Research Article

Pulmonary Circulation

Pharmacokinetics and tolerability of LIQ861, a novel dry-powder formulation of treprostinil

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Abstract

A dry-powder inhaled formulation of treprostinil (LIQ861) produced using PRINT® technology offers a substantial advantage over current nebulized therapy. Treprostinil is a synthetic prostacyclin analogue that is currently approved for inhalation administration to patients with pulmonary arterial hypertension via nebulized Tyvaso® inhalation solution. LTI-101 was a phase 1, placebo-controlled, double-blind, randomized, single-center study that evaluated the ascending single-dose pharmacokinetics of LIQ861 in healthy subjects. Six sequential, escalating doses (25, 50, 75, 100, 125, and 150 mcg) were studied to investigate treprostinil exposure from LIQ861 inhalation. Subjects ($n = 57$) were randomly assigned in a 3:1 ratio to receive a single dose of either LIQ861 ($n = 43$) or placebo ($n = 14$); 56 subjects completed all protocol-defined assessments. Following single-dose administration, treprostinil exposure from LIQ861 increased proportionally across the dose range studied, and the pharmacokinetics profile of treprostinil administered as LIQ861 was similar to prior reports of inhaled treprostinil. All doses of LIQ861 were generally well-tolerated with no deaths, serious adverse events, or dose-limiting toxicities. The most frequently reported treatment-emergent adverse events related to study drug administration were coughing and throat irritation, which are common to dry-powder formulations. Treatment-related treatment-emergent adverse events were reported more frequently at higher dose levels; however, all were assessed as mild in severity. We conclude that the pharmacokinetics profile of treprostinil using a dry-powder inhaled formulation increased in proportion to dose as anticipated and was similar to earlier reports of inhaled, nebulized treprostinil (Tyvaso®). Based on these results, a phase 3 study (INSPIRE; Clinicaltrials.gov Identifier NCT03399604) evaluating the long-term safety and tolerability of LIQ861 in patients with pulmonary arterial hypertension was initiated.

Keywords

inhaled prostacyclin, pharmacokinetics, pulmonary arterial hypertension

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Introduction

The current management of pulmonary arterial hypertension (PAH) relies on targeted therapies to address the pathophysiologic abnormalities that damage the pulmonary vasculature and result in elevated pulmonary artery pressures, dyspnea, diminished exercise capacity, right heart failure, and, ultimately, death.[1–3] The synthesis and release of prostacyclin are impaired in PAH,[4,5] and the prostacyclin (prostaglandin I2 (PGI_2)) pathway is a critical therapeutic target in the disease.[6–8] Prostacyclin therapy provokes vasodilation and also has anti-proliferative, anti-thrombotic, and anti-inflammatory effects.[2,3,9]

Despite offering significant clinical benefits to patients with PAH, PGI_2 therapies are underutilized in clinical practice,[10–12] with only 34.1% of patients enrolled in the REVEAL Registry™ (**R**egistry to **Ev**aluate **E**arly **A**nd **L**ong-term PAH Disease Management) treated with a prostacyclin analogue.[13] Lower rates of prostacyclin therapy are

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attributed, in part, to the complexities of dose up-titration coupled with challenges associated with diverse routes of administration.[6,7] PGI_2 therapies, currently approved for use in the United States, can be delivered by intravenous (IV), subcutaneous (SC),[14,15] inhaled,[16,17] and oral routes.[18,19] IV and SC therapies place patients at increased risk of catheter occlusion, thrombosis, thromboembolism, infections, sepsis, and infusion site pain.[7,12,14,20–27]

Dosing errors due to variations in breathing patterns and the inability to up-titrate, as well as the number, frequency, and duration of inhalations, are limitations of currently-available inhaled prostacyclin therapies.[7,22,28,29] Oral prostacyclins are associated with systemic side effects that may prompt treatment noncompliance or discontinuation.[7,26,30] Novel drugs that target the PGI_2 pathway and overcome the recognized limitations of the IV, SC, inhaled, and oral routes are needed to ensure that patients with PAH obtain the clinical benefits of prostacyclin therapy while reducing the risk of serious, dose-limiting, and systemic side effects.

