IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Horst OLSCHEWSKI et al.
Title:	TREPROSTINIL ADMINISTRATION BY INHALATION (as amended)
Appl. No.:	12/591,200
Filing Date:	11/12/2009
Examiner:	Sara Elizabeth Townsley
Art Unit:	1629
Confirmation Number:	4093

AMENDMENT AND REPLY ACCOMPANYING RCE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the Advisory Action mailed on June 4, 2013.

The listing of claims begins on page 2 of this document.

Remarks begin on page 4 of this document.

Listing of Claims:

1-17. (Canceled)

18. (Currently Amended) A method of treating pulmonary hypertension comprising:

administering by inhalation to a human in need thereof a therapeutically effective single event dose of an inhalable formulation with ~~an~~ a pulsed ultrasonic nebulizer, wherein said therapeutically effective single event dose comprises from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof and said therapeutically effective single event dose is inhaled in ~~10~~ 18 or less breaths by the human.

19.-24. (Canceled)

25. (Previously Presented) The method of claim 18, wherein the single event dose contains from 15 μg to 60 μg of treprostinil or a pharmaceutically acceptable salt thereof.

26. (Canceled)

27. (Previously Presented) The method of claim 18, wherein the ultrasonic nebulizer comprises an aerosolable solution having a concentration of said treprostinil or a pharmaceutically acceptable salt thereof from 500 μg/ml to 2500 μg/ml.

28. (Previously Presented) The method of claim 18, wherein said administering does not significantly disrupt gas exchange in said human.

29. (Previously Presented) The method of claim 18, wherein said administering does not significantly affect heart rate of said human.

30. (Previously Presented) The method of claim 18, wherein said administering does not significantly affect systemic arterial pressure and systemic arterial resistance of said human.

31. (Canceled)

32. (Previously Presented) The method of claim 18, wherein said administering of said therapeutically effective single event dose is performed in 5 or less breaths.

33. (Previously Presented) The method of claim 18, wherein said human receives several therapeutically effective single event doses per day.

34. (Previously Presented) The method of claim 27, wherein the concentration of said treprostinil or a pharmaceutically acceptable salt thereof in the aerosolable solution is 600 μg/ml.

35. (New) The method of claim 18, wherein the single event dose is administered in 5 minutes or less.

36. (New) The method of claim 27, wherein the single event dose is administered in 5 minutes or less.

37. (New) The method of claim 34, wherein the single event dose is administered in 5 minutes or less.

38. (New) The method of claim 18, wherein said therapeutically effective single event dose is inhaled in 12 or less breaths by the human.

39. (New) The method of claim 27, wherein said therapeutically effective single event dose is inhaled in 12 or less breaths by the human.

40. (New) The method of claim 34, wherein said therapeutically effective single event dose is inhaled in 12 or less breaths by the human.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Claims 18, 25, 27-30 and 32-40 are pending. Claim 18 is amended to recite an upper limit of 18 breaths for the single event dose based upon paragraph 74 of the present specification as published. Claim 18 is further amended to specify that the ultrasonic nebulizer is a "pulsed" ultrasonic nebulizer based upon paragraph 0068 of the specification as published. Claims 35-37 are added to cover a preferred timing embodiment for the single event dose based upon paragraph 46 of the present specification. Claims 38-40 are added to cover an upper limit of 12 breaths for the single event dose based upon paragraphs 45 and 74 of the present specification (paragraph 45 states that "20 breaths or less" may be used, while paragraph 74 specifically provides clinical results for a higher upper limit of 18 breaths and a lower upper limit of 9 breaths, thus supporting use of a number of breaths in between 9 and 18, such as 12). No new matter has been introduced.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-8, 10-23 and 25-31 stand rejected as obvious over Chaudry (US 2004/0265238) in view of Sandifer et al. (J. Appl. Physiol. 99:2363-68 (2005)) and Cloutier (US patent no. 6,521,212). Reconsideration of the rejection is respectfully requested.

