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

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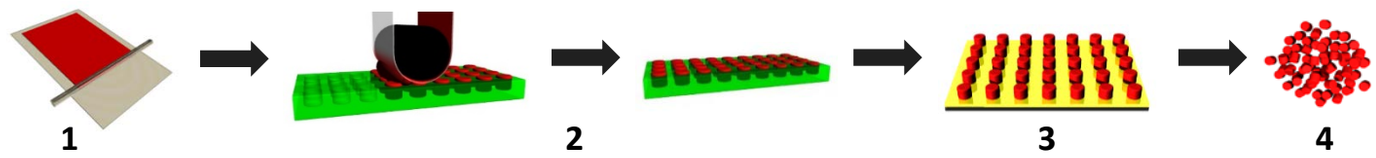
Introduction

Treprostinil (Tre) is a synthetic prostacyclin analogue approved for inhalation administration to patients with pulmonary arterial hypertension (PAH) via nebulized Tyvaso® Inhalation Solution (Tre Solution) administered four times daily. The time required for nebulizer preparation, administration and cleaning is a burden to patients. Liquidia is developing LIQ861, a convenient, dry powder inhalation formulation of Tre that offers a simple, portable alternative treatment regimen.

LIQ861 is specifically designed to improve the therapeutic profile of Tre by enhancing deep-lung delivery and achieving higher dose levels than current inhaled therapies. 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 one to two inhalations per capsule.

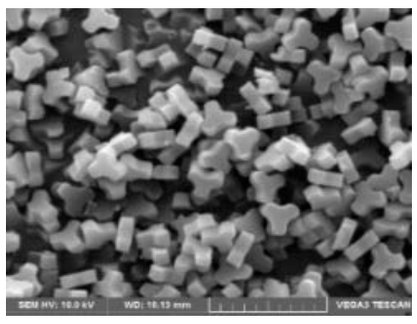
The PRINT Process

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



The core process involves four 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.

LIQ861 Particle Characterization



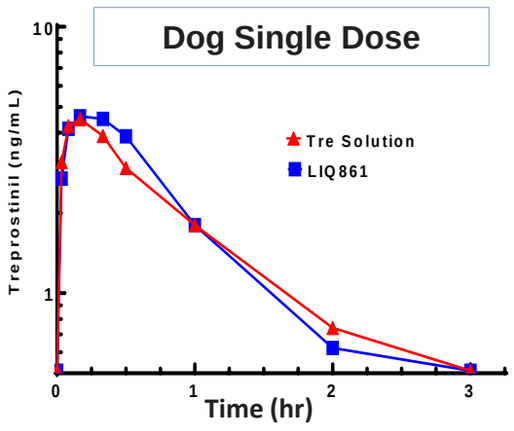
MMAD	GSD	Emitted Dose	Fine Particle Fraction
1.81	1.89	70-80%	86%