LIQ861 is an investigational, inhaled, dry-powder formulation of treprostinil designed using Liquidia's PRINT® technology (Particle Replication in Nonwetting Templates), aiming to enhance deep-lung delivery using a convenient, palm-sized dry-powder inhaler (DPI), the Plastiape RS00 Model 8 Device, for the treatment of PAH (Fig. 1). PRINT® is a proprietary particle engineering platform that enables precise production of highly uniform drug particles with independent control over their size, shape, and chemical composition. Through this approach, PRINT® enables the development of drug particles that are engineered for optimal deposition in the lung following oral inhalation (Fig. 1).[31–33] LIQ861 has the potential to overcome the limitations of current inhaled therapies and to maximize the therapeutic benefits of treprostinil for the treatment of PAH by safely delivering high doses into the lungs in one to two breaths. LTI-101 was a phase 1, placebo-controlled, double-blind, randomized, single-center, first-in-human study to evaluate the ascending single-dose pharmacokinetics (PK) of LIQ861 in healthy subjects.

Methods

Study design

This was a phase 1, placebo-controlled, double-blind, randomized, single-center study that evaluated the ascending single-dose PK of LIQ861 in healthy male and female subjects. Six sequential, escalating dose levels (25, 50, 75, 100, 125, and 150 mcg capsule strength) were investigated.

Subjects were screened within the 28 days (Days –28 to –1) prior to admission to the clinical research unit (CRU; PPD Development, Austin, TX) on Day 0 (the day prior to dosing) for baseline assessments. On Day 1, following the pre-dose collection of blood for PK, subjects were randomized in a 3:1, active-to-placebo ratio to receive a single dose of either LIQ861 or placebo at time zero. Placebo capsules contained a nearly identical preparation of excipient matrix compared with active LIQ861, with an equivalent mass of trehalose (the most abundant excipient) instead of treprostinil. In vitro aerosol performance testing was performed in accordance with General Chapter: <601> USP-29-NF-24, "Aerosol, Nasal Sprays, Metered Dose Inhalers and Dry Powder Inhalers" with a fine particle fraction of approximately 86% of emitted dose.[34]

All inhalations were conducted using the Plastiape RS00 Model 8 DPI and 2 inhalation breaths per capsule. Inhalations were made in immediate succession to minimize the amount of time needed to administer the complete dose. Variations in breathing patterns and skills were minimized by providing all subjects with in-depth training on the use of the device. An additional cohort of subjects at the 150-mcg dose was investigated due to capsule seating interference in the DPI device that occurred during drug administration for approximately half of the subjects in the original cohort. This cohort was repeated while the study remained blinded. Treatment administration by dose cohort is shown in Table 1.

Subjects remained in the CRU from admission (Day 0) until discharge by the Investigator on the day after dosing (Day 2). Subjects returned to the CRU approximately two

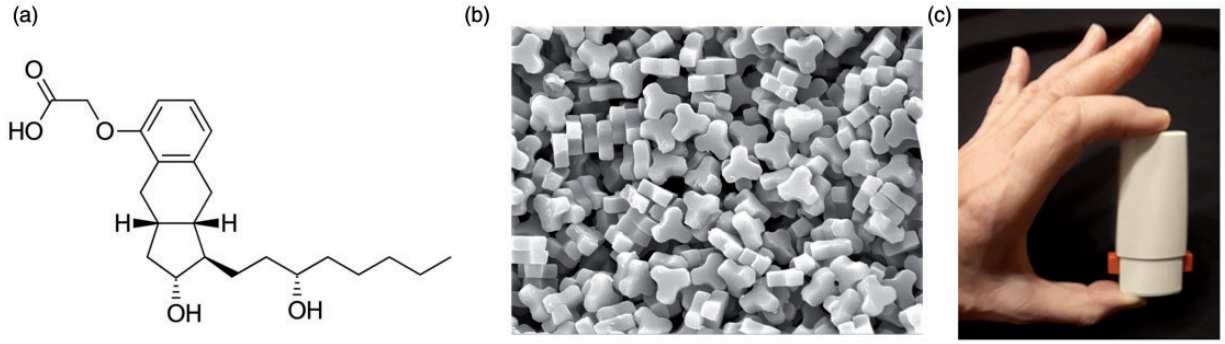

Fig. 1. LIQ861 particles and dry-powder inhaler.

Table 1. Treatment administration by cohort.

		LIQ861			Placebo		
Cohort	Treprostinil dose, mcg	Capsules administered, # × mcg	Powder weight, mg	*n*	Capsules administered, # × mcg	Powder weight, mg	*n*
1	25	1 × 25	5	6	1 × 0	15	2
2	50	1 × 50	10	7	1 × 0	15	2
3	75	1 × 75	15	6	1 × 0	15	2
4	100	2 × 50	20	6	2 × 0	30	2
5	125	1 × 75 + 1 × 50	25	6	2 × 0	30	2
6	150	2 × 75	30	12	2 × 0	30	4

mcg: micrograms; *n*: number of subjects.

days after discharge (Day 4) for completion of final assessments.

