Deeper Lung Pulmonary Delivery of Treprostinil is Associated with Delayed Systemic Absorption

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Introduction & Background

Treprostinil sodium, marketed as Remodulin®, is already approved as a continuous s.c. or i.v. infusion for the treatment of various forms of pulmonary arterial hypertension (PAH) in a number of markets.

Inhaled treprostinil sodium was recently approved (Tyvaso®) using an ultrasonic nebulizer, Nebu-Tec Optineb. The goal of this program was to enable transition from the nebulizer to the AERx Essence system (Fig. 1), using the identical treprostinil sodium formulation.

Methods

Treprostinil sodium (600 µg/mL) was used for both the Nebu-Tec Optineb® nebulizer and the AERx Essence® System. The bulk drug solution was diluted in a ratio of 19:1 by the addition of ^{99m}Tc-DTPA (2000 MBq/mL). Each mL of the radiolabeled drug solution therefore contained 100 MBq of ^{99m}Tc-DTPA and 570 µg of treprostinil sodium.

For dosing in this trial, the Nebu-Tec Optineb nebulizer cup was filled with 2 mL of radiolabeled formulation (570 µg/mL), resulting in a nebulizer loaded dose of 1140 µg treprostinil. In vitro testing predicted an emitted dose (ED) of approximately 4.36 µg treprostinil per inhalation. Combined with a fine particle fraction ($FPF_{<5\mu m}$) of 80%, the Nebu-Tec Optineb was estimated to deliver a lung dose (ED x FPF) of ~3.5 µg per inhalation, and thus, a total lung dose of ~21 µg treprostinil delivered over the 6-inhalation study dose.

AERx Essence Strip® dosage forms were each filled with 50 µL of the 570 µg/mL treprostinil solution, resulting in a loaded dose of 28.50 µg treprostinil per strip. In vitro testing produced a mean ED of 50% and a mean $FPF_{<5\mu m}$ of 90%. Thus, the predicted treprostinil lung dose (ED x FPF) was ~12.83 µg per inhalation or 25.65 µg over the 2-inhalation study dose.

Clinical Study Design and Endpoints

- Single Center, randomized, open-label, crossover study
- Target lung dose: ~25 µg treprostinil
  - AERx Essence: 2 inhalations
  - Nebutec: 6 puffs
- 14 healthy adult male subjects
- **Gamma Scintigraphy**
  - Dose-to-lung (% LD, µg)
  - Oropharyngeal deposition
  - Central-to-peripheral lung deposition
- **Pharmacokinetics**
  - AUC, Cmax, Tmax, etc.
- **Safety and Tolerability**
  - Inhaled Tolerability

Acknowledgements

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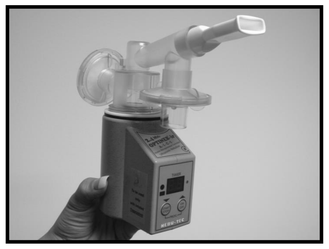
Figure 1: Picture of Devices



The Nebu-Tec OPTINEB nebulizer

The AERx Essence System

Figure 2: Lung and Oropharyngeal Dose

- The dose to the lung and the oropharynx (including mouth washings and stomach deposition) was assessed by expressing the detected activity as a percentage of the dose emitted from each delivery system following appropriate corrections for regional attenuation, background activity and radioisotope decay.
- **Treprostinil Lung Dose (Mean ± SD)**:
  - AERx Essence: 26.1 ± 5.3 µg (91.6% ± 7.9%)
  - Optineb: 19.6 ± 5.5 µg (79.4% ± 9.6%)
- **Mean Oropharyngeal Deposition** :
  - AERx Essence: 8.4% - Optineb: 20.6%

Treprostinil Lung Dose (µg)		
AERx	**Subject Number**	**OPTINEB**
15.8	S001	14.5
26.6	S002	20.1
25.4	S003	17.5
12.8	S004	24.4
27.5	S005	9.3
29.6	S006	18.4
29.9	S007	17.7
25.7	S008	30.7
30.8	S009	15.7
30.5	S010	28.0
27.2	S011	21.8
28.4	S012	20.8
25.7	S013	18.5
29.2	S014	16.8
26.1	**Mean**	**19.6**
5.3	**SD**	5.5
20.4	**CV(%)**	**27.9**
12.8	**Min**	9.3
30.8	**Max**	30.7

Oropharyngeal (% of Inhaled)		
AERx	**Subject Number**	**OPTINEB**
3.5	S001	25.3
11.1	S002	33.1
3.7	S003	22.7
31.2	S004	18.6
5.0	S005	32.2
3.1	S006	19.4
5.2	S007	29.5
3.0	S008	5.8
6.5	S009	21.2
1.7	S010	6.1
10.5	S011	7.2
7.6	S012	14.4
18.3	S013	20.0
6.5	S014	32.5
8.4	**Mean**	**20.6**
7.9	**SD**	**9.6**
94.4	**CV(%)**	**46.5**
1.7	**Min**	5.8
31.2	**Max**	33.1

Figure 3: Penetration Index

- The penetration index (sC/P) is a measure of the relative deposition in the central airways to the peripheral airways.
- The method involves drawing regions of interest in the lungs and counting the amount of deposited radioactivity in the pixels within each region. This is normalized relative to that for a radioactive gas scan (Krypton).
- **Results:**
  - OPTINEB deposits the aerosol more centrally (higher sC/P)
  - AERx deposits the aerosol more deeply (lower sC/P)

sC/P Ratio		
AERx	**Subject Number**	**OPTINEB**
1.28	**S001**	**12.41**
1.76	S002	8.47
1.33	S003	4.51
1.85	S004	1.95
1.12	**S005**	**3.37**
1.31	S006	2.78
1.96	S007	4.62
1.26	S008	1.83
1.52	S009	1.83
1.47	S010	3.97
1.22	S011	1.90
1.17	S012	3.80
1.20	**S013**	**1.48**
1.00	S014	2.57
1.39	**Mean**	**3.96**
0.29	**SD**	3.03
20.7	**CV(%)**	**76.5**
1.0	**Min**	1.5
2.0	**Max**	12.4

