Nonclinical, In Silico, and Clinical Evaluation of LIQ861 Inhalation Powder Deposition and Pharmacokinetics

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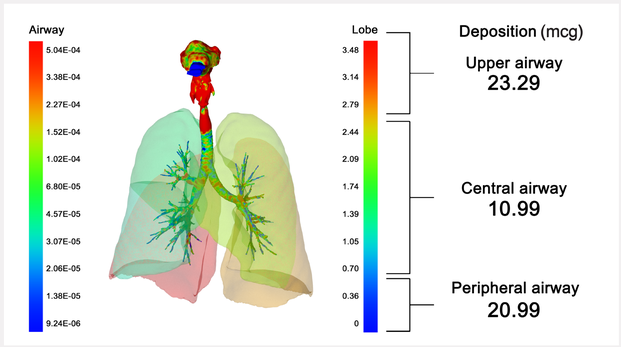
INTRODUCTION

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) uses a pulsed, ultrasonic nebulizer delivering approximately 6 mcg of treprostinil per breath, with a target maintenance dose of 9 breaths (54 mcg of treprostinil), 4 times daily. Furthermore, this product requires dose preparation and daily cleaning of the nebulizer.[1] To address some of these shortcomings, Liquidia Technologies is developing LIQ861, an inhaled, dry-powder formulation which is currently under NDA review.[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, 4 times daily. The pharmacokinetic (PK) data and lung deposition of LIQ861 inhalation powder in nonclinical, in silico, and clinical evaluations are presented in this study.

METHODS AND RESULTS

Bulk LIQ861 inhalation powder particles were prepared using PRINT® technology.[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 functional respiratory imaging (FRI) by FLUIDDA. 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; and 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 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]

Simulated lung deposition of LIQ861 inhalation powder



In vivo PK of LIQ861 and bioavailability comparison to nebulized treprostinil (Tre)

	Dose group	n	DD (mcg/kg)	C_{max} (ng/mL)	AUC_{inf} (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

Human PK of LIQ861 provide similar exposure to Tyvaso® Inhalation Solution

Human LIQ861 clinical pharmacokinetic data[4] indicate the DPI formulation has similar PK parameters and profiles to published data on nebulized treprostinil. Absorption of treprostinil from LIQ861 was rapid, with C_{max} and AUC_{inf} similar to published PK parameters for Tyvaso®,[5] when the target delivered dose of treprostinil is taken into account. In a recent open-label, crossover study in healthy subjects (LTI-102), comparable treprostinil systemic exposures were observed between LIQ861 and Tyvaso®.[6]

CONCLUSIONS

This work characterizes the PK and lung deposition of LIQ861 inhalation powder. Computational fluid dynamic 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 1 to 2 breaths, provides for a simpler and more convenient and efficient method for inhaled delivery of treprostinil.

Conflicts of interest: BWM, SA, TV, PB, and RR are employees of Liquidia Technologies. CV, CM, and BM are employees of FLUIDDA, NV.

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