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Comparative bioavailability of inhaled treprostinil administered as LIQ861 and Tyvaso® in healthy subjects

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ABSTRACT

Introduction: Treprostinil is a synthetic prostacyclin analogue approved for inhalation administration to patients with pulmonary arterial hypertension (PAH) via nebulized Tyvaso® inhalation solution. LIQ861 is an inhaled, dry-powder formulation of treprostinil produced using Print® (Particle Replication in Nonwetting Templates) technology, a proprietary process for designing and producing highly uniform drug particles.
Methods: We conducted comparative bioavailability analyses of treprostinil exposure from LIQ861 (79.5 μg capsule [approximate delivered dose of 58.1 μg treprostinil]) compared with Tyvaso® (9 breaths [approximate delivered dose of 54 μg treprostinil]).
Results: Treprostinil exposure parameters had least squares geometric mean ratios (LIQ861: Tyvaso®) between 0.9 and 1.0 with 90% confidence intervals contained within 0.8 to 1.25. LIQ861 and Tyvaso® were both well tolerated.
Discussion: Results showed comparable bioavailability of treprostinil and similar tolerability for LIQ861 and Tyvaso® administered to healthy adults.
Conclusions: Given the comparable treprostinil bioavailability and similar safety profiles of LIQ861 and Tyvaso®, LIQ861 fulfills a significant unmet need for PAH patients by maximizing the therapeutic benefits of treprostinil by safely delivering doses to the lungs in 1 to 2 breaths using a discreet, convenient, easy-to-use inhaler.

1. Introduction

Pulmonary arterial hypertension (PAH) is a multifactorial, progressive disease associated with increased pulmonary vascular resistance and pulmonary arterial pressure causing significant morbidity and mortality. The progressive nature of PAH results in right heart failure and death in the majority of patients [1,2].

PAH impacts physical function, general health, mental health, and social functioning. A review of patient health-related quality of life (HRQoL) instruments indicated that the impact of PAH on HRQoL is comparable to chronic obstructive pulmonary disease, renal failure, spinal cord injury, interstitial lung disease, or treatment-resistant cancer [3]. There is no cure for PAH, and pharmacotherapy is geared toward disease management by relieving symptoms, increasing exercise capacity, and delaying disease progression to prolong survival.

Parenteral formulations of treprostinil are frequently used in the treatment of PAH, with these agents associated with improvements in clinical, hemodynamic, and functional outcomes [4]. Inhaled prostacyclin analogue treatments, such as treprostinil inhalation solution (Tyvaso®) or iloprost inhalation solution (Ventavis®), offer alternatives to intravenous (IV) and subcutaneous (SC) prostacyclin analogues for some patients and deliver the active ingredient to the desired location of

Abbreviations: BLQ, below the limit of quantification; BMI, body mass index; CI, confidence intervals; CRU, clinical research unit; DPI, dry powder inhaler; ECG, electrocardiogram; GMR, geometric mean ratio; HRQoL, health-related quality of life; IRB, institutional review board; IV, intravenous; PAH, pulmonary arterial hypertension..

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action. A recent pharmacokinetic study confirmed the absolute bioavailability of nebulized treprostinil at doses of 18 and 36 μg compared to IV administration of treprostinil 15 ng/kg/min over 60 min [5]. However, there are important limitations to currently approved, inhaled therapies for PAH. Dosing errors due to variations in breathing patterns and tolerance issues may limit delivery to below the target treatment dose. The number of inhalations and frequency and duration of administrations can be an inconvenience to patients [6,7]. Treprostinil inhalation solution and iloprost inhalation solution both require a significant amount of time and effort to administer each dose and/or many doses per day. This can be a challenge for patients and may contribute to suboptimal dosing, reduced treatment adherence, and/or treatment discontinuation. Additionally, the nebulizer required for administration of Tyvaso® is bulky, requires electrical charging, and must be kept with the patient to ensure its availability for dosing up to 4 times per day. Administration of each 54-mcg dose requires pre-dosing preparation of the nebulizer, and the 9 synchronized breaths required can take 2 to 3 min. The time and effort required for dosing preparation, nebulizer maintenance (cleaning and drying the mouthpiece, filter, medication cup, and water chamber), and charging may contribute to suboptimal adherence.