The Accompanying Rule 131 Declaration Removes Sandifer As Prior Art

Sandifer states that it was first published Sept. 1, 2005. Applicants submit herewith a Rule 131 Declaration to remove Sandifer as prior art. The Rule 131 Declaration is in accordance with MPEP 715.02, stating that "an affidavit or declaration under **37 CFR 1.131** is required to show no more than the reference shows. *In re Stryker*, 435 F.2d 1340, 168 USPQ 372 (CCPA 1971)." Also, the exhibit to the Rule 131 Declaration has the actual dates redacted, but the Declaration confirms the activity occurred before the reference's publication date. The accompanying Rule 131 Declaration establishes that the inventors possessed as

much or more than Sandifer shows prior to its publication date of Sept. 1, 2005. Accordingly, Sandifer may not be cited in support of the rejection. For this reason alone, the rejection should be withdrawn.[1]

With Or Without Sandifer, No Teaching Of "Single Event Dose" Limitation

Claim 18 requires a "single event dose" of from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof, which is inhaled in 18 breaths or less. All dependent claims require at least this limitation, though they are also further limited. The Advisory Action attempts to separate out a single, 1 minute increment of treatment from Sandifer to satisfy this limitation. While Applicants appreciate that the USPTO may give the claims their broadest reasonable interpretation during examination, such an interpretation of "single event dose" is beyond reasonable and completely eviscerates the words. The USPTO may not completely ignore a limitation in the claim.

Sandifer teaches only 30-60 minutes events.

See p. 2364, left column, third full paragraph: "After each sheep was allowed to reach steady state for 30–60 min, treprostinil was infused at 250, 500, and 1,000 ng kg^{-1} min^{-1}. Each infusion lasted 30–60 min. The experiment was repeated with the same dose of U-44069 but with the treprostinil delivered via aerosol at 0.28 ml/min in escalating doses of 250, 500, and 1,000 ng kg^{-1} min^{-1}." (underlining added)

See also p. 2364, left column, last paragraph: "[t]o evaluate the duration of action of vasodilator aerosols, we delivered treprostinil for 30 minutes… At the end of 30 minutes, the treprostinil was stopped…" (emphasis supplied).

Based on the above citations, it is clear to a person of ordinary skill in the art reading Sandifer that treprostinil was continuously administered for a 30-60 minute period in a single event and then stopped.

[1] Although the Advisory Action also cites Cloutier, which has overlapping disclosure with Sandifer, it appears that the rejection is significantly based upon a quote in Sandifer not found in Cloutier: "less total drug can be given on a daily basis by using intermittent inhalation compared with continuous infusion" (p. 2367, right

Furthermore, the amount of treprostinil administered by Sandifer's 30-minute single event dose is far outside the claimed range of 15 μg to 90 μg in claim 18. Without agreeing or disagreeing with the rationale provided in the Advisory Action, the rejection states that Sandifer administered 1 microgram/min/kg of body weight, or 21-37 micrograms per sheep per minute according to the rejection's analysis, during a single event dose lasting 30 minutes. That corresponds to 630 to 1,110 micrograms per event. Even the lower amount of 250 nanograms is well outside the claimed range when calculated with the Advisory Action's rationale (0.250 micrograms x 21 x 30 = 157.5 micrograms). Sandifer's "single event dose" is well outside the range of 15 μg to 90 μg in claim 18. For the record, Sandifer himself acknowledges that treprostinil doses used in his experiments on sheep are much higher than those for humans, see page 2367, left column, lines 12-14: "To achieve an effect in sheep, it was necessary to administer doses of treprostinil that were much higher than those used in treating patients, regardless of route of delivery." (underlining added)

In addition, the number of breaths used to inhale Sandifer's 30-minute single event dose is far outside the claimed range of 18 breaths or less in claim 18. Even if one assumes that the Advisory Action's estimate of 10 breaths per minute applies to Sandifer's sheep, Sandifer's shortest single administering event of 30 minutes will be performed in 300 breaths, which is much greater than 18 breaths or less recited in claim 18. For the record, "the respiration rate for sheep ... is about 12 to 15 breaths per minute (depending on environmental temperature)," see page 1, left column, last paragraph, Pezzanite et al, AS-595-W, Purdue Extension (enclosed).

