CLINICAL RESEARCH PROTOCOL

A Phase 3 Open-label, Multicenter Study to Evaluate the Long-term Safety and Tolerability of Inhaled LIQ861(Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Patients

INSPIRE: *In*vestigation of the *S*afety and *P*harmacology of Dry Powder *I*nhalation of T*re*prostinil

Protocol Number:	LTI-301
Investigational Product:	LIQ861
Version:	Amendment 3 (20 March 2019)

PROTOCOL APPROVAL PAGE

Study Title:	A Phase 3 Open-label, Multicenter Study to Evaluate the Long-term Safety and Tolerability of LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Patients
Protocol Number:	LTI-301
Original Protocol Date of Issue:	20 October 2017
Current Version and Date of Issue:	Amendment 3 20 March 2019
Sponsor Name and Address:	Liquidia Technologies, Inc. 419 Davis Dr. Suite 100 Morrisville, NC

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

Sponsor Signatures:

Robert Roscigno

Robert Roscigno, PhD
Senior Vice President, Research and Development
Liquidia Technologies, Inc.

26 March 2019
(Date)

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title:	A Phase 3 Open-label, Multicenter Study to Evaluate the Long-term Safety and Tolerability of LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Patients	
Protocol Number:	LTI-301	Version: Amendment 3 (20 March 2019)

By my signature, I

- Confirm that my staff and I have carefully read and understand this protocol and the Investigator's Brochure (IB) and are thoroughly familiar with the appropriate use of the investigational drug described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study procedures provided by the Sponsor, Liquidia Technologies, or designee
- Agree to comply with US Food and Drug Administration (FDA) regulations, the International Conference on Harmonization (ICH) GCP guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement changes to the protocol without agreement from the Sponsor and prior written approval (where required) from the Institutional Review Board (IRB) or Ethics Committee (EC), except when necessary to eliminate an immediate hazard to the subjects.
- Agree to onsite monitoring of the electronic case report forms (eCRFs) and source documents by Liquidia Technologies or designee and to audit by Liquidia Technologies or designee and appropriate regulatory authorities, including, but not limited to, the FDA and IRB/EC inspectors.
- Agree to supervise the conduct of the study and maintain responsibility for training and supervising all personnel who have delegated responsibilities under my leadership. The protocol and other important study materials will be available to study staff throughout the conduct of the study.

Investigator's Signature Date

Print Name

SUMMARY OF AMENDMENT CHANGES

Date of Revision	Version	Summary of Changes
March 20, 2019	Amendment 3	1. Edited eGFR limit from < 35 to < 30 to reflect FDA's Guidance for definition of severe renal impairment. 2. Edited the exclusion criteria for the PK sub-study to < 45 for GFR. 3. Updated language in Section 3.1 to remove conflict with study procedures and time and events tables. 4. Baseline day is corrected in Section 6.2.1. 5. Clarified timing of predose PK measurements. 6. Included adverse event assessment on Day 1 of PK sub-study. 7. Clarification of study assessments that may be performed before or after study drug administration starting at Week 2 and throughout the study. 8. Addition of specific Study Termination Visit. 9. Clarified that Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) should be recorded for administration of both LIQ861 and Tyvaso. 10. Added ADE to the assessment of relatedness. 11. Updated SAE/SADE reporting requirements and contact information. 12. Clarification on drug reconciliation. 13. Updated Exclusion Criteria #3 to include intravenous (IV) prostacyclin analogues or agonists. 14. Removed examples of serious or life-threatening diseases in Exclusion Criteria #9. 15. Time and events table updated to include Study Termination Visit and Assessment of PAH Symptoms (PK Sub-study), add Day 2 for collection of Inhalation Device Survey, add expectation to collect AEs on Day 1 of PK Sub-study, and update footnotes. 16. Updated study personnel contact information. 17. Editorial updates which do not affect the content of the protocol.
January 7, 2019	Amendment 2	1. Removed second Liquidia signatory on Protocol Approval Page. 2. Updated study name from INTREPID to INSPIRE. 3. Removed consent authorized by legal representative for ICF. 4. Described in Section 1.2 that that there is a difference in the amount of treprostinil that is

		emitted during dosing and the amount of treprostinil that is contained within a capsule. 5. Updated guidance on Initial Dose in Tyvaso Transition Patients in Appendix 2 and provided rationale for alteration in Section 5.3. 6. Removed exclusion criteria for maximum Tyvaso doses and associated language throughout the protocol.
November 13, 2017	Amendment 1	1. Addition of Summary of Amendment Changes Log 2. Addition of Vital Signs assessments to annual schedule. 3. Removed the option of using a 100 µg treprostinil capsule in combination with a 25 µg or 50 µg capsule when dosing exceeds 100 µg of treprostinil. 4. Addition of respiratory rate to Vital Signs assessments. 5. Addition of a Brief Physical Examination at Month 2 (Visit 5). 6. Clarifications to study procedures, including temperature units, PK sample collection volumes, timing of procedures with respect to dosing, questionnaire administrations, and correction of erroneous footnotes in Appendix 1. 7. Removed language in Appendix 2 which allows the investigator to potentially increase the dose of LIQ861 to 75 µg within 5 days after initiating therapy in Add-on patients.