Study participants

Healthy male and female volunteers between 18 and 45 years of age (inclusive), with a body mass index (BMI) of 18–32 kg/m^2, who abstained from tobacco and nicotine use for at least two months prior to screening were eligible for enrollment. Eligible subjects were instructed not to take any prescription medication for 14 days or any dietary supplements or over-the-counter drugs for at least three days prior to CRU admission through completion of the study. Subjects provided written informed consent before participating in any study procedure.

Subjects were excluded if they had a history of asthma or other respiratory condition; a history of illicit drug or alcohol abuse or positive urine drug screen; were positive for human immunodeficiency virus, hepatitis B, and/or hepatitis C; in pregnant or lactating females; had donated plasma or blood within 7 or 30 days prior to CRU admission, respectively; had participated in another investigational drug study within the 30 days prior to CRU admission; or had surgery within six months of screening.

Pharmacokinetic analysis

Approximately 4 mL of whole blood was collected for each PK sample, yielding approximately 2 mL of plasma for analysis of treprostinil concentrations. Blood samples were collected via IV catheters implanted in peripheral arm veins and stored with Vacutainer® tubes with potassium EDTA (BD #367861 or equivalent) approximately one hour before dosing and at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, and 210 min and at 4, 6, and 8 h after study drug administration.

Treprostinil plasma concentrations were measured at PPD Laboratories (Middleton, WI) using a validated ultra-performance liquid chromatography-tandem mass spectrometry bioanalytical method (Bioanalytical Method P1313).[35] The lower limit of quantification in the assay was 0.025 ng/mL and the upper limit of quantification was 10 ng/mL. Treprostinil concentrations were summarized using descriptive statistics.

Individual treprostinil PK parameters were calculated using Phoenix® WinNonlin® v6.3 (Certara, Princeton, NJ) and summarized with descriptive statistics. Plasma concentrations below the limit of quantification (BLQ) were set to zero, unless they fell between two quantifiable samples, in which case they were treated as missing. Figures were prepared using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Dose proportionality assessments were conducted with C_{max} and AUC_{inf} using the confidence interval equivalence criterion with a power model.[36] Given the exploratory nature of the study and the corresponding wide dose range with small sample sizes, a wider acceptance interval of 0.5–2.0 was applied to establish conclusion of proportionality within the tested dosing range.[37] For both parameters, the estimate for the ratio of dose-normalized geometric mean, 90% confidence intervals, maximal proportional dose range, and threshold dose ratio to reject proportionality were calculated.

Safety assessments

Safety monitoring included an evaluation of adverse events (AEs) and assessments of electrocardiograms (ECG), respiratory signs, vital signs, clinical laboratory parameters (pre-dose and through 6–8 h post-dose), physical examinations, urinalysis, and concomitant medications. In addition, subjects in the 125-mcg and 150-mcg dose cohorts (cohorts 5 and 6) underwent continuous cardiac telemetry and were monitored by Advanced Cardiac Life Support-certified staff from 30 min prior to dosing through three hours after dose administration. This extra safety precaution was implemented due to the evidence of QTc prolongation in healthy subjects after administration of maintenance and suprather-apeutic doses (54 and 84 mcg, respectively) of treprostinil (inhaled Tyvaso®).[16]

Following each dosing, and prior to each dose escalation, the Safety Review Committee (SRC), which consisted of the Principal Investigator, the Study Medical Monitor, and a

representative from the Sponsor, convened by teleconference to review safety findings and interim PK results from each cohort. Treatment assignments remained blinded during these reviews and an unanimous agreement from voting members of the SRC was required prior to proceeding with the next sequential dose cohort. Stopping criteria were also prospectively defined in the study protocol. If a severe AE or serious adverse event (SAE) was observed in ≥2 subjects within a dose cohort, the SRC was required to stop escalation of the dose levels.

Table 2. Demographic and clinical characteristics by treatment group.

Characteristic	Treatment group, *n* (%)	
	LIQ861 (*n* = 43)	Placebo (*n* = 14)
Age at screening, years	30.3 (6.7)	26.1 (5.4)
Mean (SD)	18, 44	19, 36
Min, max		
Sex, *n* (%)		
Female	21 (48.8)	7 (50.0)
Male	22 (51.2)	7 (50.0)
Race, *n* (%)		
American Indian or Alaska Native	1 (2.3)	0 (0.0)
Asian	1 (2.3)	0 (0.0)
Black or African American	13 (30.2)	4 (28.6)
White	28 (65.1)	10 (71.4)
Ethnicity, *n* (%)		
Hispanic or Latino	18 (41.9)	8 (57.1)
Not Hispanic or Latino	25 (58.1)	6 (42.9)
BMI, kg/m^2		
Mean (SD)	25.8 (3.3)	25.9 (2.8)
Min, max	19.2, 30.6	22.1, 29.7

BMI: body mass index; max: maximum; min: minimum; *n*: number of subjects; SD: standard deviation.