LIQ861 inhalation powder is comprised of the active ingredient (treprostinil) and excipients. The powder is manufactured using Liquidia's Particle Replication In Nonwetting Templates (PRINT) technology that results in a bulk powder composed entirely of engineered particles that are precise and uniform in size, shape, and composition and designed for deposition in the lungs following oral inhalation. LIQ861 inhalation powder capsules are administered by oral inhalation using the Plastiape S.p.A. (Osnago, IT) RS00 Model 8 Monodose dry-powder inhaler (DPI), with the capability of enhancing deep-lung delivery of each dose in 1 to 2 breaths. LIQ861 has the potential to overcome the limitations of current inhaled prostacyclin analogue therapies and maximize the therapeutic benefits of treprostinil for the treatment of PAH.

This paper presents the pharmacokinetic (PK) and safety results of Study LTI-102, which was conducted to compare the bioavailability of inhaled treprostinil administered as LIQ861 and Tyvaso®. Both drug products contain treprostinil, but the formulation and method of delivery differ significantly. Doses for DPIs, such as LIQ861, are described by labeled capsule strength (i.e., total capsule fill) of the active ingredient and not the output from the DPI that is available for inhalation (i.e., target delivered dose), which is less than the labeled capsule strength. Whereas, doses for inhalation solution products delivered by a nebulizer, such as Tyvaso®, are described (labeled) by delivered dose of the active ingredient, i.e., the output of treprostinil from the nebulizer and thus available for inhalation. These dosing nomenclatures are not interchangeable. Thus, the dose for LIQ861 (capsule strength 79.5 μg) in this study was chosen because it has a similar target delivered dose (58.1 μg) as the chosen Tyvaso® dose (labeled dose strength same as target delivered dose) of 54 μg.

The primary objective of this study was to assess the comparative bioavailability of a 79.5 μg capsule dose of LIQ861 (approximate delivered dose 58.1 μg) versus 9 breaths of Tyvaso® (approximate delivered dose 54 μg). A secondary objective was to evaluate the safety of LIQ861 administration.

2. Materials and methods

2.1. Study design

This study was a Phase 1, single-center, randomized, open-label, replicate (Replicate Group), and crossover (Comparative Bioavailability Groups) study in healthy adults. The study was approved by an institutional review board (IRB) prior to enrolling subjects and all study conduct was in compliance with IRB requirements.

of LIQ861 (capsule strength 79.5 μg [target delivered dose 58.1 μg]) administered using the RS00 Model 8 DPI device and Tyvaso® (labeled strength with 9 breaths for a target delivered dose of 54 μg) administered using the commercially available Tyvaso® Inhalation System Model TD-100 nebulizer. On Day 1, subjects were randomized in a 4:1:1 ratio to the Replicate Group, Comparative Bioavailability Group 1, and Comparative Bioavailability Group 2. All groups received 2 single-dose treatments. The Replicate Group received 2 treatments with LIQ861 to assess the reproducibility of treprostinil exposure. Both Comparative Bioavailability Groups received both LIQ861 and Tyvaso® (with the order of treatments differing in the 2 groups) to assess comparable bioavailability of the 2 drug products. The doses were given on consecutive days (1 treatment [dose] per day). Blood samples for measurement of treprostinil concentrations were collected before the dose and through 6 h after dose. Subjects stayed at the clinical research unit (CRU) from Day −1 (day before the first treatment) through approximately 6 h after the Day 2 treatment. Safety assessments were collected throughout the study.

2.2. Study participants

Healthy male and female subjects between 18 and 45 years of age (inclusive), with a body mass index (BMI) of 18 to 32 kg/m^2, who abstained from tobacco and nicotine use for at least 2 months prior to screening were 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 3 days prior to CRU admission through completion of the study. Subjects were informed that their participation in the study was voluntary, and 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; were pregnant or lactating females; had clinically significant medical or psychiatric history that, in the Investigator's judgment, would compromise the subject's safety or the collection of data; had donated plasma or blood within 7 or 30 days prior to CRU admission, respectively; had participated in another investigational drug study within 30 days prior to CRU admission; or had surgery within 6 months prior to screening. The In-Check DIAL™ was used to train all subjects on the proper inspiratory technique to ensure that they were able to use the device correctly.

