Summary of PK Parameters of Treprostinil sodium

PK Parameter	Treatment C: Inhaled Treprostinil Sodium 54 mcg	Treatment D: Inhaled Treprostinil Sodium 84 mcg
AUC_{0-t} (hr*pg/mL)	974.67 (±280.53)	1352.21 (±356.05)
$AUC_{0-\infty}$ (hr*pg/mL)	1005.14 (±253.48)	1368.03 (±357.44)
C_{max} (pg/mL)	1315.83 (±430.44)	1795.92 (±634.55)
T_{max} (hr)	0.12 (±0.07)	0.12 (±0.08)
λ_z (1/hr)	1.3477 (±0.26)	1.2352 (±0.30)
$t_{1/2}$ (hr)	0.54 (±0.13)	0.62 (±0.30)
V/F (L)	45.37 (±21.13)	58.86 (±32.53)
CL/F (L/hr)	60.30 (±37.34)	67.93 (±29.09)

Source: From Page 5 of 7 (Synopsis.pdf).

4.2.8.4.2 Exposure-Response Analysis

Table 5 details the pharmacokinetic-pharmacodynamic model results showing that the slopes of the relationships for plasma concentration of parent and the predicted QTc change at Cmax. The upper one-sided 95% confidence bound of the predicted QTc is below 10 ms.

Table 5: Placebo-Corrected Change from Baseline versus Treprostinil Plasma Concentration – Estimates from Linear Mixed Model [1] QTc Individual, QTc Fridericia, QTc Bazett and QT Interval (msec) – Safety Analysis Set

QT Parameter	Slope of Plasma Concentration	Standard Error of Plasma Concentration	p-value	Predicted QTc at Average C_{max}	One-sided Upper 95% Confidence Bound of Predicted QTc	Overall Model Fit
QTcI	0.0040	0.0004	0.0000	6.8977	8.0418	<.0001
QTcF	0.0040	0.0004	0.0000	7.3455	8.4696	<.0001
QTcB	0.0065	0.0006	0.0000	13.3221	14.7745	<.0001

[1] Linear Mixed Model if fit for change from baseline (not placebo-correct) versus the plasma concentration as a fixed effect with subject included in the model as a random effect.
[2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

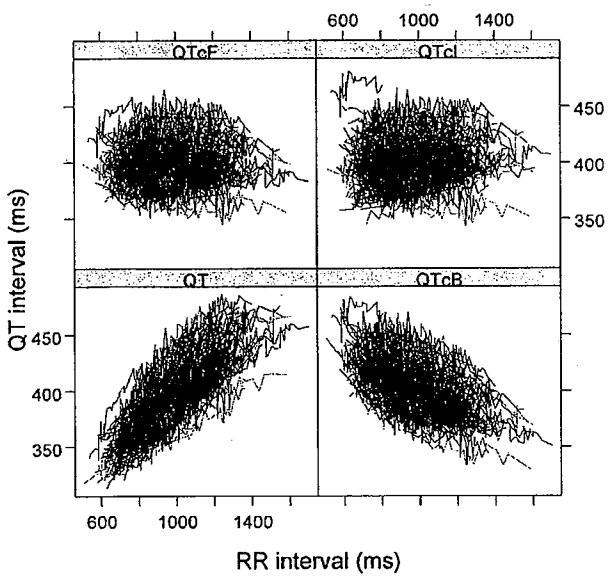
Reviewer's Analysis: A plot of ΔΔQTc vs. drug concentrations is presented in Figure 5 *in section 5.1.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The observed QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