MMAD = Mass Median Aerodynamic Diameter
GSD = Geometric Standard Deviation

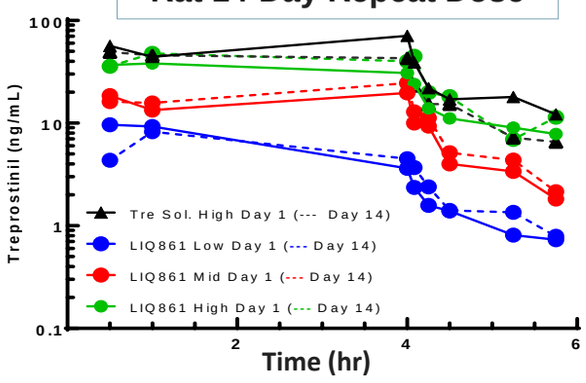
Dry Powder Inhaler

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

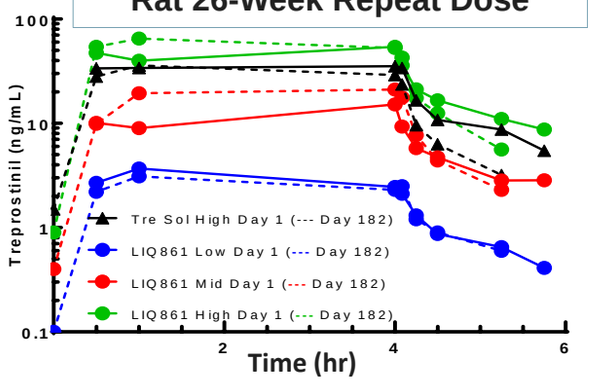
Dog Single Dose



Rat 14-Day Repeat Dose



Rat 26-Week Repeat Dose



LIQ861 Nonclinical Conclusions

1. Systemic Tre exposures (C_{max} , AUC_{last} and AUC_{inf}) were similar to simulated Tre Solution.
2. No Tre accumulation with repeated exposure.

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

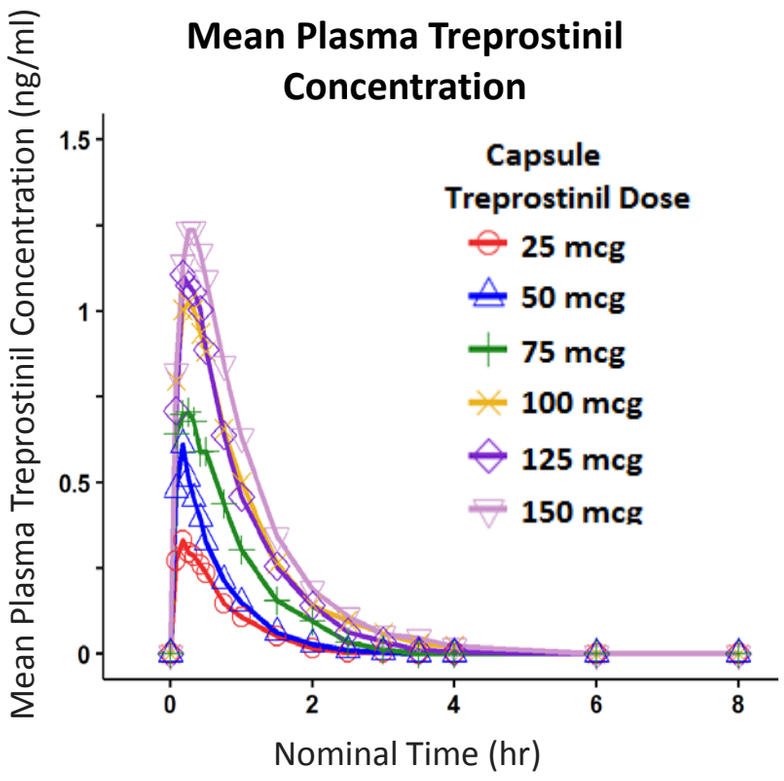
LIQ861: No SAEs; only mild AEs

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

Note: SAE = serious adverse event
Relatedness based on judgment of principal investigator.
All AEs were "mild" in severity. MedDRA preferred term coded as:
a. "painful respiration"
b. "dizziness"

Events deemed unrelated by physician include: vasovagal symptoms 5 (11.6%), headache 1 (2.3%), lightheadedness 1(2.3%), rhinorrhea 1 (7.1%), and venipuncture site pain 1 (7.1%).

LIQ861: Rapid Systemic Uptake



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 of inspiration for 10 sec per inhalation.

	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.

Phase 1 Study Conclusions

1. Tre exposure (C_{max} & AUC_{inf}) from LIQ861 was dose proportional from 25 to 150 mcg.
2. No dose limiting toxicity was observed and the maximum tolerated dose (MTD) was not reached.
3. At higher doses, 50% of subjects had measurable Tre at 4 hrs.
4. No observed proportional increase in frequency or severity of AEs from 25 to 100 mcg.
5. LIQ861 was well tolerated at Tre doses up to 150 mcg with no SAEs and only mild AEs.
6. The 150 mcg dose of LIQ861 is approximately double the maximum recommended dose of Tyvaso®.
7. A Phase 3 Study titled "Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil (INSPIRE)" in patients with PAH is in progress (NCT03399604).

Acknowledgements

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