2.3. Pharmacokinetic and safety assessments

Blood samples for measurement of plasma treprostinil concentrations were collected before the dose and at 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, and 360 min after the dose. The time windows for collecting PK samples were ± 1 min for the 5, 10, 15, and 20-min time points; ±5 min for the 30, 45, and 60-min time points; and ± 10 min for the remaining time points from 120 min through 360 min after the dose. The actual time of each blood draw was recorded.

Safety assessments included an evaluation of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory parameters.

2.4. Bioanalytical methods

Treprostinil plasma concentrations were measured using a validated, ultra-performance liquid chromatography-tandem mass spectrometry bioanalytical method, an assay using standard commercial technology. 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. Plasma concentrations

between 2 quantifiable values, in which case they were treated as missing.

2.5. Pharmacokinetic analyses

Individual treprostinil PK parameters were calculated by Nuventra using Phoenix® WinNonlin® v8.1 (Certara, Princeton, NJ), validated as per Nuventra validation VAL.001.04, and summarized with descriptive statistics. Data management and generation of the noncompartmental analysis (NCA) input file was performed using R version 3.4.0. All statistical analyses were performed using SAS® version 9.4 and SAS Studio Version 3.5. The following PK parameters were calculated using NCA: maximum observed plasma concentration (C_{max}); time to C_{max} (T_{max}); area under the plasma concentration versus time curve (AUC) from time 0 (pre-dose) to time of the last measurable non-zero plasma concentration (AUC_{last}); AUC from time 0 extrapolated to infinite time (AUC_{inf}); the percentage of the AUC extrapolated beyond the last measurable concentration (AUC_{ext}); the terminal phase elimination rate constant (λz); mean residence time (MRT); and terminal phase elimination half-life ($t½$).

2.6. Statistical methods

2.6.1. Reproducibility of Treprostinil exposure after replicate doses of LIQ861

The mean plasma concentration-time curves for treprostinil after both doses of LIQ861 in the Replicate Group were overlaid to investigate similarity. Also, the treprostinil PK parameters after both doses were examined.

2.6.2. Bioavailability

For the 8 subjects in the Comparative Bioavailability Groups, comparative bioavailability assessments were carried out for PK parameters. A linear mixed-effects model, with fixed effects for treatment (A [LIQ861] and B [Tyvaso®]), sequence (AB and BA), and period (Period 1 and Period 2) and a random effect for subjects, was used to analyze the natural log-transformed PK parameters. Differences in least squares mean C_{max} and AUC values between LIQ861 (test) and Tyvaso® (reference), and the corresponding 90% confidence intervals (CI) for the differences, were back transformed to provide least squares geometric mean ratios (GMRs). In addition, the overall within-subject coefficient of variation (WCV) was calculated.

2.6.3. Safety analyses

Safety data were summarized by treatment using descriptive statistics for continuous data and counts for categorical data. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

3. Results

Twenty-three of 24 subjects completed the study. One subject in the Replicate Group discontinued following the first treatment with LIQ861 because of TEAEs (hyperhidrosis, dyspnea, nausea, and vomiting); this subject did not receive the second treatment with LIQ861.

In the Replicate Group, 10 of 16 (62.5%) of subjects were male and 6 of 16 (37.5%) were female. Half of the subjects were Black (50.0%), 7 subjects (43.8%) were White, and 1 subject (6.2%) was Other. Most subjects were not of Hispanic or Latino ethnic origin (68.8%). The mean age at screening was 32.8 (± 4.6) years, mean BMI was 26.3 (± 2.9) kg/m^2, and mean weight was 77.7 (± 11.6) kg.

In the Comparative Bioavailability Groups, 4 of 8 (50.0%) of subjects were male and the remaining subjects (50.0%) were female. Most subjects were Black (75.0%), 1 subject (12.5%) was White, and 1 subject (12.5%) was Other. Most subjects were not of Hispanic or Latino ethnic mean BMI was 26.2 (± 2.40) kg/m^2, and mean weight was 73.2 (± 6.62) kg.

3.1. Pharmacokinetic results

For subjects in the Replicate Group, similar treprostinil PK parameters and overlapping mean plasma treprostinil concentration-time profiles for replicate LIQ861 treatments suggest treprostinil exposure was reproducible across doses (Table 1 and Fig. 1).