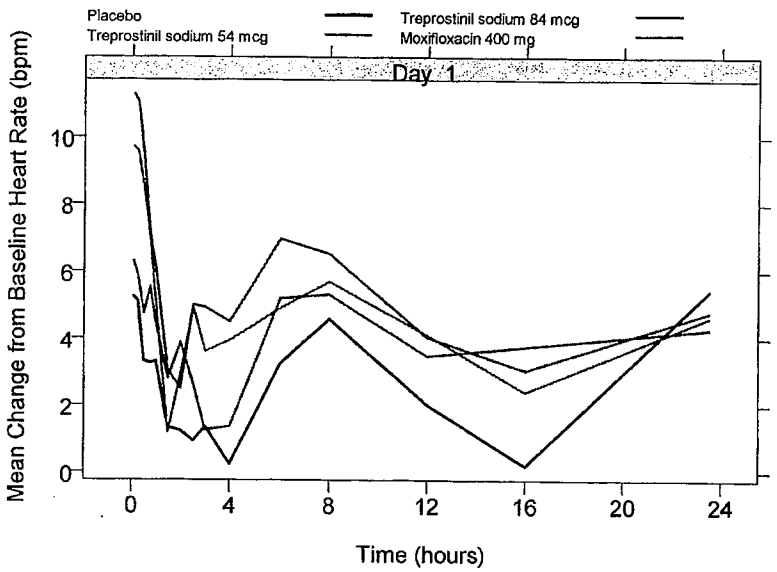
We also evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcI) and RR. We used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in the following table, it appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Correction Method	Treprostinil sodium 54 mcg (N=60)	Treprostinil sodium 84 mcg (N=60)	Moxifloxacin (N=60)	Placebo (N=60)	ALL (N=240)
QTcB	0.0048	0.0048	0.0056	0.0043	0.0049
QTcF	0.0013	0.0012	0.0015	0.0010	0.0013
QTcI	0.0016	0.0018	0.0021	0.0016	0.0018

Figure 3 shows there are increases in heart rate immediately after dosing of treprostinil.

Figure 3: Change from baseline heart rate (bpm) in placebo, Treprostinil sodium 54 mcg, Treprostinil 84 mcg and Moxifloxacin 400 mg.



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Treprostinil sodium

The statistical reviewer used linear model to analyze the ΔQTcF effect at each time point. The model includes sex and baseline QTcF as covariates. The analysis results are listed in the following tables.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for Treprostinil sodium 54 mcg

	ΔQTcF Treprostinil sodium 54 mcg		ΔQTcF Placebo		ΔΔQTcF	
Time	Mean	Std Err.	Mean	Std Err.	Mean	90% CI
5 min	-3.9	1.2	-10.3	1.2	6.3	(3.6, 9.1)
15 min	-6.0	1.1	-10.4	1.1	4.5	(2.0, 6.9)
30 min	-5.8	1.1	-8.8	1.1	3.0	(0.4, 5.5)
45 min	-5.5	1.2	-8.6	1.2	3.1	(0.4, 5.8)
1 hr	-2.4	1.1	-7.8	1.1	5.4	(2.8, 8.0)
1.5 hr	-1.6	1.1	-5.4	1.1	3.8	(1.2, 6.4)
2 hr	0.2	1.0	-3.8	1.0	4.0	(1.5, 6.4)
2.5 hr	-0.9	1.1	-4.7	1.1	3.8	(1.4, 6.3)
3 hr	-0.5	1.0	-3.7	1.0	3.2	(0.9, 5.5)
4 hr	-3.2	1.1	-1.7	1.1	-1.4	(-3.9, 1.1)
6 hr	-1.8	0.9	-3.1	0.9	1.3	(-0.9, 3.6)
8 hr	-2.7	1.0	-3.3	1.0	0.6	(-1.7, 2.8)
12 hr	-2.6	1.0	-2.5	1.0	-0.1	(-2.5, 2.2)
16 hr	-4.6	1.2	-4.2	1.2	-0.4	(-3.1, 2.3)
23.5 hr	-5.3	1.0	-4.6	1.0	-0.7	(-3.1, 1.7)

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Treprostinil sodium 84 mcg

	ΔQTcF Treprostinil sodium 84 mcg		ΔQTcF Placebo		ΔΔQTcF	
Time	Mean	Std Err.	Mean	Std Err.	Mean	90% CI
5 min	-1.7	1.2	-10.3	1.2	8.5	(5.8, **11.3**)
15 min	-3.5	1.1	-10.4	1.1	7.0	(4.5, 9.5)
30 min	-3.4	1.1	-8.8	1.1	5.5	(2.9, 8.0)
45 min	-3.6	1.2	-8.6	1.2	5.0	(2.2, 7.7)
1 hr	-1.5	1.1	-7.8	1.1	6.3	(3.7, 8.9)
1.5 hr	-0.5	1.1	-5.4	1.1	4.9	(2.2, 7.5)
2 hr	-2.3	1.1	-3.8	1.0	1.5	(-1.0, 3.9)
2.5 hr	-0.7	1.1	-4.7	1.1	4.0	(1.5, 6.5)
3 hr	-0.7	1.0	-3.7	1.0	3.0	(0.7, 5.3)
4 hr	-0.7	1.1	-1.7	1.1	1.1	(-1.4, 3.5)
6 hr	-1.9	1.0	-3.1	0.9	1.3	(-1.0, 3.5)
8 hr	-3.2	1.0	-3.3	1.0	0.1	(-2.1, 2.3)
12 hr	-3.1	1.0	-2.5	1.0	-0.6	(-3.0, 1.8)
16 hr	-3.7	1.2	-4.2	1.2	0.5	(-2.2, 3.2)
23.5 hr	-4.5	1.0	-4.6	1.0	0.0	(-2.4, 2.4)