The PTO improperly disregards Applicants' surprising/unexpected results relying on Sandifer

Applicants emphasize that the combination of a) the claimed dosing regimen of treprostinil and b) administration with a pulsed ultrasonic nebulizer recited in the pending claims represents surprising/unexpected results because it provides a significant improvement in quality of life for pulmonary hypertension patients due to its substantially greater

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column). This quote is mentioned several different places in the Advisory Action, including p. 3, paragraph 7 and page 4, first paragraph.

convenience compared to the only other available inhaled prostacyclin on the market. This was shown previously in the Rule 132 Declarations of Drs. Rubin and Gotzkowsky filed on May 23, 2012 and August 10, 2012 respectively.

Although Applicants provided similar comments on pages 11-12 of their response filed January 16, 2013, the PTO disregarded Applicants' surprising/unexpected results on pages 2-3 of the Advisory Action using the following comments to support its position:

> "Sandifer differs from the instant claims only in that the patient population is sheep rather than humans, and the type of aerosol delivery device is not identified. As discussed above, Sandifer discloses administration of inhaled aerosol treprostinil at a dose of 21-37 mcg/min, which falls within the range of 15-90 mcg/min as recited by instant claim 18 (again, assuming 10 human breaths is equivalent to approximately 1 minute of inhalation), with the advantages of minimal effects on systemic hemodynamics, and reduced total amount of drug required, in turn reducing costs. Thus, the explicit disclosure of Sandifer would have given one of ordinary skill in the art a reasonable expectation of success in treating pulmonary hypertension with doses of intermittently inhaled aerosol treprostinil falling within the scope of the instant claims, e.g., 1 mcg/kg/min (equivalent to 70 mcg/min or 70 mcg per 10 breaths for a 70 kg human)."

First, the PTO is incorrect in its assertion that Sandifer differs from the instant claims only in that the patient population. Besides the PTO's acknowledged difference, Sandifer does not teach at least each of the following elements of claim 18: a) said therapeutically effective single event dose is inhaled in **18 or less breaths** by the human; b) said therapeutically effective single event dose comprises **from 15 µg to 90 µg** of treprostinil or a pharmaceutically acceptable salt thereof. Applicants will explain below why one of ordinary skill in the art would not have arrived at elements a) and b).

Second, the PTO is incorrect that Sandifer does not identify the type of aerosol delivery system because Sandifer's first full paragraph in the left column on page 2364 clearly states that "[d]rug aerosolization was performed with a Healthline Medical AM-601 Medicator Aerosol Delivery System."

Sandifer performs his experiments on sheep. To model pulmonary hypertension, Sandifer induces acute pulmonary vasoconstriction in his sheep by infusing U-44069 at 1000 $ng \cdot kg^{-1}min^{-1}$ for 180 min, see page 2364, left column. In his inhalation experiments, Sandifer

continuously delivers treprostinil via aerosol for 30-60 min at 0.28ml/min in doses 250, 500 and 1000 $ng \cdot kg^{-1} \cdot min^{-1}$. One of ordinary skill in the art would not be able to arrive, based on Sandifer, at the particular dosing regimen recited in claim 18, namely at administering to a **human suffering from pulmonary hypertension** a therapeutically effective single event dose of an inhalable formulation with a pulsed ultrasonic nebulizer, wherein said therapeutically effective single event dose comprises from **15 µg to 90 µg of treprostinil** or a pharmaceutically acceptable salt thereof and said therapeutically effective single event dose is inhaled in **18 or less breaths** by the human for the following reasons:

1) Sandifer uses continuous aerosol delivery in a single administering event that lasts 30-60 min. Sandifer's mode of administration is very different from the pulsed ultrasonic nebulizer recited in claim 18. Furthermore, as explained above, even the shortest of Sandifer's single administering events involves many more breaths than 18 or less breaths recited in claim 18. Sandifer does not teach or suggest the presently claimed methods.

2) As Applicants explained before, see e.g. January 16th response, pages 7-8, not every compound that can be administered by inhalation can be administered in a pulsed ultrasonic nebulizer.

In sum, contrary to the PTO's assertions on page 3 of the Advisory Action, Sandifer does not give one of ordinary skill in the art a reasonable expectation of success to arrive at the presently claimed method in claim 18. For the record, one of ordinary skill in the art would not be able to arrive at the surprising/unexpected results discussed above, nor predict the surprisingly robust patient benefits shown in the previously submitted Rule 132 Declarations by making the changes in the inhalation method that are recited in claim 18.