SYNOPSIS	
PROTOCOL TITLE	A Phase 3 Open-label, Multicenter Study to Evaluate the Long-term Safety and Tolerability of LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension WHO Group 1 (PAH) Patients
PROTOCOL NUMBER	LTI-301
INVESTIGATIONAL PRODUCT	LIQ861 at capsule strengths of 25 µg, 50 µg, 75 µg and 100 µg treprostinil. LIQ861 will be administered using the RS00 Model 8 dry powder inhalation (DPI) device (Plastiape S.p.A.; Osnago, Italy) at dose levels of 25 µg to 150 µg treprostinil QID in individual patients. Dosing at levels above 150 µg treprostinil QID will require authorization from the Sponsor.
STUDY OBJECTIVES	The primary objective of this study is to evaluate the long-term safety and tolerability of LIQ861 in patients with PAH. The secondary objective of this study is to evaluate the comparative bioavailability of treprostinil between two formulations of inhaled therapy.
STUDY DESIGN & DURATION	Study LTI-301 is a Phase 3 open-label, multicenter study in patients with PAH to evaluate the long-term safety and tolerability of LIQ861. The study will evaluate the long-term safety and tolerability of LIQ861 in PAH patients who have been on stable doses of Tyvaso® for at least 3 months ("Tyvaso Transition"), or who are taking no more than 2 approved non-prostacyclin oral PAH therapies ("LIQ861 Add-on"). A subset of patients will be enrolled in a one-directional crossover to compare bioavailability and pharmacokinetics of treprostinil as they transition from Tyvaso to LIQ861. At least 100 PAH patients will be enrolled in the study to evaluate the long-term safety and tolerability of LIQ861. Dose titration schedules for Tyvaso Transition and LIQ861 Add-on patients are described in Appendix 2. All patients will be treated on an outpatient basis until regulatory approval of LIQ861. Scheduled study visits to the clinic will occur at Screening, Baseline (Day 1), Week 2, Month 1, Month 2, Month 4, and every 4 months thereafter (Month 8, Month 12, etc.). Beginning with Month 6, patients will be called to assess safety and LIQ861 tolerance every 4 months (Month 6, Month 10, etc.) During this time, dose titration may be ordered at the Investigator's discretion and in accordance with the guidance provided in Appendix 2. ***Sub-Study - Comparative Bioavailability Assessment*** At least 18 PAH patients on Tyvaso will participate in a comparative bioavailability sub-study ("PK sub-study") comparing treprostinil exposure in a one-directional crossover design that utilizes the patient's prescribed Tyvaso dose as the comparator to LIQ861. A stable dose of Tyvaso is defined as remaining on one dose administered QID for at least 3 months.

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	The dose titration schedule for Tyvaso Transition patients is described in Appendix 2. Patients participating in this sub-study will have a trough level PK blood sample collected prior to self-administering their Tyvaso dose at the Investigational site at Baseline (morning dose Day 1), under the supervision of study staff. Following administration of Tyvaso, blood will be collected for PK analysis of treprostinil through 4 hours post-dose and the patients will remain in the clinic for safety observations per Investigator discretion. After the 4 hour post-dose blood draw, the patients will be transitioned to LIQ861 for subsequent doses of treprostinil in accordance with their typical dosing regimen. If the initial LIQ861 dose (based on the instructions in Appendix 2) is tolerated, patients will take two more doses of LIQ861, 4 hours apart, during Day 1. If the initial LIQ861 dose is not tolerated, dose adjustments may be made as needed during the next two doses taken on Day 1. On the morning of Day 2, patients will have a trough level PK blood sample collected prior to self-administering their LIQ861 dose at the Investigational site, under the supervision of study staff. This dose should be the same as the last tolerated dose taken on Day 1. Following administration of LIQ861, blood will be collected for PK analysis of treprostinil through 4 hours post-dose. After the final PK blood collection on Day 2, patients will continue in the study, with QID dosing of LIQ861, following the procedures and visit schedule for all other study patients.
NUMBER OF SUBJECTS	A minimum of 100 patients will be enrolled and observed to support evaluation of safety and tolerance for LIQ861 use. Patients will continue to receive LIQ861 and the study will continue until LIQ861 is commercially available or the study is terminated by the Sponsor. Patients may withdraw from study participation at any time and the patient's physician may request withdrawal for medical or safety reasons at any time. The PK sub-study will contain at least 18 patients with full PK profiles for each formulation of inhaled treprostinil, all of whom will continue in the study upon completion of Day 2 PK collections.
NUMBER OF SITES	Up to 50 sites
PARTICIPATING COUNTRIES	United States (US)
SUBJECT POPULATION	Patients with WHO Group 1 PAH who are • Stable (at least 3 months on same dose) on Tyvaso therapy, or; • on no more than two approved stable background therapies for ≥ 3 months **Inclusion Criteria** A patient will be eligible for inclusion in this study only if <u>all</u> of the following criteria are met:

