Poster 50

Pharmacokinetic (PK) performance of LIQ861 and evaluation of comparative bioavailability with Tyvaso® in healthy subjects (Study LTI-102)

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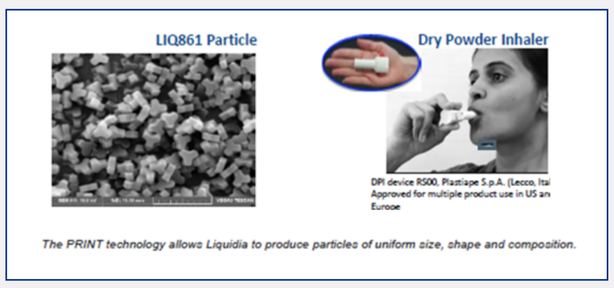
BACKGROUND

- LIQ861 is an inhaled, dry-powder formulation of treprostinil produced using PRINT® (Particle Replication in Nonwetting Templates) technology, a proprietary process that allows the design and manufacture of highly uniform drug particles.
- The trefoil shape of particles in the LIQ861 formulation of treprostinil was selected based on its highly aerodynamic properties that support deep lung delivery.
- Enhanced lung deposition achieves higher tolerated dose levels than current inhaled therapies with 4 times daily (QID) delivery of treprostinil doses in 1 to 2 breaths using the RS00 Model 8 Device (Plastiape S.p.A. Osgnago IT), a convenient, disposable dry-powder inhaler (DPI) **(Figure 1)**.

Figure 1. LIQ861 particles and dry-powder inhaler



- Liquidia is pursuing approval of LIQ861 for the treatment of pulmonary arterial hypertension via the 505(b)(2) pathway.
- A phase 1, placebo-controlled, double-blind, randomized, single-center study (LTI-101) evaluated the ascending single-dose pharmacokinetics (PK) of LIQ861 in healthy subjects.[1]
  - Following single-dose administration, treprostinil exposure from LIQ861 increased proportionally across the dose range studied.
  - All doses of LIQ861 were generally well tolerated with no deaths, serious adverse events (SAEs), or dose-limiting toxicities reported.
  - The most frequently reported treatment-emergent adverse events (TEAEs) related to study drug administration were coughing and throat irritation, which are known side effects of treprostinil inhalation solution.
- Results suggest that patients may tolerate higher inhaled doses of treprostinil when delivered as a PRINT dry powder at doses above 150 µg of LIQ861, which represent treprostinil plasma levels greater than 84 µg, the maximum tolerated dose for Tyvaso®.

OBJECTIVES

- The primary objective of the current study LTI-102 was to determine the comparative bioavailability of Liquidia Technologies inhaled treprostinil particles developed with their proprietary PRINT technology and delivered with the Plastiape RS00 Model 8 dry powder inhaler (DPI) device, comparing a 79.5-µg capsule dose of LIQ861 (approximate delivered dose 56.6 µg trepostinil) to 9 breaths of Tyvaso® (approximate delivered dose 54 µg treprostinil).
- A secondary objective was to evaluate the safety of LIQ861 in healthy male and female subjects.

METHODS

- This was an open-label, crossover study that enrolled healthy subjects 18 to 45 years of age inclusive.
- Subjects were randomized to 1 of 3 treatment sequences (LIQ861/LIQ861, Tyvaso®/LIQ861, and LIQ861/Tyvaso®) with each sequence consisting of 2 periods **(Table 1)**:

Table 1. Treatment sequence and time period for administration of LIQ861 and Tyvaso®

	Time Period	
Treatment Sequence	**Period 1—Day 1**	**Period 2—Day 2**
Sequence 1 (n=16)	Treatment A	Treatment A
Sequence 2 (n=4)	Treatment A	Treatment B
Sequence 3 (n=4)	Treatment B	Treatment A

Treatment A: a single capsule dose of 79.5 µg LIQ861 administered in 2 breaths using the RS00 Model 8 (Plastiape S.p.A. Osgnago IT) DPI Device.
Treatment B: 9 breaths (54 µg) of Tyvaso® administered using the Tyvaso Inhalation System.