Results

Subject characteristics

Fifty-seven subjects were enrolled in the study, and 56 subjects completed all protocol-defined assessments. One subject in cohort 2 (50 mcg) withdrew consent from PK sample collections after the 10-min post-dose timepoint complaining of painful venipuncture and was replaced, which resulted in a total of seven subjects on active treatment in this cohort. The subject who was withdrawn consented to continued observation and safety assessments and was included in the safety population.

Demographic characteristics were well-balanced between the LIQ861 and placebo groups (Table 2). Similar proportions of male and female subjects were enrolled and subjects in both treatment groups were predominantly White. Mean age and BMI were similar in both treatment groups.

PK of LIQ861

Plasma treprostinil concentrations in subjects who received LIQ861 were quantifiable by five minutes after dosing (time of first post-dose sample collection) in all but one subject. Absorption of treprostinil was rapid, with median T_{max} ranging from 0.18 to 0.31 h across all dose levels (Table 3). Following peak concentrations, treprostinil plasma levels declined in a monophasic manner. Plasma concentrations of treprostinil were BLQ in the 25-, 50-, and 75-mcg dose cohorts by 3.5 h post-dose and in the 100-, 125-, and 150-mcg cohorts by six hours post-dose. Treprostinil plasma concentrations over time by dose are shown in Fig. 2.

Geometric means for C_{max} ranged from 0.31 to 1.25 ng/mL across the dose cohorts. Geometric means for AUC_{inf} ranged from 0.28 h*ng/mL in cohort 1 (25 mcg) to 1.36 h*ng/mL in cohort 6 (150 mcg).

Dose proportionality was assessed based on C_{max} and AUC_{inf} over the tested dose range of 25–150 mcg treprostinil administered as LIQ861. The apparent clearance (CL/F)

Table 3. Treprostinil pharmacokinetic parameters following inhalation administration of LIQ861.

Parameter	LIQ861, mcg					
	25	50	75	100	125	150
n	6	6	6	6	6	12
C_{max} (ng/mL)	0.31(0.19–0.54)	0.45 (0.12–1.03)	0.68 (0.43–1.11)	1.04(0.73–1.54)	1.08 (0.51–1.96)	1.25 (0.70–2.34)
T_{max} (h)	0.21 (0.16–0.45)	0.18 (0.08–0.42)	0.25 (0.08–0.42)	0.29 (0.17–0.50)	0.24 (0.16–0.41)	0.31 (0.08–0.47)
AUC_{last} (h*ng/mL)	0.25 (0.16–0.36)	0.31 (0.07–0.73)	0.68 (0.40–1.26)	1.16 (0.78–1.44)	1.01 (0.36–1.87)	1.32 (0.58–2.84)
AUC_{inf} (h*ng/mL)	0.28 (0.18–0.39)	0.34 (0.08–0.75)	0.72 (0.45–1.29)	1.20 (0.82–1.47)	1.04 (0.38–1.91)	1.36 (0.62–2.94)
$t_{1/2}$ (h)	0.50 (0.41–0.72)	0.42 (0.25–0.52)	0.60 (0.52–0.98)	0.70 (0.47–0.97)	0.52 (0.44–0.65)	0.64 (0.46–0.95)
CL/F (L/h)	90.9 (64.8–136.0)	149.0 (66.6–624.0)	105.0 (58.0–169.0)	83.4 (67.9–122.0)	120.0 (65.6–329.0)	110.0 (51.0–243.0)

Note: Data are geometric mean and range or median and range for T_{max}.

AUC_{inf}: area under the plasma concentration–time curve from 0 to infinity; AUC_{last}: area under the plasma concentration–time curve from time 0 to time of last measurable plasma concentration; CL/F: clearance; C_{max}: maximum plasma concentration; max: maximum; min: minimum; *n*: number of subjects; $t_{1/2}$: terminal elimination half-life; T_{max}: time to reach C_{max}