The PTO failed to establish a *prima facie* case of obviousness at least because it failed to make its obviousness analysis explicit.

On pages 2, last paragraph, the PTO clarified that "the rejection relies upon two rationales: MPEP § 2143 (G) (some teaching, suggestion, or motivation in the prior art) and

MPEP § 2143 (A) (combining prior art elements according to known methods to yield predictable results)."

A) The PTO cannot rely on the rationale from MPEP § 2143 (A) at least because the PTO failed to articulate the required findings 1) and 3)

MPEP § 2143 (A) states as follows:

"To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Then, **Office personnel must articulate the following**:

- (1) a finding that the prior art included **each element** claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
- (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;
- (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were **predictable**; and
- (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v.*

Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396. **If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.**" (emphasis added)

Applicants respectfully submit that in the present rejection, the PTO failed to articulate at least findings 1) and 3) of MPEP § 2143(A).

With respect to finding 1), the PTO failed to articulate at least which reference teaches a therapeutically effective single event dose comprising from **15 µg to 90 µg** of treprostinil or a pharmaceutically acceptable salt thereof, which dose is inhaled in **18 or less** breaths by the human. As Applicants explained above, Sandifer does not teach this element of claim 18.

With respect to finding 3), the PTO failed to articulate at least why selecting an ultrasonic nebulizer from Chaudry's list of inhalation devices in paragraphs 0052-0057, while selecting treprostinil from Chaudry's list of hypertension reducing agents in paragraphs 0022-0027 would be predictable to one of ordinary skill in the art especially in view of the evidence provided by Applicants demonstrating that not every hypertension reducing agent in Chaudry's paragraphs 0022-0027 can be administered by every inhalation device in Chaudry's paragraphs 0052-0057, see pages 7-8 of the response filed January 16, 2013, where Applicants provide evidence that iloprost listed among hypertension reducing agents in Chaudry's paragraphs 0022-0027 cannot be administered by a metered dose inhaler, which is mentioned among possible inhalation devices in Chaudry's paragraph 0052-0057.

In sum, the PTO cannot rely on the obviousness rationale from MPEP § 2143 (A) for the reasons discussed above.

B) The PTO cannot rely on the rationale from MPEP § 2143 (G) at least because the PTO failed to articulate the required finding (2)

MPEP § 2143 (G) states as follows:

"To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Then, **Office personnel must articulate the following**:

- (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- (2) **a finding that there was reasonable expectation of success;** and
- (3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success. *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). **If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art**." (emphasis added)

Applicants respectfully submit that the PTO failed to articulate the required finding 2) at least because the PTO failed to explain why one of ordinary skill in the art would have a reasonable expectation of success to arrive at the dosing regimen recited in claim 18, namely administering to a **human suffering from pulmonary hypertension** a therapeutically effective single event dose of an inhalable formulation with a pulsed ultrasonic nebulizer, wherein said therapeutically effective single event dose comprises from **15 µg to 90 µg of treprostinil** or a pharmaceutically acceptable salt thereof and said therapeutically effective single event dose is inhaled in **18 or less breaths** by the human. Applicants provided above a reasoned explanation on why one of ordinary skill would not have a reasonable expectation of success for arriving at such dosing regimen based Sandifer.

In sum, the PTO cannot rely on the obviousness rationale from MPEP § 2143 (G) for the reasons discussed above.

DOUBLE PATENTING REJECTION

Claims 18, 25, 27-30 and 32-34 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1, 4-17 and 52-59 of co-pending Application No. 11/748,205 in view of Chaudry et al. (US Pub. No. 2004/0265328), Byron (Proc. Am. Thor. Soc. (1), pp. 321-328, 2004) and Cloutier et al. (USPN 6,521,212). Applicants will address this rejection at such time (if ever) that it becomes non-provisional.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date JUL 0 2 2013

By _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Appl. No.: 12/591,200

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Art Unit: 1629

Confirmation Number: 4093

DECLARATION UNDER 37 C.F.R. § 1.131 OF LEWIS RUBIN, M.D.

I, Lewis Rubin, do hereby declare:

1. I am Emeritus Professor of Medicine and the Emeritus Director of the Pulmonary and Critical Care Division of the University of California, San Diego School of Medicine.