- Sequence 1 assessed the reproducibility of LIQ861 dosing 79.5 µg capsule dose (approximate delivered dose 56.6 µg trepostinil) and systemic levels of treprostinil.
  - LIQ861 was administered in 2 breaths using the RS00 Model 8 Dry Powder Inhaler.
- Sequences 2 and 3 evaluated the rate and extent of treprostinil exposure following administration of LIQ861 79.5 µg capsule dose (approximate delivered dose 56.6 µg trepostinil) compared with 9 breaths (approximately 54 µg) of Tyvaso®.
  - Tyvaso® was administered in 9 breaths using the TD-300 Tyvaso Inhalation System.[2,3]
- Each period and dose of LIQ861 and Tyvaso® were separated by at least 24 hours.

DEMOGRAPHICS

- Demographic and clinical characteristics of subjects were similar between treatment groups **(Table 2)**.

Table 2. Demographic characteristics at screening

Characteristic	Sequence 1 (n=16)	Sequence 2 and 3 (n=8)
Age, years		
• Mean (SD)	32.8 (4.6)	30.2 (8.3)
• Min, max	24, 43	20, 44
Sex, n (%)		
• Female	6 (37.5)	4 (50.0)
• Male	10 (62.5)	4 (50.0)

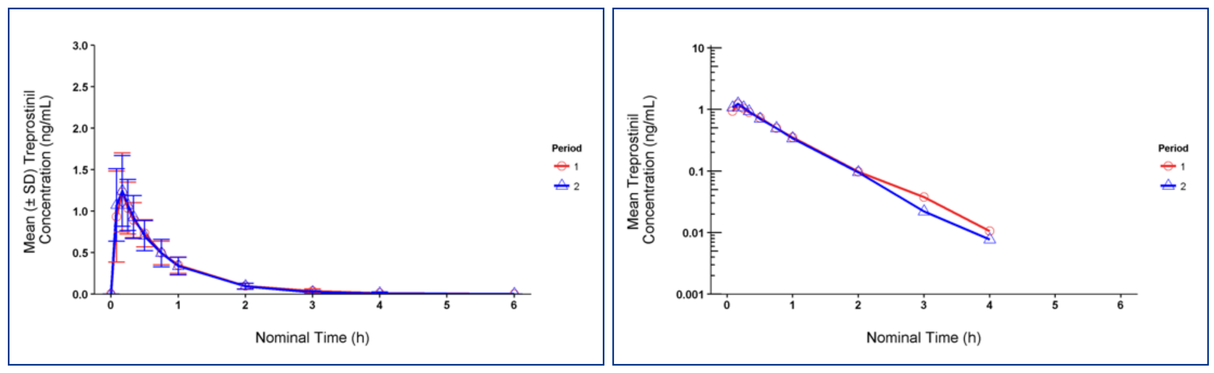
Max, maximum; min, minimum; SD, standard deviation.

PHARMACOKINETIC RESULTS

SEQUENCE 1

- During Sequence 1 (a 2-period replicate for LIQ861), the PK parameters between the 2 periods were nearly identical with low variability **(Figure 2)**.
- C_{max}, mean AUC_{inf}, and the median time to C_{max} (T_{max}) of a single dose of 79.5 µg LIQ861 were 1.25 ng/ml, 1.01hr•ng/ml, and 0.17 hours, respectively.

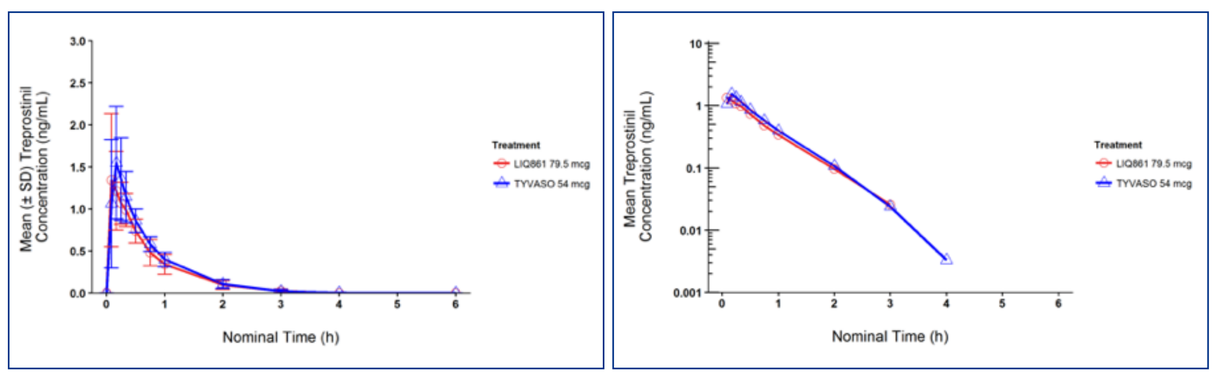
Figure 2. Mean plasma treprostinil concentration time plots overlaid by period for Sequence 1 (linear and semi-log)



