Phase 1 Safety and Pharmacokinetic Study of Inhaled LIQ861, a New Dry Powder Formulation of Treprostinil

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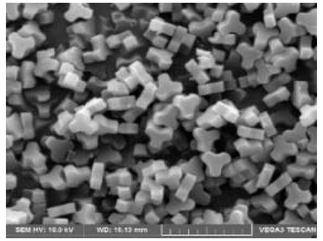
Introduction

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. 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 designed to have ideal aerodynamic properties for deep-lung delivery. Liquidia conducted a Phase 1 safety, tolerability and PK single ascending dose study in healthy volunteer subjects who received 25 mcg to 150 mcg in two inhalations per capsule using a palm-sized dry powder inhaler (DPI) device (RS00 Model 8, Plastiape SpA, Lecco, Italy). The study's primary objectives were to characterize Tre PK, evaluate the safety and tolerability of inhaled LIQ861 and assess the performance of the DPI.

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

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

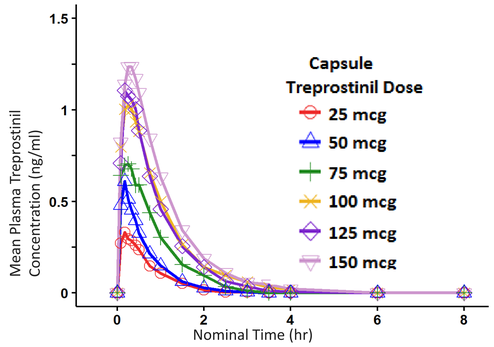
Results

Fifty-seven subjects (29 M/28 F; 18 to 44 years old) were enrolled. The median Tre T_{max} within cohorts was between 10 and 20 min post-dose and both C_{max} and AUC_{inf} were dose proportional. The 90% CI for the ratio of dose-normalized geometric means ranged from 0.514 to 1.02 for C_{max} and 0.65 to 1.4 for AUC_{inf}.

All reported treatment–emergent adverse events (AEs) that were related to treatment were mild, with the most frequent AEs reported as a mild cough and throat irritation. No dose-limiting toxicities were observed and no SAEs were reported. 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 was generally well tolerated at all dose levels evaluated in the study. No notable or significant findings were reported with vital signs, physical examinations and laboratory evaluations.

LIQ861: Rapid Systemic Uptake



	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 (all other values are mean)
b. One subject in the 50 mcg cohort withdrew consent for further PK blood draws after 10 min (data not included)

LIQ861: No SAEs; only mild AEs

Related Adverse Events (AEs) by Treatment Group				
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 Flush	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"

Methods: Phase 1 Ascending Single Dose Escalation Study Trial Design

Successive gender-balanced cohorts of 8 healthy volunteers were randomly assigned to active (n=6) or placebo (n=2). Dosing was initiated at a dose level of 25 mcg Tre. Additional cohorts of 8 subjects were enrolled to investigate escalating single doses of LIQ861 at 50, 75, 100, 125, and 150 mcg Tre. PK samples and safety assessments were performed approximately 1 h before dosing and at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, and 210 min and 4, 6, and 8 h post-dose. A Safety Review Committee was consulted after each cohort to review safety findings and interim PK results. Tre PK parameters and dose proportionality were characterized.

	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	4

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 all treatment related AEs were mild in severity.**
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 & References

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PRINT Technology: http://liquidia.com/print-technology/