Figure 4: Mean PK Profiles

- AUC and Cmax were normalized for treprostinil lung dose.
- **Results**:
  - Mean AUCs were comparable when normalized for lung dose.
  - OPTINEB has a higher mean C_{max} and more rapid T_{max}
  - AERx has a lower mean C_{max} and slower T_{max}

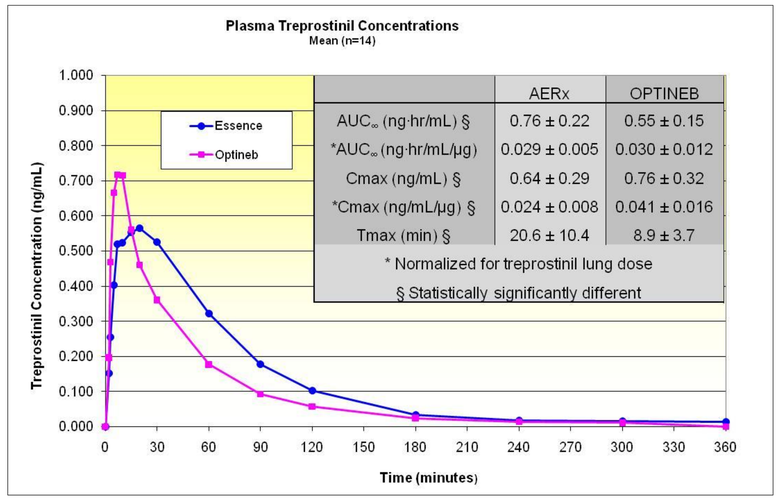
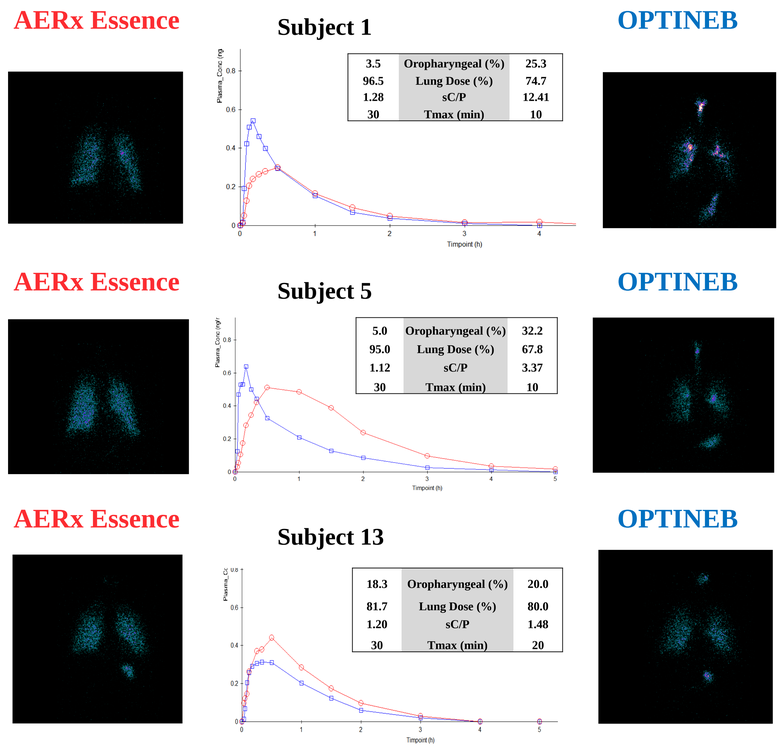


Fig. 5: Selected Lung Images & PK Profiles



- Subject 1: High sC/P for Optineb associated with rapid T_{max}
- Subject 5: Moderate sC/P for Optineb associated with rapid T_{max}
- Subject 13: Low sC/P for Optineb associated with delayed T_{max}
- AERx Essence: Low sC/P associated with delayed T_{max}

SUMMARY

- Both treatment paradigms were well tolerated and there were no SAEs. Cough was the most frequently reported adverse event.
- Mean oropharyngeal deposition was lower for AERx Essence (8.4% ± 7.9%) than for Optineb (20.6% ± 9.6%).
- Mean lung deposition was 91.6 ± 7.9% (26.1 ± 5.3 µg) for AERx Essence versus 79.4 ± 9.6% (19.6 ± 5.5 µg) for Optineb.
- Lung deposition was more peripheral for AERx Essence (sC/P = 1.39, CV=21%) than for Optineb (sC/P = 3.96, CV=77%).
- Mean $AUCs_{0\rightarrow\infty}$ were comparable when normalized for lung dose.
- Peak systemic drug concentration (mean C_{max}) was ~40% lower for AERx (0.024 ng/mL/µg) than for Optineb (0.041 ng/mL/µg).
- Systemic absorption was less rapid (mean T_{max}) for AERx Essence (21 ± 10 min) than for Optineb (9 ± 4 min).
- **The difference in deposition patterns within the lung influenced the rate but not the extent of absorption of treprostinil.**
- **Deeper lung delivery of treprostinil is associated with slower absorption (delayed T_{max}) and a lower C_{max}.**