SEQUENCES 2 and 3

- In the crossover sequence 2 and 3, in the 8 patients receiving a single dose of each treatment, the absorption rate was comparable between LIQ861 and Tyvaso® with peak concentrations achieved at approximately 0.13 and 0.17 hours (median T_{max}) post inhalation for LIQ861 and Tyvaso®, respectively.
- Following peak concentrations, mean plasma concentrations of treprostinil decreased in a monophasic manner with similar rate of elimination for both treatments (approximate mean half-life of 0.5 hours for LIQ861 and Tyvaso®) **(Figure 3)**.

Figure 3. Mean plasma treprostinil concentration time plots overlaid by treatment for Sequences 2 and 3



COMPARATIVE BIOAVAILABILITY

- During Sequences 2 and 3 (LIQ861 and Tyvaso® crossover to determine the comparative bioavailability of treprostinil), the geometric mean ratios (LIQ861/Tyvaso®) were 0.923, 0.947, and 0.931 for AUC_{inf}, AUC_{last}, and C_{max}, respectively, and the 90% CIs for these ratios were within the acceptable equivalence limits of 0.80 to 1.25 **(Table 3)**.

Table 3. Summary of statistical assessment of comparative bioavailability results

Agent	Parameter	GMR	90% CI	Within Subject % CV
LIQ861 79.5 µg vs Tyvaso® 54 µg	AUC_{inf}	0.923	0.802, 1.064	14.6
LIQ861 79.5 µg vs Tyvaso® 54 µg	AUC_{last}	0.947	0.812, 1.103	15.8
LIQ861 79.5 µg vs Tyvaso® 54 µg	C_{max}	0.931	0.819, 1.059	13.3

CI, confidence interval; CV, coefficient of variation; GMR, geometric least-squares mean ratio.

SAFETY AND TOLERABILITY

- Overall, administration of LIQ861 and Tyvaso® was well tolerated, with minimal differences between the 2 treatments.
- There were no deaths or SAEs and only one subject withdrawal from the study due to TEAEs.
- All TEAEs were expected based on the known safety profile of inhaled treprostinil.
- The most commonly reported were cough and nausea.

CONCLUSIONS

The assessment of the comparative bioavailability of LIQ861 and Tyvaso® demonstrated that treprostinil exposure from a single capsule dose of 79.5 µg LIQ861 (approximate delivered dose 56.6 µg trepostinil) was comparable to 9 breaths of Tyvaso® (approximately 54 µg dose). These results confirm that LIQ861 and Tyvaso® have comparable treprostinil systemic exposures. LIQ861 and Tyvaso® were generally well tolerated in this study, with no deaths, SAEs, or dose-limiting toxicities. All TEAEs associated with LIQ861and Tyvaso® were mild and consistent with known prostanoid effects.

References

1. Royal M, Roscigno R, Vaughn T, Anderson S, Wargin WW, Williams RL, et al. Preclinical and phase 1 clinical characterization of LIQ861, a new dry powder formulation of treprostinil. Poster presented at: 6th World Symposium on Pulmonary Hypertension; February 2018; Nice, France.
2. United Therapeutics Corporation. Tyvaso (package insert). North Carolina: United Therapeutics Corporation, 2017.
3. United Therapeutics Corporation. TD-300 Tyvaso Inhalation System. North Carolina: United Therapeutics Corporation, 2018.