2. I have extensive experience and background in the field of treating pulmonary hypertension, including a B.A. from Yeshiva University and an M.D. from Albert Einstein College of Medicine. My Curriculum Vitae submitted in this application with my prior Declaration provides additional details on my qualifications and experience.

3. I am a citizen of the United States of America.

4. I am a co-inventor of the subject matter claimed in U.S. patent application Ser. No. 12/591,200.

5. I am a paid consultant of United Therapeutics, the assignee of the above-identified patent application.

6. I am familiar with the Advisory Action dated June 24, 2013 in U.S. patent application Ser. No. 12/591,200, which indicates how the rejection may be partially based upon a certain statement found in the Sandifer reference.

7. Specifically, the Advisory Action stated that Sandifer would have given one of ordinary skill a reasonable expectation of success and would have provided an expectation of certain benefits, quoting from Sandifer as follows: "less total drug can be given on a daily basis by using intermittent inhalation compared with continuous infusion" (p. 2367, right column, Sandifer, as quoted in the Advisory Action on page 3).

8. Without agreeing or disagreeing with any conclusion drawn in the rejection about the teachings of Sandifer, I am providing this Declaration to establish that the co-inventors and I performed inhalation methods with pulmonary hypertension patients using treprostinil prior to Sept. 1, 2005, which is prior to the publication date of Sandifer. The methods we performed prior to Sept. 1, 2005 included at least as much of the disclosure found in Sandifer that is cited in the Advisory Action, except that our method used human pulmonary hypertension patients rather than a sheep model. Specifically, attached as Exhibit A to this Declaration is a redacted clinical trial report synopsis setting forth details of a clinical trial. The dates and certain other details have been redacted, but the explanation of how the trial was conducted and the results of that particular trial are retained. All results described in Exhibit A were obtained prior to Sept. 1, 2005.

9. In Exhibit A, the reference to the "OptiNeb device, NEBU-TEC GmbH" is a reference to an ultrasonic nebulizer. The ultrasonic nebulizer was used to administer pulmonary hypertension patients the indicated amounts of treprostinil, including one single event dose of 2 minutes providing about 40 micrograms of treprostinil. As indicated in Exhibit A, the results showed dose-dependent reduction of pulmonary vascular resistance and pulmonary arterial pressure in human pulmonary hypertension patients.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 21st day of June, 2013.

Lewis Rubin, M.D.

EXHIBIT A

CLINICAL TRIAL REPORT SYNOPSIS

Investigation into efficacy, haemodynamic effects and safety of Inhaled treprostinil sodium and placebo in patients with pulmonary arterial hypertension

Investigator Driven Study

The study was performed according to Good Clinical Practice regulations

SYNOPSIS

LungRx Corporation	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Products: Not applicable	Volume:	
Name of Active Ingredient: Treprostinil sodium	Page:	

Title of Study:	Investigation into efficacy, haemodynamic effects and safety of inhaled treprostinil sodium and placebo in patients with pulmonary arterial hypertension
Investigators	
Study center:	
Publication (reference):	None at the time of report
Study period (years):	**Clinical Phase:**
Objectives:	Primary: To assess the 1) Pulmonary vascular resistance (PVR, [dyn s cm-5]) following inhaled treprostinil or placebo Secondary: To assess 2) Pulmonary arterial pressure (PAP, [mmHG]) 3) Cardiac output (CO, [L/min]) 4) Systemic arterial pressure (SAP, [mm HG]) and heart rate (HR, [beats/min]) 5) Systemic arterial oxygen saturation (SaO2, [mm HG]) and venous oxygen saturation (SvO2, [mm HG]) 6) Tolerability of ascending single doses of inhaled treprostinil (TRE) and placebo (PLA).
Methodology:	Mono-center, randomized, parallel groups, single-blind, single dose consecutive inhalation; assessment for three hours following aerosolation. Inhalation with OptiNeb device, NEBU-TEC GmbH, Elsenfeld, Germany PAP, PVR, CO, and SvO2 were measured with a Swan-Ganz thermodilution pulmonary catheter and SAP besides SaO2 with a femoral artery catheter. The study consists of three study parts (D, E, F) to be differentiated by three single doses of inhaled treprostinil. The same methods and design were applied for all three study parts and treatment groups. For all treatments or study parts the same group of patients treated with PLA served as control. In a random order, within study part D patients were either treated with TRE 16 µg/ml or PLA inhaled for 6 minutes.
Number of subjects (planned and analyzed):	Sixteen subjects (8 subjects each with TRE or PLA) were planned and participated in study part D. Six patients with TRE were included into study part E and F as planned. There was no drop out. As PLA was administered to one group of patients, a total of 28 subjects were enrolled and completed the study as planned. Data of all subjects were analyzed.
Diagnosis and main criteria for inclusion:	Male and female patients with pulmonary hypertension (PH), either idiopathic/primary, or due to collagen vascular or congenital heart disease, to HIV infection, to chronic thromboembolic PH or pulmonary fibrosis; NYHA functional classes II-IV; no other severe pulmonary disease in the medical history which could have interfered with the inhalation procedure.