In the Comparative Bioavailability Groups, treprostinil absorption was rapid after LIQ861 and Tyvaso® administration with median T_{max} values of approximately 0.13- and 0.17-h post-inhalation for LIQ861 and Tyvaso®, respectively. After C_{max} was achieved, mean plasma concentrations of treprostinil decreased in a monophasic manner with similar rates of elimination for both treatments (approximate mean half-lives of 0.5 h) (Fig. 2). Also, treprostinil PK parameters after LIQ861 administration were similar to those after Tyvaso® administration (Table 1).

Comparative bioavailability assessments of C_{max} and AUC values are summarized in Table 2. The LS GMRs (LIQ861/Tyvaso®) and corresponding 90% CIs for AUC_{inf}, AUC_{last}, and C_{max} were 0.923 (0.802 to 1.064), 0.947 (0.812 to 1.103), and 0.931 (0.819 to 1.059), respectively. WCVs for AUC_{inf}, AUC_{last}, and C_{max} after LIQ861 administration were 14.6%, 15.8%, and 13.3%, respectively.

3.2. Safety results

Overall, both LIQ861 and Tyvaso® were well tolerated. Eighteen (75.0%) subjects (N = 24 across the study) experienced 1 or more TEAEs. Common TEAEs (cough [50.0% subjects], throat irritation [45.8%], nausea [16.7%], and headache [16.7%]) were expected based on the known safety profile of inhaled treprostinil. The most common TEAE was cough which was reported in 12 (50.0%) of 24 subjects. Most TEAEs were mild, 2 (8.3%) of 24 subjects reported moderate TEAEs, and

Table 1
Treprostinil PK Parameters in Study LTI-102 (Replicate Group and Comparative Bioavailability Group).

Treatment	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)
Replicate Group					
LIQ861 Dose 1 (n = 16)	1.25 (0.505)	0.17 (0.10, 0.57)	0.975 (0.198)	1.01 (0.198)	0.647 (0.142)
LIQ861 Dose 2 (n = 15)	1.28 (0.378)	0.17 (0.08, 0.50)	0.950 (0.216)	0.995 (0.209)	0.610 (0.164)
Comparative Bioavailability Groups					
LIQ861 (n = 8)	1.48 (0.668)	0.13 (0.08, 0.33)	1.01 (0.0926)	1.04 (0.102)	0.546 (0.117)
Tyvaso® (n = 8)	1.60 (0.722)	0.17 (0.13, 0.25)	1.09 (0.217)	1.14 (0.198)	0.520 (0.0925)

AUC_{inf} = area under the plasma concentration versus time curve from time 0 extrapolated to infinite time;
AUC_{last} = AUC from time 0 to time of the last measurable non-zero plasma concentration; C_{max} = maximum observed plasma concentration; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = half-life; T_{max} = time to C_{max}.
Data are from the 16 subjects in the Replicate Group who took single doses of LIQ861 on 2 occasions (except for one subject who did not take the second dose) and the 8 subjects in the Comparative Bioavailability Groups who took one dose of LIQ861 and one dose of Tyvaso®. There were 4 subjects in each of the 2 Comparative Bioavailability Groups who took the 2 treatments in the opposite order.
Data are mean (SD) for all parameters except for T_{max} which is median (mini-