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	1. An Institutional Review Board (IRB) approved informed consent is signed and dated by the patient prior to any study-related activities. 2. The patient is 18 years of age or older. 3. If the patient is a female of childbearing potential, then the patient has a negative pregnancy test at the Baseline Visit and agrees to practice adequate birth control throughout the duration of the study. If the patient is postmenopausal or has documented surgical sterilization, a pregnancy test and birth control is not necessary. It is the Investigator's responsibility for determining whether the patient has adequate birth control for study participation. 4. The patient has been diagnosed with PAH belonging to the following subgroups of the updated Nice Clinical Classification Group 1, which include: a. Idiopathic PAH (1.1), or b. Heritable PAH (1.2), or c. Drug and toxin induced PAH (1.3), or d. PAH associated with connective tissue disease (1.4.1), HIV infection (1.4.2), or congenital heart disease (1.4.4) with simple systemic-to-pulmonary shunt at least 1 year after surgical repair 5. The patient is NYHA Functional Class II - IV at Screening and: a. has documented stable doses of Tyvaso for at least 3 months prior to screening and is willing and able to transition from their prescribed dose of inhaled therapy to study drug, or b. has documented stable doses of no more than two approved oral therapies for at least 3 months prior to screening and is willing and able to add LIQ861 to their treatment regimen. 6. The patient can complete a baseline six-minute walk distance (6MWD) $\geq$ 150 m. 7. The patient has had evidence of FEV1 $\geq$ 60% and FEV1/FVC ratio $\geq$ 60% during the 6-month period prior to enrollment. **Exclusion Criteria** A Patient is not eligible for inclusion in the study if any of the following criteria apply: 1. The patient's clinical condition is such that, in the opinion of the Investigator, they are not expected to remain clinically stable for the duration of the study. 2. Patients with pulmonary hypertension (PH) in the Updated Nice Classification Groups 2-5, or PAH Group 1 subgroups not covered by the inclusion criteria (e.g., associated with portal hypertension [1.4.3] or with schistosomiasis [1.4.5])

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	3. The patient is currently taking oral or IV prostacyclin analogues or agonists, including treprostinil and selexipag 4. The patient has had any PAH medication (except for anticoagulants) discontinued within 14 days of Baseline. 5. The patient has had a new type of chronic therapy (including but not limited to oxygen, a different class of vasodilator, diuretic, digoxin, and digitalis) for pulmonary hypertension added within 30 days of Baseline. 6. The patient has uncontrolled systemic hypertension as evidenced by persistent systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg. 7. The patient has a history of hemodynamically significant left-sided heart disease including, but not limited to: aortic or mitral valve disease, pericardial constriction, restrictive or congestive cardiomyopathy, or coronary artery disease (CAD). 8. The patient has had an atrial septostomy. 9. The patient has any serious or life-threatening disease other than conditions associated with PAH. 10. The patient is taking any excluded medications listed in the Investigator's Brochure, namely inhibitors and inducers of CYP2C8 (See Appendix 3). 11. The patient has a hypersensitivity or allergy to any of the ingredients of LIQ861 or other clinically relevant allergies (clinical relevance per Investigator judgment). 12. The patient has had a pulmonary infarction (defined as infarction in more than one lung segment documented by V/Q scan or pulmonary angiography) within two weeks of Screening. 13. The patient has had a stroke or transient ischemic attack (TIA) within six months of Screening. 14. The patient has evidence of an active uncontrolled sepsis or systemic infection during Screening. 15. The patient is pregnant or lactating. 16. The patient has any musculoskeletal disease or any other disease that would limit ambulation. 17. The patient has participated in an investigational product or device study within the 30 days prior to Screening. 18. The patient has current evidence of drug abuse in the opinion of the Investigator. 19. The patient has severe hepatic impairment as evidenced by any history of ascites AND encephalopathy. 20. The patient has severe renal impairment (eGFR < 30).

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	Additional Exclusion Criteria for PK Sub-Study 1. The patient meets any of Primary Exclusion Criteria #1 – 19. 2. The patient has moderate or severe renal impairment (eGFR < 45).
SAFETY ANALYSES	The primary endpoint will be the incidence of treatment-emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) grouped by MedDRA System Organ Class, dose level, time on drug, and relationship to dose titration. Safety endpoints are as follows: • Incidence of treatment-emergent drug/device-related adverse events • Changes from Baseline to Month 2/Early Termination in clinical laboratory, physical exam findings, and vital signs.
EXPLORATORY ANALYSES	For all patients: • Change from Baseline to Week 2 and Months 1, 2, 4 and every 4 months thereafter in 6MWD • Change from Baseline to Week 2 and Months 1, 2, 4 and every 4 months thereafter in NYHA Functional Class status • Change from Baseline to Week 2 and Months 1, 2, 4 and every 4 months thereafter in NT-proBNP levels • Change from Baseline to Month 2, Month 4, and every 12 months thereafter in the Minnesota Living with Heart Failure Quality of Life Questionnaire • Time to and reason for discontinuation of LIQ861 For transitioning from Tyvaso only: • Proportion of patients maintaining a sustained treatment transition through the end of Month 2. Sustained treatment transition is defined as meeting all of the following conditions: 1) current treatment with LIQ861 through at least 2 months beyond transition from Tyvaso, 2) no interruptions to study treatment totaling more than 7 days prior to the end of Month 2, and 3) no treatment with any prostacyclin or prostacyclin analogs apart from administration of LIQ861. • Comparison of LIQ861 dose achieved at sustained treatment to previous Tyvaso dose • Patient satisfaction with the LIQ861 DPI compared to the inhalation device from which they are transitioning using a simple questionnaire assessing device preference (Appendix 5).
PHARMACOKINETIC ANALYSES	For patients in the PK sub-study only: • Individual pharmacokinetic parameters for treprostinil will be summarized by treatment using descriptive statistics. Pharmacokinetic parameters such as the maximum observed plasma concentration (Cmax), time to Cmax (Tmax), the area under the plasma concentration versus time curve from time 0 (predose) to time infinity (AUCinf), AUC from time 0 to time of last measurable plasma concentration (AUClast), the percentage of

