Nonclinical, *In-silico*, and Clinical Evaluation of LIQ861 Inhalation Powder Deposition and Pharmacokinetics

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INTRODUCTION

Inhaled prostacyclin (PGI) therapies offer significant important clinical benefits to patients with Pulmonary Arterial Hypertension (PAH), compared to other PGI delivery routes. Current approved PGI inhaled therapies are delivered using nebulization, which can present a treatment burden on patients. For instance, Tyvaso® (treprostinil inhalation solution, United Therapeutics, Silver Spring, MD) uses a pulsed, ultrasonic nebulizer delivering approximately 6 mcg of treprostinil per breath, with a target maintenance dose of nine breaths (54 mcg of treprostinil), four times daily. Furthermore, this product requires dose preparation and daily cleaning of the nebulizer [1]. To address some of these shortcomings, Liquidia Technologies (Research Triangle Park, USA) is developing LIQ861, an inhaled, dry-powder formulation which is currently in Phase 3 development [2]. LIQ861 is designed for efficient, deep-lung delivery using a convenient, disposable dry powder inhaler (DPI), for delivery of treprostinil doses in 1–2 breaths, four times daily. The pharmacokinetic data (PK) and lung deposition of LIQ861 inhalation powder in nonclinical, *in silico*, and clinical studies are presented in this study.

METHODS

Bulk LIQ861 inhalation powder particles were prepared using PRINT technology, a proprietary manufacturing process that uses mold templates to produce monodisperse, shape specific particles. Specific details of the PRINT manufacturing process for inhaled products can be found elsewhere [3]. Primary particles of LIQ861 are approximately 1 micron in diameter trefoil geometry, and composed of approximately 0.5% treprostinil blended in a soluble, trehalose-based formulation.

In silico simulation of the lung deposition of LIQ861 was performed using the Functional Respiratory Imaging (FRI) by FLUIDDA (Kontich, Belgium). FRI is an *in silico* technique based on patient-specific 3-D airway geometry extracted from computed tomography (CT)

scans; inhalation profile and inhaler characteristics; and Computational Fluid Dynamics (CFD) simulations to model lung deposition. In this study, CT scans of 10 healthy subjects were selected from the FLUIDDA database. For LIQ861 modeling, a representative dose of 75 mcg with the following characteristics was used as input to the simulation: capsule fill weight, 15 mg; mass median aerodynamic diameter (MMAD), 2.1 microns; geometric standard deviation (GSD), 1.6; delivered dose (DD): 55.3 mcg; fine particle fraction (FPF): 85.7% of DD; respirable dose (RD): 47.39 mcg.

The *in vivo* PK of treprostinil when administered as bulk LIQ861 inhalation powder to rats and dogs were compared to a nebulized treprostinil solution designed to be of similar composition to Tyvaso. The study design and nonclinical pharmacokinetic parameters of LIQ861 and inhaled treprostinil solution in are summarized in Table 1.

Table 1.

Nonclinical pharmacokinetic parameters of LIQ861 and nebulized treprostinil

	Dose group	n	Delivered Dose (ug/kg)	Cmax (ng/mL)	AUCinf (hr*ng/mL)	F_{rel}
Beagle (single dose)	Tre solution	4	3.55	4.0	3.64	—
	LIQ861	4	3.25	3.1	3.02	0.90
Rat (single dose)	Tre solution	6	78.5	16.4	62.1	—
	LIQ861	6	27.3	6.28	25.8	1.2
	LIQ861	6	76.2	43.6	130	2.2
	LIQ861	6	150	44.3	165	1.4
Rat (14-day)	Tre solution	6	161	52.6	197	—
	LIQ861	6	16.2	8.25	27.2	1.4
	LIQ861	6	42.8	24.5	86.0	1.6
	LIQ861	6	128	50.9	213	1.4

The ascending single-dose PK of LIQ861 were evaluated in a Phase 1 placebo-controlled, double-blinded, randomized study in 56 healthy subjects (LTI-101) [4]. Six escalating doses (25, 50, 75, 100, 125, and 150 mcg) were studied. Blood samples were collected for pharmacokinetic analysis, and individual treprostinil PK parameters were calculated using Phoenix® WinNonlin® v6.3 (Certara, Princeton, NJ) and summarized with descriptive statistics.

RESULTS

The i*n vivo* treprostinil PK profiles in rats and dogs were similar whether treprostinil was delivered as bulk LIQ861 inhalation powder or as treprostinil solution. The relative bioavailability (F_{rel}) of treprostinil administered as bulk LIQ861 inhalation powder compared with nebulized treprostinil solution, based on dose-corrected AUC, ranged between 0.8 and 2.2 for all LIQ861 groups studied, demonstrating generally similar treprostinil PK profiles for the two formulations.