The largest upper bounds of the 2-sided 90% CI for the mean difference between Treprostinil sodium 54 mcg and placebo, and between Treprostinil sodium 84 mcg and placebo were 9.1 ms and 11.3 ms, respectively.

This reviewer also calculated raw mean difference between the study drug and placebo after baseline correction. The largest 90% CI upper bound of the mean difference between treprostinil sodium 84 mcg and placebo was still slightly above 10 ms.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data and selected 3 time points after dose at 2, 3, and 4 hours. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 5.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence bound is 5.1 ms at 3 hours.

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

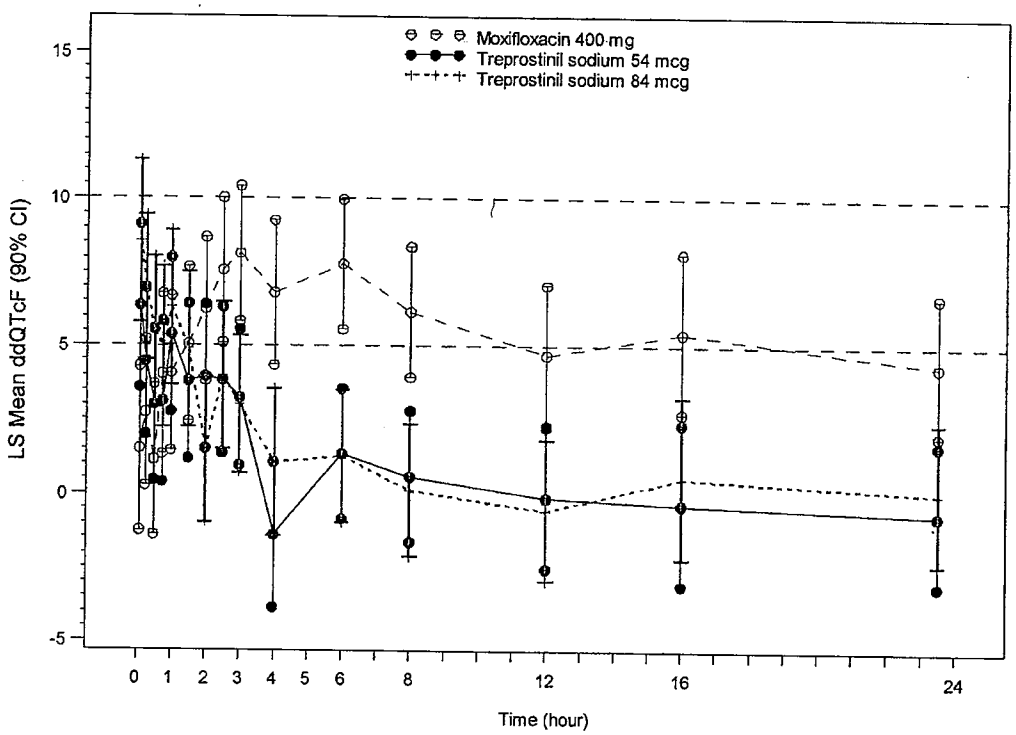
	ΔQTcF Moxifloxacin		ΔQTcF Placebo		ΔΔQTcF		
Time/(hr)	Mean	Std Err.	Mean	Std Err.	Diff LS Mean	Unadjusted 90% CI	Adjusted 90% CI*
2	2.5	1.0	-3.8	1.0	6.2	(3.8, 8.7)	(3.1, 9.4)
3	4.4	1.0	-3.7	1.0	8.1	(5.8, 10.4)	(5.1, 11.1)
4	5.1	1.1	-1.7	1.1	6.8	(4.3, 9.3)	(3.6, 10.0)