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	AUC that is extrapolated beyond the last measurable concentration (AUCext), the terminal phase rate constant (λz), the apparent systemic clearance (CL/F), the apparent volume of distribution in the terminal phase (Vz/F), mean residence time (MRT), and the terminal phase half-life (t½) will be calculated using non-compartmental analyses. • An assessment of comparative bioavailability of treprostinil will also be made between LIQ861 and Tyvaso based on dose-normalized AUCinf calculations for the two treatments.
STATISTICAL CONSIDERATIONS	• Individual and mean plots of plasma concentrations versus time after administration of treprostinil will be constructed and displayed for relevant treatment comparisons. • Plasma concentrations will be summarized by treatment using descriptive statistics (sample size, mean, median, coefficient of variation [CV%], standard deviation [SD], minimum, and maximum). Corresponding by-patient data listings will be tabulated. • Derived plasma PK parameters will be summarized by treatment using descriptive statistics (sample size, arithmetic and geometric mean, CV%, SD of the arithmetic mean, median, minimum, and maximum). • The number and percentage of patients who experience at least 1 AE will be presented by severity, relationship to study drug, MedDRA System Organ Class (SOC), preferred term, and dose level of one or both drugs administered. Clinically significant vital signs findings and changes from Baseline values will be tabulated and summarized. Clinical laboratory results will be tabulated.

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ABBREVIATIONS

6MWD	Six-minute walk distance
6MWT	Six-minute walk test
βhCG	beta-human chorionic gonadotropin
λ_z	terminal phase rate constant (first-order)
ADE	Adverse Device Event
AE	adverse event
AUC	Area under the curve
BLQ	Below the Limit of Quantification
CFR	Code of Federal Regulations
CL/F	apparent clearance
Cmax	peak plasma concentration, observed
CV	Coefficient of Variation
DPI	Dry Powder Inhalation
EC	Ethics committee
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
Frel	Relative Bioavailability
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IND	Investigational New Drug
IRB/EC	Institutional Review Board/Independent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MLWHF	Minnesota Living with Heart Failure
mmHg	millimeters of mercury
MRT	mean residence time
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PH	Pulmonary Hypertension
PK	pharmacokinetic
PRINT	Particle Replication in Nonwetting Templates
QID	Four times a day
QOL	Quality of life
SADE	Serious Adverse Device Effect
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$t_{½}$	elimination half-life
TAD	Tyvaso Approximate Dose
TEAE	Treatment-Emergent Adverse Event
Tmax	time to peak plasma concentration, observed
Vz/F	volume of distribution
WHO	World Health Organization

1. INTRODUCTION

1.1. Background & Rationale for LIQ861 Development

Pulmonary arterial hypertension (PAH) is a complex, multifactorial, progressive, and life-threatening disease characterized by proliferative and obstructive changes in the pulmonary vasculature and involving numerous biochemical pathways and cell types. The disease is characterized by elevated pulmonary arterial pressure and right ventricular failure that carries a poor prognosis associated with significant morbidity and mortality, having a historical survival rate of less than five years. Endothelial dysfunction is thought to occur early on, leading to cell proliferation and structural changes in the pulmonary vasculature that lead to increased pulmonary arterial pressure (PAP) and resultant right ventricular enlargement and dysfunction. In addition, endothelial dysfunction results in chronically impaired production of vasoactive mediators, such as nitric oxide (NO) and prostacyclin, along with prolonged overexpression of vasoconstrictors, such as endothelin-1 (Channick, Voswinckel et al. 2012).

PAH is part of a larger classification for pulmonary hypertension, which is divided into five groups based on World Health Organization (WHO) criteria (designated as WHO Groups 1 through 5), as defined at the 5th World Symposium on Pulmonary Hypertension in Nice, France (Simonneau, Gatzoulis et al. 2013). PAH is used to describe exclusively WHO Group 1. Pulmonary hypertension (PH) is used to describe the remaining four groups (WHO Groups 2-5) and also when referring to all 5 groups collectively.

- WHO Group 1 - PAH: Pulmonary arterial hypertension.
- WHO Group 2 - PH: Pulmonary hypertension secondary to left heart disease.
- WHO Group 3 - PH: Pulmonary hypertension secondary to lung diseases or hypoxemia.
- WHO Group 4 - PH: Chronic thromboembolic pulmonary hypertension.
- WHO Group 5 - PH: Pulmonary hypertension with unknown mechanisms.

