Preclinical and Phase 1 Clinical Characterization of LIQ861, a New Dry Powder Formulation of Treprostinil

Royal M[1], Roscigno R[1], Vaughn T[1], Anderson S[1], Wargin W W[2], Williams Jr. RL[2], Forsythe C[3], Hunt T[3], Normand P[4], Hantash M[4], Dillberger J[5].

[1] Liquidia Technologies, RTP, NC, USA. [2] Nuventra, Inc., Durham, NC, USA. [3] PPD Development, LLC Austin, TX, USA. [4] ITR Laboratories, Montreal, Quebec, Canada. [5] J. Dillberger LLC, Nashville, IN, USA

Introduction

Treprostinil (Tre), a synthetic prostacyclin analogue, currently is approved for inhalation administration to patients with pulmonary arterial hypertension (PAH) via nebulized Tyvaso® Inhalation Solution (Tre Solution) administered four times per day. The time typically required for nebulizer preparation, dose administration and cleaning is a burden to patients. A convenient, dry powder inhalation formulation of Tre offers a simple, portable treatment regimen that is a meaningful improvement over the current nebulized therapy.

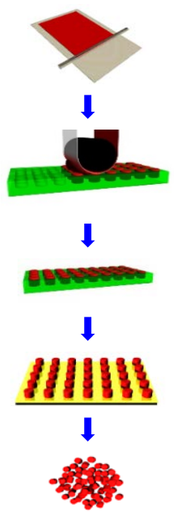
Liquidia is developing LIQ861, a dry powder formulation of treprostinil, specifically designed to improve deep lung delivery and the safety profile of the inhaled route. Using our proprietary PRINT® technology, LIQ861 particles are a precise, uniform size (1µm) and trefoil pollen-like shape. We conducted single-dose pharmacokinetic (PK) studies in rats and dogs and repeat-dose toxicity studies in rats. Subsequently, LIQ861 was evaluated in a Phase 1 safety, tolerability and PK single ascending dose study in healthy adult subjects who received 25 mcg to 150 mcg in two inhalations per capsule.

The PRINT Process

The core process involves four basic steps:

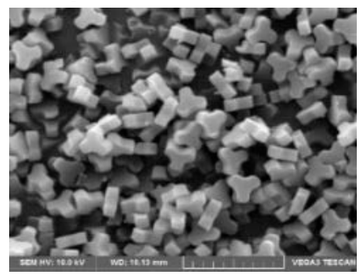
1. Create a film of the desired composition on a delivery sheet.
2. Laminate the film with a mold where the material fills the mold cavities.
3. Remove particles from the mold.
4. Collect particles to create a particle suspension or dry powder.

The PRINT process allows Liquidia to produce particles of uniform size, shape and composition.



Particle Characterization

Treprostinil Particles



MMAD	GSD	Emitted Dose	Fine Particle Fraction
1.81	1.89	70-80%	86%

MMAD = Mass Median Aerodynamic Diameter
GSD = Geometric Standard Deviation

Dry Powder Inhaler

Dry Powder Inhalation (DPI) device RS00, Approved for multiple product use in US and Europe , Plastiape S.p.A (Lecco, Italy)

Animal Study Designs

Single Administration PK Study in Anesthetized Male Beagle Dogs:

- Administered via endotracheal tube and controlled ventilation (Spangler Box)
- Tre Solution (Simulated) – Pari LC Plus Jet Nebulizer
- LIQ861 – Linear Powder Feeder
- Lung Deposition = 70%

Treatment	No. of Animals	Exposure Duration (min)	Mean Tre PDD (µg/kg)	Total Tre Mass (µg)	MMAD (GSD)	Blood collection (post inhalation) min
Tre Solution	4	1	3.55	62.8	4.3 (2.4)	2, 5, 10, 20, 30, 60, 120 and 180
LIQ861	4	2.5	3.25	52.3	2.5 (1.8)	

Repeat Dose Toxicity Study (14 Days & 26 weeks)

- Administered via flow-past nose-only inhalation exposure system
- Tre Solution (Simulated) – clinical nebulizer (Sidestream)
- LIQ861 – Piston Feed/Rotating Brush Generator
- Lung Deposition = 10%