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 4: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose absolute QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**
Baseline	241	3612	231 (95.9%)	3586 (99.3%)	10 (4.1%)	26 (0.7%)
Moxifloxacin	60	900	59 (98.3%)	898 (99.8%)	1 (1.7%)	2 (0.2%)
Placebo	60	895	59 (98.3%)	894 (99.9%)	1 (1.7%)	1 (0.1%)
Treprostinil sodium 54 mcg	60	898	58 (96.7%)	893 (99.4%)	2 (3.3%)	5 (0.6%)
Treprostinil sodium 84 mcg	60	895	60 (100%)	895 (100%)	0 (0.0%)	0 (0.0%)

Table 11 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 11: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Moxifloxacin	60	900	59 (98.3%)	899 (99.9%)	1 (1.7%)	1 (0.1%)
Placebo	60	895	60 (100%)	895 (100%)	0 (0.0%)	0 (0.0%)
Treprostinil sodium 54 mcg	60	897	60 (100%)	897 (100%)	0 (0.0%)	0 (0.0%)
Treprostinil sodium 84 mcg	60	893	60 (100%)	893 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the PR mean differences between Treprostinil sodium 54 mcg and placebo and between Treprostinil sodium 84 mcg and placebo are 4.0 ms and 3.7 ms, respectively. The outlier analysis results for PR are presented in Table 13.

Table 12: Analysis results of ΔΔPR by treatment group

	Treprostinil sodium 54 mcg		**Treprostinil sodium 84 mcg**	
Time	**LS Mean**	**90% CI**	**LS Mean**	**90% CI**
5 min	1.5	(-1.0, 4.0)	0.6	(-1.9, 3.1)
15 min	-0.6	(-3.2, 2.0)	-1.8	(-4.4, 0.8)
30 min	-2.5	(-5.2, 0.2)	-3.9	(-6.6, -1.2)
45 min	-1.9	(-4.6, 0.8)	-4.2	(-6.9, -1.5)
1 hr	-1.9	(-4.6, 0.7)	-4.4	(-7.0, -1.7)
1.5 hr	1.0	(-1.5, 3.6)	-1.6	(-4.1, 1.0)
2 hr	1.0	(-1.3, 3.3)	-1.7	(-4.0, 0.6)
2.5 hr	0.1	(-2.2, 2.4)	-2.7	(-5.0, -0.4)
3 hr	-0.7	(-3.1, 1.6)	-1.6	(-4.0, 0.7)
4 hr	-2.0	(-4.0, 0.1)	-2.2	(-4.3, -0.2)
6 hr	-0.4	(-2.5, 1.7)	-0.1	(-2.2, 2.0)
8 hr	0.6	(-1.4, 2.5)	0.4	(-1.5, 2.4)
12 hr	1.1	(-0.9, 3.1)	1.8	(-0.2, 3.7)
16 hr	-0.3	(-2.7, 2.1)	-0.2	(-2.6, 2.3)
23.5 hr	-0.3	(-2.5, 1.8)	-2.0	(-4.1, 0.2)

Table 13: Categorical Analysis for PR

	Total N		**PR ≥ 200 ms**	
TreatmentGroup	#Subj	#Obs	#Subj. (%)	#Obs. (%)
Baseline	241	3612	16 (6.6%)	122 (3.4%)
Treprostinil sodium 54 mcg	60	898	4 (6.7%)	32 (3.6%)
Treprostinil sodium 84 mcg	60	895	4 (6.7%)	17 (1.9%)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the QRS mean differences between Treprostinil sodium 54 mcg and placebo and Treprostinil sodium 84 mcg and placebo are 2.1 ms and 2.3 ms, respectively. No subject experienced any absolute QRS interval greater than 120 ms.