PAH initially presents as exertional dyspnea, lethargy, and fatigue and is often confused for other disease states. As PAH progresses and right ventricular failure develops, exertional chest pain (i.e., angina), exertional syncope, and peripheral edema may develop. Following confirmation of diagnosis based on hemodynamic parameters, treatment is recommended to lower pulmonary pressures and treat the symptoms of PAH. Although no cure exists for PAH, treatment of PAH is directed at improving hemodynamic measures (Badesch, Abman et al. 2007), New York Heart Association (NYHA) functional class (Miller-Davis, Marden et al. 2006), the six-minute walk distance (6MWD) (Babu, Padmakumar et al. 2016), quality of life (QOL) (Babu, Padmakumar et al. 2016), and, in some studies, survival.

The severity of PAH may be classified according to the NYHA heart failure guidelines as follows:

- NYHA Class I: Patients with cardiac disease having no limitation of activities; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- NYHA Class II: Patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest, however ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

- NYHA Class III: Patients with cardiac disease resulting in marked limitation of activity; they are comfortable at rest, however less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- NYHA Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest with discomfort increasing if any physical activity is undertaken.

Treprostinil is a chemically stable tricyclic benzidine prostanoid with vasodilator properties that is capable of reducing pulmonary vasoconstriction with minimal effects on systemic blood pressure (Channick, Voswinckel et al. 2012). Treprostinil has been approved for the treatment of PAH and is marketed by the United Therapeutics Corporation under the trade names Orenitram® (extended release oral tablets), Remodulin® (subcutaneous or IV infusion) and Tyvaso (inhaled via ultrasonic, pulsed delivery device). Tyvaso was shown to be effective in the treatment of PAH, with an advantage of the inhaled route of administration being that it brings the drug very near the desired site of action (pulmonary arteries in the lungs) (McLaughlin, Benza et al. 2010).

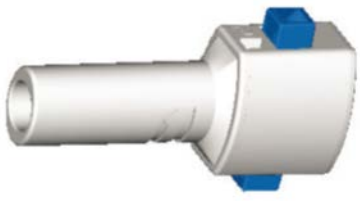
One of the greatest impediments to patient treatment satisfaction with Tyvaso is inconvenience. Currently, patients on Tyvaso may require more than 36 breaths per day with the use of a bulky nebulizer. The use of a discrete, hand-held dry powder inhaler to deliver treprostinil to the lungs would represent a major improvement in convenience and patient satisfaction, thereby improving the quality of life for PAH patients. Thus, Liquidia is pursuing approval of LIQ861, an inhalation dry powder formulation of treprostinil that is produced using Liquidia's PRINT® Technology (Particle Replication in Nonwetting Templates), as an alternative to Tyvaso for the treatment of patients with PAH (WHO Group 1).

1.2. Description of LIQ861

LIQ861 is a capsule containing a dry powder mixture of treprostinil and excipients (bulk powder) designed for inhalation using a dry powder inhalation device. The bulk powder is generated from a treprostinil/excipient matrix from which particles of precise size (1 µm) and shape ("pollen-shaped") are created and filled into a hydroxypropyl methylcellulose (HPMC) capsule (size 3). LIQ861 capsules are provided in capsule strengths of 25 µg, 50 µg, 75 µg and 100 µg treprostinil.

The LIQ861 capsule is intended for use with a handheld monodose dry powder inhalation device. The device chosen for clinical trials is the RS00 Model 8 manufactured by Plastiape. The overall design of the RS00 Model 8 device is shown in Figure 1.

Figure 1. RS00 Model 8 Dry Powder Inhalation Device



The mouthpiece contains a mesh that aids in particle size reduction and prevents capsule ingestion during inhalation. The inhaler body component contains 2 side buttons, each housing 4 pins for piercing a capsule. A capsule piercing area is located internally, adjacent to the pins. When a

capsule is inserted in this area, depressing the buttons causes the button pins to pierce the capsule ends, thereby preparing the capsule for emptying. Above the capsule piercing area, there are 2 tangential air inlets and a circular chamber. These allow the capsule to spin when the patient inhales through the device. Capsule spinning creates a centrifugal effect on the powder that promotes efficient emptying. Emitted doses from each capsule are less than the labeled capsule strengths of treprostinil, which correspond to the amount of powder with which each capsule is filled.

1.3. Development Program

A first-in-human study was performed at the PPD Phase 1 Clinic in Austin, TX under a US Investigational New Drug (IND). Study LTI-101 was a Phase 1, single-center, placebo-controlled, double-blinded, randomized study to evaluate the safety and tolerability of the LIQ861 formulation and to characterize the pharmacokinetics (PK) of treprostinil as an inhaled dry powder. Cohorts of 8 healthy volunteers were randomly assigned in a 3:1 ratio to receive a single dose of either LIQ861 (n = 6) or placebo (n = 2) at dose levels of 25, 50, 75, 100, 125, and 150 µg treprostinil. Blood for measurement of treprostinil concentrations was collected through 8 hours post-dose for determination of treprostinil noncompartmental PK parameters.