LungRx Corporation	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Products: Not applicable	Volume:	
Name of Active Ingredient: Treprostinil sodium	Page:	

Test products, doses and mode of administration, batch number:
Treprostinil 16 µg/ml inhaled for 6 minutes, equivalent to about 16 µg of TRE
Treprostinil 48 µg/ml inhaled for 6 minutes, equivalent to about 48 µg of TRE
Treprostinil 96 µg/ml inhaled for 2 minutes, equivalent to about 40 µg of TRE
20 mL vial containing treprostinil sodium equivalent to 1.0 mg/mL of TRE
The content of the vials has been diluted with saline 0.9% to obtain the respective dose
Batch no: 803520B

Duration of treatment of the study:
Three study parts D, E, F, each with single dose inhalations for each subject and a duration of measurement of haemodynamic effects for 180 minutes after end of inhalation.
Investigations in PLA patients were performed in study part F. In a random order, patients were either treated with TRE 16 µg/ml or PLA.

Reference therapy, dose and mode of administration, batch number:
Placebo inhaled for 6 minutes
20 mL vial containing solvent of treprostinil, i.e. all substances except treprostinil sodium
Dissolution of the solvent for the preparation of PLA was performed as of to obtain 1 µg/ml of TRE
Batch no: 803354A

Criteria for evaluation: Investigational parameters were measured for 3 hours at -10, 0, 15, 30, 45, 60, 90, 120, 150 and 180 minutes (min) after end of inhalation. Mean values and SEM were calculated as well as change (%) of the baseline value (-10 min).

Safety: Heart rate, systemic arterial blood pressure, adverse events.

Statistical methods: All data were summarized by means of descriptive statistics. Mean values and SEM were calculated. Appropriate curves and figures were displayed.

LungRx Corporation	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Products: Not applicable	Volume:	
Name of Active Ingredient: Treprostinil sodium	Page:	

Summary of efficacy results:

Inhaled TRE shows a dose-dependent reduction of PVR and PAP regarding extent and duration of effect independent from the inhalation periods applied as shown in Fig 20 summarizing the effects of 48 µg/ml of TRE and in Fig 19 summarizing the effects of 96 µg/ml of TRE. SAP, SaO2 and SvO2 exhibit some deviations from baseline, and HR a slight decrease but no dose-dependent effects are seen. CO shows a slight increase for about 60 to 90 min. Despite the higher dose of 96 µg/ml no significant dose dependent effect in the two higher doses is seen for CO. Therefore, spillover effects may be ruled out as no concomitant decrease of blood pressure regulatory parameters, i.e. of SAP or an increase in HR, was evaluated despite dose escalation and reducing the time of inhalation in study part F.

No dose and time-of-inhalation limiting factors occurred so far. Shortening the time of inhalation by two thirds did not reduce the extent or duration of effect. Therefore, the use of TRE may be expanded to patients with loss of effect of other medications as well as to those patients where an increase in dose is required for whatever reason. This fact contributes to an unrestricted use of TRE in the indication in contrast to other medications.

The changes seen for PLA in some parameters may have been induced by the inhalation procedure itself. This is supported by the fact that no saline but the solvent of TRE including all compounds except TRE was used as PLA.