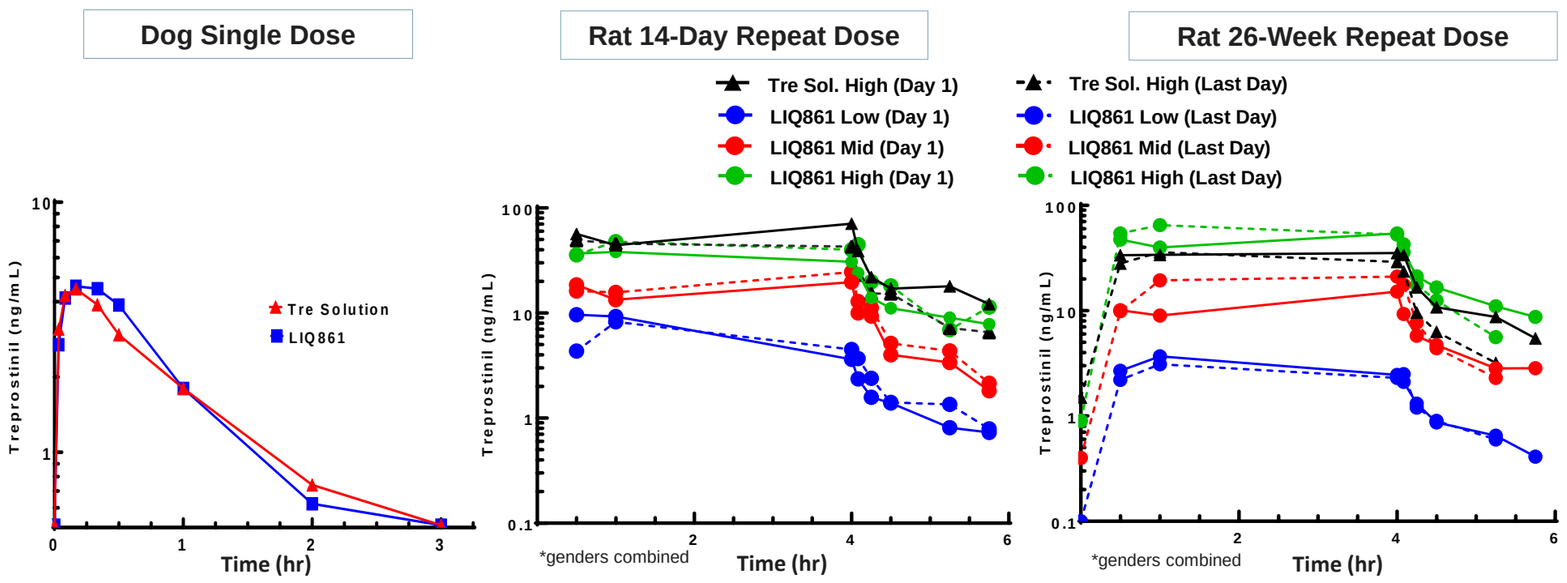
TK Dose Groups	No. of Animals	Exposure Duration (min)	Mean Tre PDD (µg/kg)	Aerosol Conc. (µg/L)	MMAD (GSD)	Blood collection Day 1 & 14 from start of inhalation
Tre Solution	10/Sex	240	161	10.5	0.6 (2.4)	30, 60, 240 (end of inhalation), 245, 255, 270, 315, 345 min
LIQ861	10/Sex	240	16.2 (L) 42.8 (M) 128 (H)	1.1 2.8 8.4	1.2 (2.1) 1.7 (1.9) 1.9 (1.9)	

TK Dose Groups	No. of Animals	Exposure Duration (min)	Mean Tre PDD (µg/kg)	Aerosol Conc. (µg/L)	MMAD (GSD)	Blood collection Day 1 & 182 from start of inhalation
Tre Solution	10/Sex	240	146	10.2	0.5 (2.4)	0, 30, 60, 240 (end of inhalation), 245, 255, 270, 315, 345 min
LIQ861	10/Sex	240	7.3 (L) 37.2 (M) 152.4 (H)	0.5 2.6 10.6	1.8 (2.0) 2.0 (2.0) 1.9 (1.9)	

PDD= Pulmonary Delivered Dose L = Low dose M= Mid Dose H = High Dose

Animal Pharmacokinetic Data

Similar Treprostinil Exposure with LIQ861 or Simulated Tre Solution



Conclusions

1. Systemic treprostinil exposures (C_{max}, AUC_{last}, and AUC_{inf}) were similar when administered as LIQ861 Dry Powder or Simulated Tre Solution.
2. No evidence of treprostinil accumulation with repeated exposure of LIQ861 or Simulated Tre Solution.