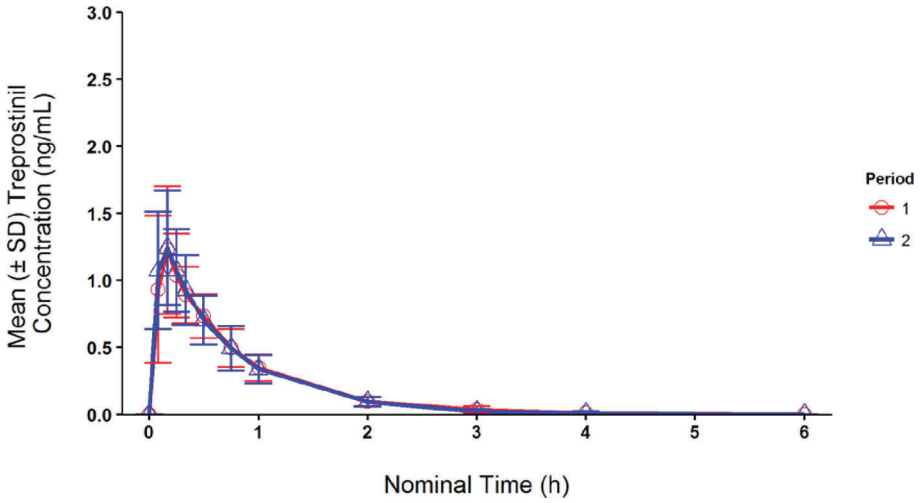

Fig. 1. Mean Plasma Treprostinil Concentration-Time Curves for the LIQ861 Doses in the Replicate Group.

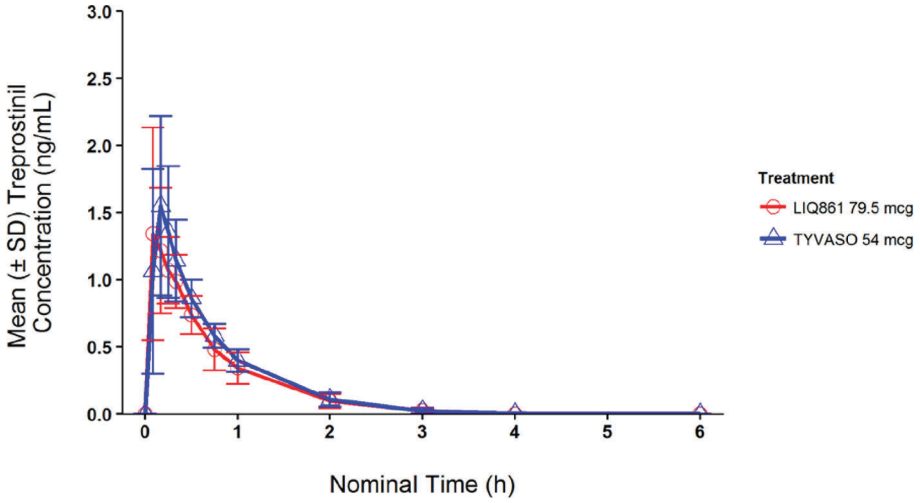

Fig. 2. Mean Plasma Treprostinil Concentration-Time Curves After Administration of LIQ861 and Tyvaso® (Comparative Bioavailability Groups).

Table 2
Comparative Bioavailability Results.

Treprostinil PK Parameter	LS GMR	
	Point Estimate	90% CI
AUC_{inf}	0.923	(0.802, 1.064)
AUC_{last}	0.947	(0.812, 1.103)
C_{max}	0.931	(0.819, 1.059)

AUC_{inf} = area under the plasma concentration versus time curve from time 0 extrapolated to infinite time;
$AUCl_{ast}$ = AUC from time 0 to time of the last measurable non-zero plasma concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; LS GMR = Least Squares Geometric Mean Ratio LIQ861 (79.5 μg): Tyvaso® (54 μg); PK = pharmacokinetic.
Data are from the 8 subjects in the Comparative Bioavailability Groups.

no subject reported a severe TEAE.

In the Comparative Bioavailability Groups, in which both LIQ861 and Tyvaso® were administered to subjects, TEAEs were generally comparable between treatments with 4 subjects (50%) having 1 or more TEAEs after receiving LIQ861 compared with 3 subjects (37.5%) after receiving Tyvaso®. The only TEAE experienced by >1 subject after either treatment was cough which was observed in 3 (37.5%) of 8 receiving Tyvaso®. All TEAEs in the Comparative Bioavailability Groups were mild.