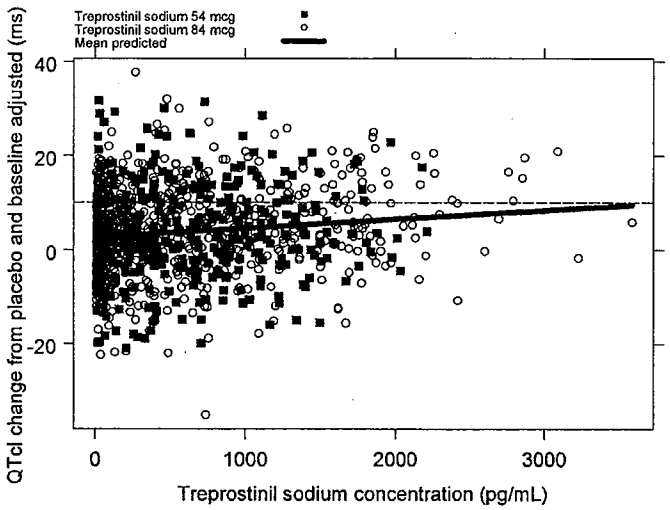
Table 14: Analysis results of ΔΔQRS by treatment group

	Treprostinil sodium 54 mcg		Treprostinil sodium 84 mcg	
Time	**LS Mean**	**90% CI**	**LS Mean**	**90% CI**
5 min	0.8	(-0.2, 1.7)	1.0	(0.1, 2.0)
15 min	0.8	(-0.2, 1.8)	0.7	(-0.3, 1.6)
30 min	0.6	(-0.3, 1.5)	1.0	(0.1, 1.9)
45 min	1.0	(0.1, 2.0)	1.0	(0.1, 2.0)
1 hr	0.6	(-0.3, 1.6)	1.2	(0.3, 2.1)
1.5 hr	1.0	(0.1, 1.9)	1.4	(0.5, 2.3)
2 hr	1.2	(0.3, 2.1)	0.9	(0.1, 1.8)
2.5 hr	0.2	(-0.7, 1.1)	0.2	(-0.7, 1.1)
3 hr	0.6	(-0.3, 1.5)	0.7	(-0.2, 1.6)
4 hr	0.1	(-0.8, 1.0)	0.6	(-0.3, 1.4)
6 hr	0.0	(-0.8, 0.9)	0.9	(0.1, 1.8)
8 hr	0.1	(-0.7, 0.9)	0.6	(-0.2, 1.5)
12 hr	-1.3	(-2.2, -0.5)	-0.6	(-1.4, 0.3)
16 hr	-0.1	(-1.0, 0.7)	0.7	(-0.2, 1.6)
23.5 hr	0.5	(-0.3, 1.4)	0.8	(-0.1, 1.7)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔΔQTcI and Treprostinil concentrations visualized in Figure 4 is shallow.

Figure 5: Relationship between ΔΔQTcI and treprostinil concentrations after 54 and 84 mcg single dose



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 97% of the ECGs were annotated in the primary lead-II, with less than 0.1% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS intervals

There were no clinically relevant effects on the PR and QRS intervals. Except for 2 subjects who had an absolute PR interval of 206 ms post-treatment at only one time point, all subjects who had an absolute PR interval over 200 ms post treatment had elevated measurements at baseline as well. No subject experienced an absolute QRS interval increase of over 120 ms.

5.4.4 MGPS data mining analysis for treprostinil and AEs related to QT prolongation

An MGPS data mining analysis of the AERS database for adverse events related to QT-prolongation with treprostinil was conducted. There were no reports of TdP. The signal scores (EBGM) values for cardiac arrest and sudden death indicated that the incidence was very similar to the background rate in the general population.

Configuration: CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 299
Dimension: 2 **Selection Criteria:** Generic name(Treprostinil) + PT(...) **Where:** EBGM > 1.0
2 rows Sorted by Generic name, EBGM desc

Generic name	Level 1	PT	HLT	N	EBGM	EB05	EB95	PRR
Treprostinil	Platelet Aggregation Inhibitors Excl. Heparin	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	5	2.13	1.01	4.06	3.05
Treprostinil	Platelet Aggregation Inhibitors Excl. Heparin	Sudden death	Death and sudden death	1	1.01	0.236	3.11	3.63

ID:	299
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	12/05/2008 00:00:00
Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	Empirica Signal Administrator
Created On:	12/10/2008 22:06:35 EST
User:	Suchitra Balakrishnan
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 12/05/2008 00:00:00 loaded on 2008-12-09 10:00:11.0