Results - safety:

Tolerability of inhaled TRE proved to be excellent for all three doses, i.e. following 16 µg/ml and 48 µg/ml of TRE inhaled for 6 mintes or 96 µg/ml inhaled for two minutes. No adverse events were reported, and neither of the haemodynamic parameters determined exhibited any adverse profile of the compound. Following inhalation of PLA no adverse events were reported either.

Conclusions:

Inhaled TRE shows dose dependent efficacy following increasing single doses of 16, 48 and 96 µg/ml inhaled for 6 and 2 minutes in patiernts with pulmonary hypertension. A dose related effect is achieved regarding extent and duration of reduction of pulmonal vascular resistance and pulmonal arterial pressure. No dose-limiting effects prohibit a further reduction of the time of inhalation or an additional raise in dose.

Furthermore, parameters indicative for a spillover accompanied by systemic compensatory effects such as changes in cardiac output, systemic arterial pressure and heart rate do not exhibit such properties for TRE so far.

The results also demonstrate an extended and long lasting haemodynamic effect for at least 3 hours demonstrating a therapeutic novelty in this disease. Additionally, TRE may be administered to all patients independent from the severity of the condition as a dose range from 16 µg/ml up to 96 µg/ml proved to be effective and safe.

1 LIST OF ABBREVIATIONS

AMG	Arzneimittelgesetz, German Pharmaceutical Code
CO	Cardiac output
Fig	Figure
GCP	Good Clinical Practice
HR	Heart rate
µg	Microgram
min	Minutes
mL	Milliliters
mm Hg	Millimeter mercury
PAP	Pulmonal arterial pressure
PLA	Placebo
PVR	Pulmonary vascular resistance
SaO2	Systemic arterial oxygen saturation
SAP	Systemic arterial pressure
SEM	Standard Error of the Mean
SvO2	Venous oxygen saturation
TRE	Treprostinil

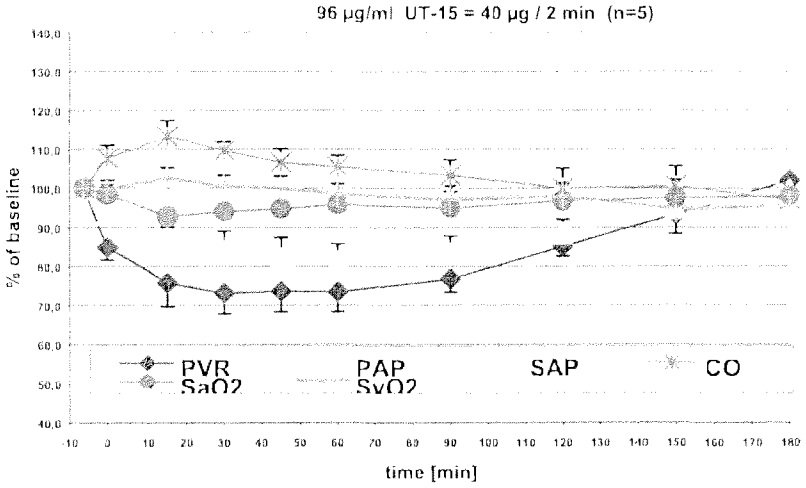

Figure 19: Haemodynamic effects following inhalation of 96 µg/ml of TRE – Part F

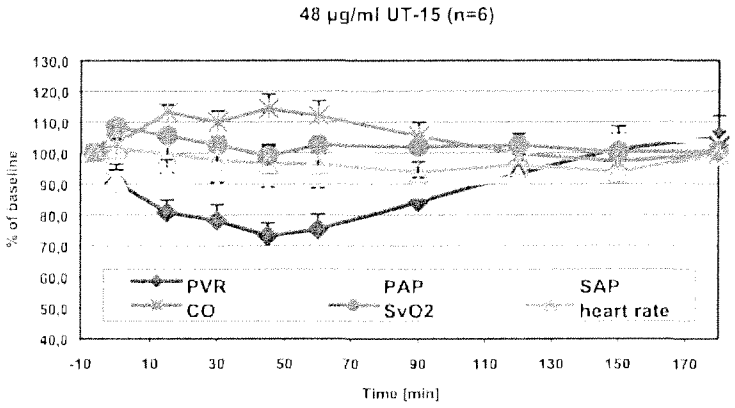

Figure 20: Haemodynamic effects following inhalation of 48 µg/ml of TRE – Part E