4. Discussion

A limited clinical pharmacology program was conducted to establish a PK bridge between treprostinil administered as LIQ861 (capsule strength of 79.5 μg and delivered via DPI with target delivered dose of 58.1 μg) and the reference drug, treprostinil solution for inhalation (Tyvaso®) (labeled strength with 9 breaths for a target delivered dose via nebulizer of 54 μg). The 2 doses are expected to result in approximately the same treprostinil exposure based on the target delivered dose which is a more valid comparison of the doses than the labeled dose strength because of the different labeling conventions for the 2 types of drug delivery systems. A previous Phase 1 study (LTI-101) was a randomized, double-blind, placebo-controlled, single ascending dose study that examined the PK characteristics/profile and safety of LIQ861 [8]. Results from that study established the dose proportionality of treprostinil exposure and its tolerability after administration of LIQ861 (25 to 150 μg dose range); furthermore, the treprostinil PK profile after LIQ861 administration was similar to the published treprostinil PK profile after Tyvaso® administration [9,10]. This comparative bioavailability study (Study LTI-102) was conducted to examine the PK of both LIQ861 and

Tyvaso® within the same study.

Similar PK parameters and superimposable treprostinil plasma concentration-time curves from replicate LIQ861 doses demonstrated the consistency of treprostinil exposure across repeated administrations of the same dose of LIQ861. The comparative bioavailability assessment demonstrated that treprostinil exposure from a single capsule dose of 79.5 μg LIQ861 (approximate delivered dose 58.1 μg) is comparable to treprostinil exposure from 9 breaths of Tyvaso® (approximate delivered dose 54 μg). For AUC_{inf}, AUC_{last}, and C_{max}, the LS GMRs (LIQ861: Tyvaso®) were between 0.9 and 1.0 with corresponding 90% CIs contained entirely within 0.8 to 1.25.

Both LIQ861 and Tyvaso® were well tolerated with no deaths, SAEs, or dose-limiting toxicities. The safety profile of LIQ861 was consistent with previous clinical experience with inhaled treprostinil and dry-powder inhalation in general [11–13]. Most TEAEs associated with LIQ861and Tyvaso® were mild in intensity and consistent with the known effects of inhaled prostanoids.

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Inhaled prostacyclin and prostacyclin analogues offer alternatives to IV and SC dosing for some patients and have the added benefit of delivering the active ingredient to the target organ (i.e., the lungs). LIQ861 was designed to enhance treprostinil deep-lung delivery and ease of administration in PAH patients. While there is only a small difference in time required for administration between LIQ861 at approximately 1 min compared to 2 to 3 min for Tyvaso®, the DPI for LIQ861 offers several conveniences to patients including portability, ease of use, and no need for cleaning or charging. Importantly, global satisfaction with inhaled prostacyclins is highest for medications that are perceived by patients as effective and convenient. In turn, treatment satisfaction is associated with improved quality of life [14]. LIQ861 provides patients with a discreet, pocket-sized, handheld DPI to deliver drug to the lungs. This represents a major improvement in convenience that may result in increased treatment satisfaction and improved quality of life in PAH patients.

A limitation of this study is that it was based on the responses of healthy subjects, and these findings may not be generalizable to the intended PAH population. However, the Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil (INSPIRE) trial was a Phase 3, open-label, multicenter trial that enrolled adult patients with World Health Organization Group 1 PAH. Patients were transitioned from a stable dose of Tyvaso® (Transitions) or added LIQ861 to ≤2 approved, oral PAH therapies (Add-ons). Initial dose was comparable to the Tyvaso® dose at baseline for the Transitions patients or 26.5 μg 4 times a day (QID) for Add-ons, with dose titration allowed up to 159 μg. At the Month 2 assessment, 74% of Transitions and 71% of Add-Ons achieved a dose ≥79.5 μg QID [15]. Improvements in exercise capacity, risk scoring, and quality of life in the study suggest that LIQ861 is delivered to the site of action and well tolerated at clinically effective doses in PAH patients.

5. Conclusions

In conclusion, comparable treprostinil bioavailability was demonstrated after administration of LIQ861 (79.5 μg capsule) and Tyvaso® (9 breaths for a 54-mcg dose), and both were well tolerated. Thus, LIQ861 may fulfill a significant unmet need for PAH patients by maximizing the therapeutic benefits of treprostinil by safely delivering doses into the lungs in 1 to 2 breaths using a small, discreet inhaler and potentially improving treatment adherence by making treatment less burdensome.

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Prior publication

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Declaration of Competing Interest

Robert Roscigno, Toby Vaughn, Ed Parsley, Lewis Rubin, and Mike Eldon are consultants working for Liquidia Technologies. Thomas Hunt is an employee of PPD, a contract research organization for Liquidia Technologies.

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