Dimension: 2 **Selection Criteria:** Generic name(Treprostinil) + PT(Cardiac arrest, Convulsion, Sudden cardiac death, Sudden death, Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia) **Where:** EBGM > 1.0

SELECT * FROM OutputData_299 WHERE (DIM=2 AND EBGM>1.0 AND ((P1='D' AND ITEM1 IN ('Treprostinil') AND P2='E' AND ITEM2 IN ('Cardiac arrest','Convulsion','Sudden cardiac death','Sudden death','Torsade de pointes','Ventricular arrhythmia','Ventricular fibrillation','Ventricular flutter','Ventricular tachyarrhythmia','Ventricular tachycardia')))) ORDER BY ITEM1,EBGM desc

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	[redacted] 9 inhalations) four times daily	b(4)
Maximum tolerated dose	The maximum tolerated dose is currently being evaluated in healthy volunteers in protocol RIN-PH-102 (Submission No. 0063). In this study a dose of 120 µg may be tested if deemed appropriate.	
Principal adverse events	To date, the most common adverse events (>10%) occurring in the Phase 3 trial include cough, headache, nausea, dizziness, fatigue, throat irritation, jaw pain, and flushing.	
Maximum dose tested	Single Dose	Patients: 120 µg Healthy Volunteers: 30 µg; protocol RIN-PH-102 is currently ongoing
	Multiple Dose	The most common dose in patients is [redacted] .9 inhalations) four times daily with some patients receiving doses of [redacted] 12 inhalations) four times daily.
Exposures Achieved at Maximum Tested Dose	Single Dose	Blood samples for treprostinil plasma analysis have been obtained in ongoing studies being conducted in Giessen, Germany (LRX-TRE-INH-005) and San Diego, CA (LRX-TRE-INH-006). To date, preliminary pharmacokinetic analysis has been performed using data from patients with PAH who received single treprostinil doses ranging from 0.24 to 2.08 µg/kg (average 0.84 µg/kg) calculated on the basis of measured weight loss of the nebulizer. These doses were administered to 15 patients over time periods ranging from 1 to 6 minutes. Total doses ranged from 20 to 106 µg. Noncompartmental pharmacokinetic parameters were calculated and C_{max} values ranged from 0.59 to 4.57 ng/mL and AUC values ranged from 43.8 to 236.4 min·ng/mL. In study LRX-TRIUMPH BA.001, single doses (15 and 30 µg) of inhaled treprostinil sodium were administered to healthy volunteers with a mean C_{max} (CV%) of 0.354 (38.76) and 0.698 (20.19) ng/mL, respectively, and a mean (CV%) AUC_{inf} of 0.2556 (32.98) and 0.6349 (27.83) hr*ng/mL, respectively.
	Multiple Dose	There are currently no data available describing the pharmacokinetics of inhaled treprostinil sodium following multiple doses. Due to the route of administration, the frequency of administration, and the short t½ of the elimination phase, accumulation of treprostinil within the systemic circulation following multiple doses is not expected.
Range of linear PK	15 to 30 µg; however more information on linearity will be obtained in	

b(4)