The median treprostinil Tmax was between 10 and 20 minutes post-dose administration. Dose proportionality was assessed based on Cmax and AUCinf and concluded to be proportional over the entire tested dose range of 25 to 150 µg treprostinil. The LIQ861 formulation was found to be well-tolerated after single-dose administration with no serious or unexpected adverse events. The most commonly reported related adverse events (AEs) were cough, throat irritation, inspiratory tightness, lightheadedness, and headache; all were described as mild in severity. There were no serious AEs.

Additional information on the development of the LIQ861 product may be found in the most current version of the Investigator's Brochure.

1.4. Rationale for the Current Study

Study LTI-301 is a Phase 3 open-label, multicenter study in patients with PAH to evaluate the long-term safety and tolerability of LIQ861 and the comparative bioavailability in patients transitioning from Tyvaso to LIQ861.

2. STUDY OBJECTIVES

The primary objective of this study is to evaluate the long-term safety and tolerability of LIQ861 in patients with PAH.

The secondary objective of this study is to evaluate the comparative bioavailability of treprostinil between two formulations of inhaled therapy

3. INVESTIGATIONAL PLAN

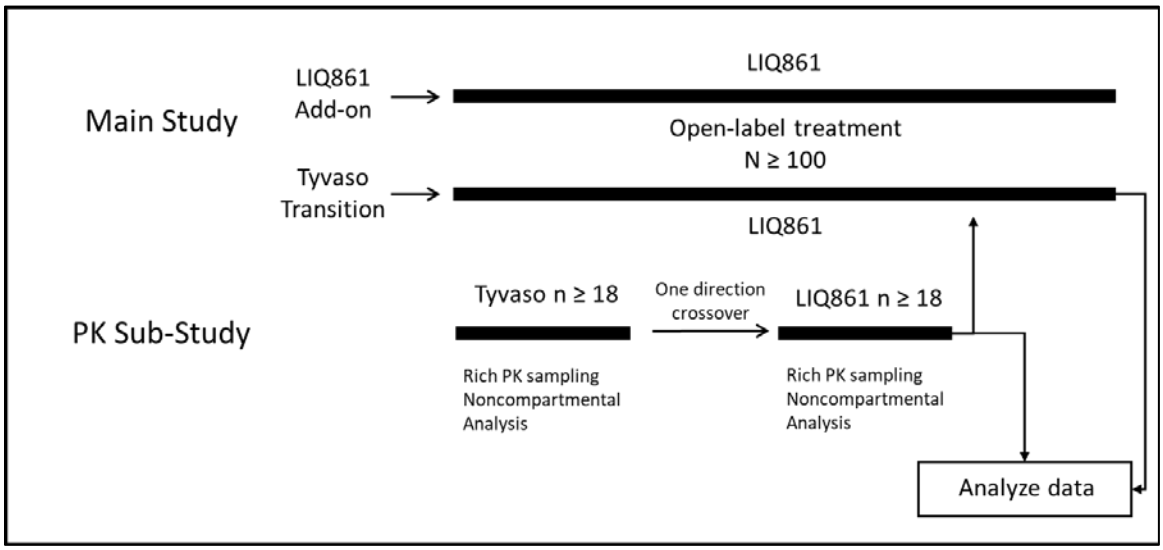
3.1. Overall Study Design and Plan

Study LTI-301 is a Phase 3 open-label, multicenter study in patients with PAH to evaluate the long-term safety and tolerability of LIQ861.

The study will evaluate the long-term safety and tolerability of LIQ861 in PAH patients who have been on stable doses of Tyvaso (treprostinil) inhalation solution for at least 3 months ("Tyvaso Transition"), or who are taking no more than 2 approved non-prostacyclin oral PAH therapies ("LIQ861 Add-on").

A subset of patients will be enrolled in a one-directional crossover to compare the bioavailability and pharmacokinetics of treprostinil as they transition from Tyvaso to LIQ861.

Figure 2. Schematic of LTI-301 Study Design



At least 100 PAH patients will be enrolled in the study to evaluate the long-term safety and tolerability of LIQ861. All patients will be treated on an outpatient basis until regulatory approval of LIQ861.

Tyvaso Transition patients will receive training on the use of the dry powder inhalation (DPI) device and then administer their first dose of LIQ861 at the Investigational site at the Baseline Visit (Day 1) under the supervision of study staff and will remain in the clinic for safety per Investigator discretion. The initial LIQ861 treprostinil dose will be matched to the comparable prescribed Tyvaso dose at transition (Appendix 2); subsequently, LIQ861 will be maintained on a QID dosing schedule for the duration of the study. During this time, dose titration may be ordered at the Investigator's discretion and in accordance with the Guidance for LIQ861 Dose Selection and Titration (Appendix 2).

Add-on patients will receive training on the use of the DPI and then administer their first dose of LIQ861 at the Investigational site at Baseline (Day 1) under the supervision of study staff. Study drug will be administered for LIQ861 Add-on patients initially at 25µg treprostinil in LIQ861 QID with timing of dose titrations chosen at the Investigator's discretion while maintaining a QID dosing schedule (Appendix 2). Alterations to the dosing interval (e.g., 3 times a day or 5 times a day) must be approved by the Sponsor.