In silico modeling using FRI further characterized the deposition of LIQ861 particles in the respiratory tract of healthy human subjects. Using realistic airway models derived from healthy

volunteers, the simulations indicate high intrathoracic deposition of LIQ861. Figure 1 shows simulated deposition of LIQ861 in the oropharynx, trachea, central lung, and peripheral lung. This modeling data supports that LIQ861 provides targeted delivery of treprostinil to the deep lung, as expected for an efficient inhaled treatment for PAH.

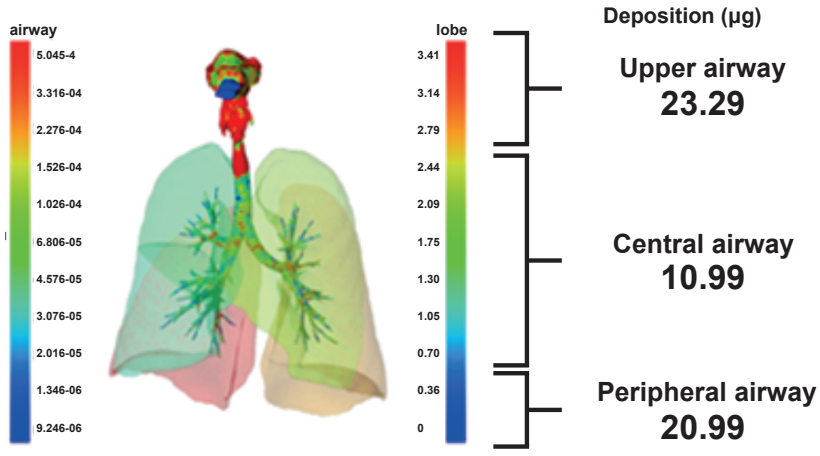

Figure 1. Simulated intrathoracic deposition of LIQ861 inhalation powder.

Human LIQ861 clinical pharmacokinetic data indicates the DPI formulation has similar PK parameters and profiles to published data on nebulized treprostinil. Absorption of treprostinil from LIQ861 was rapid, with median Tmax ranging from 0.18 to 0.31 hours across all dose levels. Geometric means for Cmax ranged from 0.311 ng/mL to 1.25 ng/mL across the dose cohorts. Geometric means for AUCinf ranged from 0.275 h*ng/mL in Cohort 1 (25 mcg) to 1.36 h*ng/mL in Cohort 6 (150 mcg) [4]. When the target delivered dose of treprostinil is considered, these PK parameters are similar to published Cmax and AUC values for delivered doses of 18 to 90 mcg from the Tyvaso nebulizer [5].

CONCLUSIONS

This work characterizes the PK and lung deposition of LIQ861 inhalation powder. CFD simulations suggest high intrathoracic and peripheral lung deposition of LIQ861. Furthermore, nonclinical and clinical data suggest that similar PK exposures between LIQ861 and Tyvaso inhalation solution may be expected, despite differences in device design, formulation, dosing and administration. LIQ861 inhalation powder, delivered via a DPI in one to two breaths provides for a simpler, convenient, and efficient method for inhaled delivery of treprostinil.

CONFLICTS OF INTEREST

SA, TV, PB, RR, and BWM are employees of Liquidia Technologies. CH, CM, and BM are employees of FLUIDDA, Inc.

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REFERENCES

1. Tyvaso Prescribing Information.

2. Hill NS *et al.*: INSPIRE: A Phase 3 Open-Label, Multicenter Study to Evaluate the Safety and Tolerability of LIQ861 in Pulmonary Arterial Hypertension (PAH) [presentation]. In *ISHLT 39th Annual Meeting & Scientific Sessions*. 2019, Apr 3. Orlando, FL.

3. Maynor BW: 21st Century Particle Engineering: Particle Design, Manufacture and Scale-up of PRINT(R) Technology. *Respiratory Drug Delivery 2018*. 2018, Volume 1: 211–220.

4. Royal M, Roscigno R *et al.*: Preclinical and Phase 1 Clinical Characterization of LIQ861, a New Dry Powder Formulation of Treprostinil [poster]. In: *World Symposium on Pulmonary Hypertension*. 2018, February 27–March 1. Nice, France.

5. Kumar P, Thudium E, Laliberte K, Zaccardelli D, Nelsen A: A comprehensive review of treprostinil pharmacokinetics via four routes of administration. *Clinical Pharmacokinetics* 2016, 55: 1495–1505.