	RIN-PH-102.	
Accumulation at steady state	There are currently no data available describing the pharmacokinetics of inhaled treprostinil sodium at steady state. Due to the route of administration and characteristics of the elimination phase, accumulation of treprostinil within the systemic circulation following multiple doses is not expected.	
Metabolites	A Phase 1 single-center, open-label, mass balance, urinary metabolite profiling, and safety study of [^{14}C] treprostinil following an 8-hour subcutaneous infusion of 15 ng/kg/min (specific activity of ~80 µCi) treprostinil sodium in six normal healthy male subjects was conducted. Five urinary metabolites (HU1, HU2, HU3, HU4 and HU5) accounted for 13.8%, 14.3%, 15.5%, 10.6% and 10.2% of the administered dose, respectively. HU5 was identified as treprostinil sodium-glucuronide. HU4, HU3 and HU2 were the products of oxidation of the 3-hydroxyloctyl side chain. The structure of HU1 remained unidentified. The biological activity and metabolic fate of these metabolites are unknown. There are no data available describing the pharmacokinetics of the metabolites of treprostinil sodium.	
Absorption	Absolute/Relative Bioavailability	The mean (%CV) absolute bioavailability of inhaled treprostinil sodium following single doses of 15 and 30 µg in healthy volunteers was 78.1 (36.6%) and 86.9 (33.1%), respectively. The reference arm of the study involved administration of intravenous treprostinil sodium at a dose of 15 ng/kg/min for 60 minutes.
	Tmax	The median (range) Tmax of inhaled treprostinil sodium following single doses of 15 and 30 µg in healthy volunteers was 0.08 (0.08 – 0.5) and 0.17 (0.08 – 0.25) hours, respectively.
Distribution	Vd/F or Vd	The mean (%CV) volume of distribution (Vz/F) of inhaled treprostinil sodium following single doses of 15 and 30 µg in healthy volunteers was 52.4 (60%) and 56.4 (46%) liters, respectively.
	% bound	In vitro studies indicated that treprostinil is on average (+/-SD) 91% +/- 0.21 bound to plasma protein over the concentration range of 0.33 to 10 µg/mL
Elimination	Route	A Phase 1 single-center, open-label, mass balance, urinary metabolite profiling, and safety study of [^{14}C] treprostinil following an 8-hour subcutaneous infusion of 15 ng/kg/min (specific activity of ~80 µCi) treprostinil sodium in six normal healthy male subjects was conducted. Urinary excretion was the main route of elimination of [14C] treprostinil sodium derived radioactivity with a mean of 75.6% of the administered radioactivity excreted within 8 hours from the termination of infusion and 78.6% through 224 hours. HPLC profiling of urine aliquots showed 3.7% of the dose was excreted as unchanged drug.

		Additional data gathered in the study described indicated that radioactivity in the feces accounted for another 13.4% of the administered radioactivity.
	Terminal t½	The mean (%CV) terminal half-lives of inhaled treprostinil sodium following single doses of 15 and 30 µg in healthy volunteers were 0.53 (26.9%) and 0.79 (46.8%) hours, respectively.
	CL/F or CL	The mean (%CV) clearance of inhaled treprostinil sodium following single doses of 15 and 30 µg in healthy volunteers was 77.0 (97.3%) and 50.3 (23.9%) liters/hour, respectively.
Intrinsic Factors	Age	No specific studies have been performed with inhaled treprostinil sodium in special populations. The data for intravenous and subcutaneous treprostinil indicated that age (≥65 years of age) does not appear to be important factor in altering the pharmacokinetic properties of treprostinil. Seventeen of 187 patients enrolled in the two subcutaneous treprostinil Phase 3 trials (P01:04 and P01:05) were elderly patients (≥ 65 years of age). The outcome of the multivariate analysis showed that being elderly accounted for less than 3% of the inter-patient variability in clearance. This small difference was considered to be not clinically important.
	Sex	Gender did not appear to have an impact on the treprostinil CL/F term. No specific studies have been performed with inhaled treprostinil sodium in special populations. The data for intravenous and subcutaneous treprostinil may be applicable. One of the patient factors assessed in the multivariate analysis in the two subcutaneous treprostinil Phase 3 trials (P01:04 and P01:05) was gender.
	Race	No specific studies have been performed with inhaled treprostinil sodium in special populations. There is also no data available describing any differences in the pharmacokinetics of subcutaneous or intravenous treprostinil in different races.
	Hepatic & Renal Impairment	**Hepatic Impairment** The pharmacokinetics of subcutaneous treprostinil in patients with mild or moderate hepatic dysfunction was evaluated in an open-label Phase 2 study in patients with portopulmonary hypertension (PPHTN) (P02:01). Based on the clinical criteria for PPHTN, all patients with this diagnosis had hepatic dysfunction. The pharmacokinetics of treprostinil in the 9 patients following a 150-minute continuous subcutaneous infusion at a