Scheduled study visits to the clinic will occur at Screening, Baseline (Day 1), Week 2, Month 1, Month 2, Month 4, and every 4 months thereafter (e.g., Month 8, Month 12, etc.) until study termination or regulatory approval. During this time, dose titration may be ordered at the Investigator's discretion and in accordance with the Guidance for LIQ861 Dose Selection and Titration (Appendix 2).

Telephone contact to assess adverse events (AEs), concomitant medications, and PAH symptoms will be made every 4 months beginning at Month 6 (e.g., Month 6, Month 10, etc.) until the Study Termination Visit. Telephone contact is not necessary during months in which a study visit is scheduled. The Study Termination Visit will occur after regulatory approval of LIQ861 or after the Sponsor decides to terminate the development program.

Patients that clinically worsen on open-label LIQ861, as determined by Investigator's discretion may be withdrawn from the study and rescue therapy initiated per standard of care.

Sub-Study - Comparative Bioavailability Assessment

At least 18 PAH patients on Tyvaso (stable doses QID for at least 3 months) will be included in a comparative bioavailability sub-study ("PK sub-study") comparing treprostinil exposure in a one-directional crossover design that utilizes the patient's prescribed Tyvaso dose as the comparator to LIQ861.

The dose titration schedule for these patients is described in Appendix 2.

Patients participating in this sub-study will have a trough level PK blood sample collected prior to self-administering their Tyvaso dose at the Investigational site at Baseline (morning dose Day 1), under the supervision of study staff. Following administration of Tyvaso, blood will be collected for PK analysis of treprostinil through 4 hours post-dose and the patients will remain in the clinic for safety observations per Investigator discretion. After the 4 hour post-dose blood draw, the patients will be transitioned to LIQ861 for subsequent doses of treprostinil in accordance with their typical dosing regimen. If the initial LIQ861 dose (based on the instructions in Appendix 2) is tolerated, patients will take two more doses of LIQ861, 4 hours apart, during Day 1. If the initial LIQ861 dose is not tolerated, dose adjustments may be made as needed during the next two doses taken on Day 1.

On the morning of Day 2, patients will have a trough level PK blood sample collected prior to self-administering their LIQ861 dose at the Investigational site, under the supervision of study staff. This dose should be the same as the last tolerated dose taken on Day 1. Following administration of LIQ861, blood will be collected for PK analysis of treprostinil through 4 hours post-dose. After the final PK blood collection on Day 2, patients will continue in the study, with QID dosing of LIQ861, following the procedures and visit schedule for all other study patients.

3.2. Endpoints

3.2.1. Primary Endpoint

The primary endpoint will be the incidence of Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) grouped by MedDRA System Organ Class, dose level, time on drug, and relationship to dose titration.

3.2.2. Safety Endpoints

Safety endpoints are as follows:

- Incidence of treatment-emergent drug/device-related adverse events
- Changes from Baseline to Month 2/Early Termination in clinical laboratory, physical exam findings, and vital signs

3.2.3. Pharmacokinetic Endpoints

For patients in the PK sub-study only:

- Individual pharmacokinetic parameters for treprostinil will be summarized by treatment using descriptive statistics. Pharmacokinetic parameters such as the maximum observed plasma concentration (Cmax), time to Cmax (Tmax), the area under the plasma concentration versus time curve from time 0 (predose) to time infinity (AUCinf), AUC from time 0 to time of last measurable plasma concentration (AUClast), the percentage of AUC that is extrapolated beyond the last measurable concentration (AUCext), the terminal phase rate constant (λz), the apparent systemic clearance (CL/F), the apparent volume of distribution in the terminal phase (Vz/F), mean residence time (MRT), and the terminal phase half-life (t½) will be calculated using non-compartmental analyses.
- An assessment of comparative bioavailability of treprostinil will also be made between LIQ861 and Tyvaso based on dose-normalized AUCinf calculations for the two treatments.

3.2.4. Exploratory Endpoints

For all patients:

- Change from Baseline to Week 2 and Months 1, 2, 4 and every 4 months thereafter in 6MWD
- Change from Baseline to Week 2 and Months 1, 2, 4 and every 4 months thereafter in NYHA Functional Class status
- Change from Baseline to Week 2 and Months 1, 2, 4 and every 4 months thereafter in NT-proBNP levels
- Change from Baseline to Month 2, Month 4, and every 12 months thereafter in the Minnesota Living with Heart Failure (MLWHF) Quality of Life Questionnaire
- Time to and reason for discontinuation of LIQ861

For transitioning from Tyvaso only:

- Proportion of patients maintaining a sustained treatment transition through the end of Month 2. Sustained treatment transition is defined as meeting the following conditions: 1) current treatment with LIQ861 through at least 2 months beyond transition from Tyvaso, 2) no interruptions to study treatment totaling more than 7 days prior to the end of Month 2, and 3) no treatment with any prostacyclin or prostacyclin analogs apart from administration of LIQ861.
- Comparison of LIQ861 dose achieved at sustained treatment to previous Tyvaso dose
- Patient satisfaction with the LIQ861 DPI compared to the inhalation device from which they are transitioning from using a simple questionnaire to assess device preference (Appendix 5).