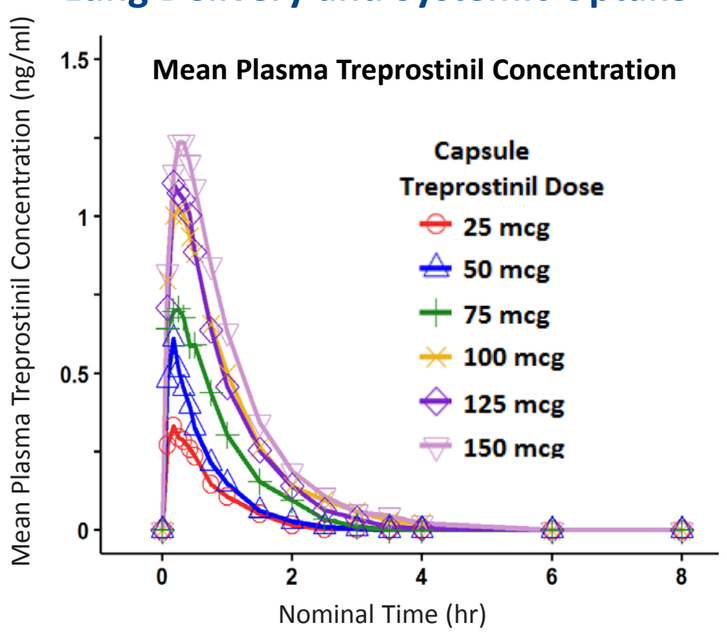
Phase I Ascending Single Dose Escalation Study Trial Design

	LIQ861		Placebo	
Administered Dose (Treprostinil)	Capsules Administered	N	Capsules Administered	N
25 mcg	1	6	1	2
50 mcg	1	7	1	2
75 mcg	1	6	1	2
100 mcg	2 (2x50)	6	2	2
125 mcg	2 (1x75, 1x50)	6	2	2
150 mcg	2 (2x75)	12	2	2

Abbreviations: N= number of subjects

Blood collected for testing at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 minutes and 4, 6 and 8 hrs post dosing. Subjects were instructed to use two inhalations per capsule and hold their breath at end inspiration for 10 seconds.

LIQ861 Dry Powder Formulation: Rapid Lung Delivery and Systemic Uptake



Conclusions

1. Treprostinil exposure (C_{max}, AUC_{inf}) when administered as LIQ861 is dose proportional from 25 to 150 mcg.
2. At both 100 mcg and 150 mcg doses, 50% of individuals had measurable treprostinil at 4 hrs.
3. No observed increase in frequency or severity of TEAEs from 25 to 100 mcg. Most TEAEs (>75%) occurred in 125 & 150 mcg cohorts. All were mild.
4. LIQ861 is safe and well tolerated at treprostinil doses up to 150 mcg with no SAEs and only mild TEAEs. This is an emitted dose ~50% higher than Tyvaso® maximum tolerated dose in healthy volunteers (84 mcg - Nelsen 2010).
5. Repeat dose studies with LIQ861 in patients with PAH are warranted.

LIQ861 Summary: No SAEs; only mild TEAEs

Reported Adverse Events (AEs) by Relatedness and Treatment

Adverse Event	LIQ861 (N=43)		PRINT Placebo (N=14)	
	No (%) of Subjects	No. of Events	No (%) of Subjects	No. of Events
Related to treatment	***29 (67.4%)***	***40***	***0***	***0***
Cough	11 (25.6%)	11	0	0
Throat irritation	9 (20.9%)	9	0	0
End-Inspiratory Tightness [a]	6 (14.0%)	6	0	0
Lightheadedness [b]	5 (11.6%)	5	0	0
Headache	4 (9.3%)	4	0	0
Nausea	3 (7.0%)	3	0	0
Dizziness	1 (2.3%)	1	0	0
Hot Flash	1 (2.3%)	1	0	0
Unrelated to treatment	***7 (16.3%)***	***8***	***2 (14.3%)***	***2***
Vasovagal symptoms [c]	5 (11.6%)	5	0	0
Headache	1 (2.3%)	1	0	0
Lightheadedness [b]	1 (2.3%)	1	0	0
Sensation of warmth	1 (2.3%)	1	0	0
Rhinorrhea	0	0	1 (7.1%)	1
Venipuncture site pain	0	0	1 (7.1%)	1

Note: SAE = serious adverse event; TEAE = treatment-emergent AE
Percentage of specific reported AEs are a function of relatedness to treatment administration, based on judgment of principal investigator.
All AEs were "mild" in severity.
a. MedDRA preferred term was coded as "painful respiration"
b. MedDRA preferred term was coded as "dizziness"
c. MedDRA preferred term was coded as "presyncope"

LIQ861 PK Results

	Treprostinil (mcg)					
	25	50 [b]	75	100	125	150
C_{max} (ng/mL)	0.329	0.572	0.728	1.08	1.19	1.33
T_{max} (h) [a]	0.21	0.18	0.25	0.29	0.24	0.31
$T_{1/2}$ (h)	0.507	0.434	0.617	0.722	0.523	0.648
AUC_{Inf} (h*ng/mL)	0.285	0.428	0.766	1.22	1.16	1.50

a. T_{max} reports median values
b. One subject in the 50 mcg cohort withdrew consent for further PK blood draws after 10 min and was not included in the PK analyses.

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