		fixed rate of 10 ng/kg/min was investigated. The results of P02:01 was compared to a group of healthy adult male and female volunteers administered a similar treprostinil dose via the same route in a different study (P01:07). The mean apparent treprostinil plasma clearance values (CL/F) in patients with mild hepatic dysfunction (n= 5) and moderate hepatic dysfunction (n=4) were markedly reduced by 61% and 80%, respectively, while the apparent elimination half-lives in patients with hepatic dysfunction remained similar to that in healthy adult volunteers. It was concluded that the lower values of CL/F in patients with hepatic dysfunction were largely due to lower apparent volume of distribution (V_z/F). **Renal Impairment** On average, less than 5% of a subcutaneous treprostinil dose was excreted by kidney as unchanged drug (P01:07 and P01:10). Since renal excretion does not play a significant role in the elimination of treprostinil, to date no pharmacokinetic study in patients with various degrees of renal dysfunction has been performed. In the multivariate analysis for patient factors on steady-state plasma clearance values obtained in two Phase III Trials (P01:04 and P01:05), serum creatinine was used as a surrogate for renal function since individual patient urinary creatinine clearance values were not available. Of 186 patients included in the analysis, 176 patients (94.6%) had normal serum creatinine levels, 8 (4.3%) had slightly elevated serum creatinine levels, and 2 (1.0%) had high serum creatinine levels. The outcome of the analysis showed that serum creatinine was associated with plasma treprostinil clearance. This finding was deemed an artifact because in two stand-alone studies (P01:07 and P01:10), it was determined that the renal excretion of unchanged treprostinil plays an insignificant role in its elimination.
Extrinsic Factors	Drug interactions	Investigators have performed studies with inhaled treprostinil sodium in combination with sildenafil and bosentan as described in the Clinical Investigators' Brochure, however no specific drug interaction studies have been performed with inhaled treprostinil. The data for intravenous and subcutaneous treprostinil is expected to be applicable, as described below. Specific drug-drug interactions were conducted with warfarin and acetaminophen with no change in C_{max} and AUC. In addition, a

		multivariate analysis was conducted for the subcutaneous treprostinil sodium Phase 3 trials which demonstrated no significant drug interactions during the course of the study.
	Food Effects	Evaluation of the effect of food on treprostinil pharmacokinetics has not been evaluated as treprostinil sodium is currently being delivered via the inhaled route of administration.
Expected High Clinical Exposure Scenario	The expected high clinical exposure scenario would involve a physician prescribing a dose of inhaled treprostinil sodium in a patient with mild to moderate liver dysfunction which may result in an AUC that is two times what is expected in a patient without liver dysfunction. In order to test this scenario in the QTc study an inhaled treprostinil sodium dose of at least 90 µg should be tested. Based on the data gathered in the RIN-PH-102 that is expected to begin in September 2007, the QTc study will be designed with a supratherapeutic dose that is the maximum tolerated dose in healthy volunteers.	

6.2 TABLE OF STUDY ASSESSMENTS

TRIAL PHASE (EACH TREATMENT PERIOD)	Screening Day -28 to Day -2 (Performed Once)	CONFINEMENT AT CLINICAL RESEARCH UNIT (EACH TREATMENT PERIOD)			Early Discontinuation or End of Study Discharge
		Check-in Day -2	Baseline Day 1	Treatment Day 1	
Informed Consent	X				
Eligibility (Inclusion/Exclusion)	X	X[a]			
Prior Medication Assessment	X	X[a]			
Medical History	X	X[a]			
Vital Signs	X	X		X[d]	X
Physical Exam	X	X			X
Clinical Laboratory Tests ▫ CBC with differential ▫ Clinical Chemistry ▫ Urinalysis	X	X			X
Clinical Laboratory Tests ▫ HIV Antibody Screen ▫ Hepatitis B Screen ▫ Hepatitis C Screen	X				
Pregnancy Screen (females only)	X	X			X
FSH (if necessary to document postmenopausal status)	X				
Urine Drug/Alcohol Screen	X	X			
12 lead ECG from H-12			X[a]	X[a]	
Safety 12-lead ECG	X	X		X[d]	X
Study Drug Administration					
Pharmacokinetic Sampling				X[b]	
Adverse Events Query				X[e]	X
Concomitant Medication				X	X

[a] Updated and/or reviewed. [b] Pharmacokinetic samples were collected at predose (0hour) 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. [c] ECGs were obtained on Day -1 and Day 1 at the following times: after planned (Day -1) or actual (Day 1) dose administration: 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 23.5 hours after dose administration. [d] Vital signs (HR, RR, blood pressure) and 12-lead safety ECG were collected 2-3 hours after dose administration on Day 1. [e] Adverse Events were queried at approximately 2-3 hours after the dose of study medication on Day 1. Adverse events were also recorded when spontaneously reported throughout the course of the study

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