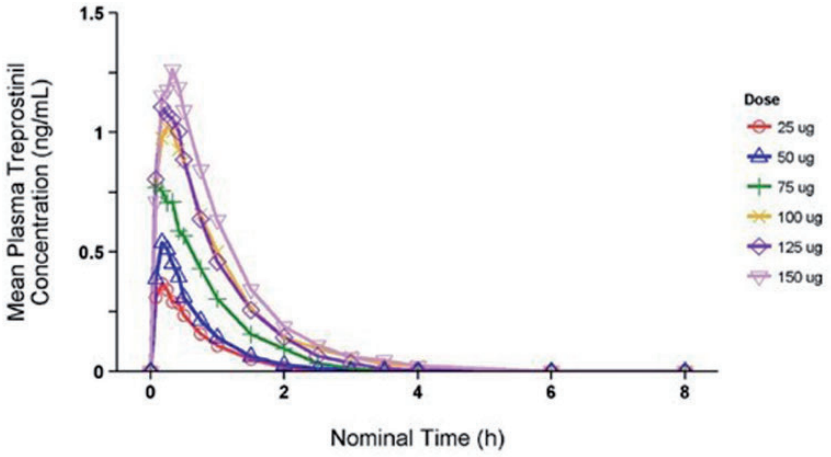

Fig. 2. Mean plasma treprostinil concentration over time.

of treprostinil was observed to be independent of administered dose (geometric means ranged from 83.4 to 149.0 L/h).

Safety and tolerability

Overall, treprostinil administered by inhalation as LIQ861 was well-tolerated by study subjects. There were no deaths, SAEs, dose-limiting toxicities, or treatment-emergent adverse events (TEAEs) that led to study withdrawal. Approximately half of the subjects who received active treatment (55.8%) experienced a TEAE compared with 14.3% on placebo (Table 4). The majority of subjects on active treatment who reported a TEAE had an event that was considered related to study treatment by the Investigator (19/24 subjects; 79.2%).

The most common TEAEs related to study drug administration were cough (25.6%) and throat irritation (20.9%) (Table 5). Painful respiration and dizziness were both experienced by 14% of subjects on active treatment. Treatment-related TEAEs were reported more frequently at higher dose levels (Table 4). All treatment-related events were reported as mild in severity. TEAEs considered unrelated to study treatment that were reported during the study were associated with vasovagal symptoms that occurred during or around the time of PK venipuncture and included presyncope ($n = 5$), dizziness ($n = 1$), feeling hot ($n = 1$), and headache ($n = 1$) in subjects who received LIQ861 and rhinorrhea ($n = 1$) and vessel puncture site pain ($n = 1$) in subjects who received placebo.

There were no clinically significant changes in laboratory parameters, vital signs, physical examination findings, or ECG parameters observed during the study in either treatment group. A slight prolongation in QTc interval, which is consistent with the known pharmacodynamic effects of treprostinil, was observed in subjects administered more than 100 mcg, but no subjects had a prolongation of more than 60 msec from baseline or a QTc interval that exceeded 450 msec.

Discussion

Study LTI-101 is the first clinical trial to evaluate the safety and PK of treprostinil administered as LIQ861, a novel dry-powder formulation, to healthy subjects. Our results showed that administration of single doses of LIQ861 resulted in rapid absorption of treprostinil (T_{max} 0.18–0.31 h) and median values for T_{max} that were consistent across the dose range. Approximately 50% of subjects in the higher dose cohorts (100, 125, and 150 mcg) continued to show measurable concentrations of treprostinil at 4 h post-dosing with all doses well-tolerated. Observed exposures of treprostinil after inhalation of LIQ861 increased proportionally with doses between 25 and 150 mcg. Mean maximum observed plasma concentration (C_{max}) and area under the plasma concentration versus time curve from time 0 (pre-dose) to infinity (AUC_{inf}) values from this study were compared with mean exposure levels reported in the published literature and in the Drug Approval Reviews from the US Food and Drug Administration for Tyvaso®.[16,38,39] Commonalities between the exposures observed in study LTI-101 and those reported for Tyvaso® were used to project a Tyvaso® transition dose for LIQ861 for patients participating in phase 3 clinical trials.

A systemic exposure was achieved with fewer inhalations than required for Tyvaso® and no unexpected safety issues, with subjects experiencing only mild, class-related AEs. LIQ861 may improve the therapeutic profile of treprostinil by enhancing deep-lung delivery and achieving higher dose levels than current inhaled therapies while overcoming some of the limitations of prostacyclin therapies delivered by the IV, SC, and oral routes.

There is a clear need for new, more convenient PAH therapies that offer sustained long-term benefits and improved safety and tolerability profiles while increasing the utilization of drugs that target the prostacyclin pathway.[40] Oral agents may overcome some of the limitations associated with IV, SC, and inhaled PGI_2 therapy. Treprostinil[18] and selexipag[19] are oral prostacyclin agonists

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