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

A patient will be eligible for inclusion in this study only if the following criteria are met:

1. An Institutional Review Board (IRB) approved informed consent is signed and dated by the patient prior to any study-related activities.
2. The patient is 18 years of age or older.

3. If the patient is a female of childbearing potential, then the patient has a negative pregnancy test at the Baseline Visit and agrees to practice adequate birth control throughout the duration of the study. If the patient is postmenopausal or has documented surgical sterilization, a pregnancy test and birth control is not necessary. It is the Investigator's responsibility for determining whether the patient has adequate birth control for study participation.
4. The patient has been diagnosed with PAH belonging to the following subgroups of the updated Nice Clinical Classification Group 1 (Simonneau, Gatzoulis et al. 2013), which include:
   a. Idiopathic PAH (1.1), or
   b. Heritable PAH (1.2), or
   c. Drug and toxin induced PAH (1.3), or
   d. PAH associated with connective tissue disease (1.4.1), HIV infection (1.4.2), or congenital heart disease (1.4.4) with simple systemic-to-pulmonary shunt at least 1 year after surgical repair
5. The patient has been diagnosed with PAH and is NYHA Functional Class II - IV at Screening.
   a. has documented stable doses of approved inhaled therapy for at least 3 months prior to screening and is willing and able to transition from their prescribed dose of inhaled therapy to study drug, or
   b. has documented stable doses of no more than two approved oral therapies for at least 3 months prior to screening and is willing and able to add LIQ861 to their treatment regimen.
6. The patient can complete a baseline six-minute walk distance (6MWD) ≥ 150 m.
7. The patient has had evidence of FEV1 ≥ 60% and FEV1/FVC ratio ≥ 60% during the 6-month period prior to enrollment.

4.2. Exclusion Criteria

A Patient is not eligible for inclusion in the study if any of the following criteria apply:

1. The patient's clinical condition is such that, in the opinion of the Investigator, they are not expected to remain clinically stable for the duration of the study.
2. Patients with PH in the Updated Nice Classification Groups 2-5, or PAH Group 1 subgroups not covered by the inclusion criteria (e.g., associated with portal hypertension [1.4.3] or with schistosomiasis [1.4.5]).
3. The patient is currently taking oral or intravenous (IV) prostacyclin analogues or agonists, including treprostinil and selexipag.
4. The patient has had any PAH medication (except for anticoagulants) discontinued within 14 days of Baseline.
5. The patient has had a new type of chronic therapy (including but not limited to oxygen, a different class of vasodilator, diuretic, digoxin, and digitalis) for pulmonary hypertension added within 30 days of Baseline.
6. The patient has uncontrolled systemic hypertension as evidenced by persistent systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.

7. The patient has a history of hemodynamically significant left-sided heart disease including, but not limited to: aortic or mitral valve disease, pericardial constriction, restrictive or congestive cardiomyopathy, or coronary artery disease (CAD).
8. The patient has had an atrial septostomy.
9. The patient has any serious or life-threatening disease other than conditions associated with PAH.
10. The patient is taking any excluded medications listed in the Investigator's Brochure, namely inhibitors and inducers of CYP2C8 (See Appendix 3).
11. The patient has a hypersensitivity or allergy to any of the ingredients of LIQ861 or other clinically relevant allergies (clinical relevance per Investigator judgment).
12. The patient has had a pulmonary infarction (defined as infarction in more than one lung segment documented by V/Q scan or pulmonary angiography) within two weeks of Screening.
13. The patient has had a stroke or transient ischemic attack (TIA) within six months of Screening.
14. The patient has evidence of an active uncontrolled sepsis or systemic infection during Screening.
15. The patient is pregnant or lactating.
16. The patient has any musculoskeletal disease or any other disease that would limit ambulation.
17. The patient has participated in an investigational product or device study within the 30 days prior to Screening.
18. The patient has current evidence of drug abuse in the opinion of the Investigator.
19. The patient has severe hepatic impairment as evidenced by any history of ascites AND encephalopathy.
20. The patient has severe renal impairment (eGFR < 30).

Additional Exclusion Criteria for PK Sub-Study

1. The patient meets any of Primary Exclusion Criteria #1 – 19.
2. The patient has moderate or severe renal impairment (eGFR < 45).

4.3. Removal of Patients from Therapy/Premature Discontinuation

Patients will be encouraged to complete the study and all assessments. A patient will be discontinued from the study for the following medical or administrative reasons:

- Occurrence of a TEAE that represents an unacceptable risk to the patient and when continued participation in the investigational study is not warranted, in judgment of the Investigator. The Investigator must follow the patient until the AE resolves or satisfactorily stabilizes
- Patient request
- Pregnancy

- Significant non-compliance with study procedures or dosing regimen

The Investigator may discontinue individual patients from the study at any time. Patients may voluntarily withdraw at any time.

All patients withdrawn from the study because of a TEAE will continue to be followed for at least 4 months after removal from LIQ861 treatment or until the adverse event(s) resolves or stabilizes (Section 6.2.7).

The Investigator will be responsible for obtaining final clinical assessments on patients that early terminate from the study. If a patient is discontinued or withdraws from the study after receiving at least one dose of LIQ861 and withdraws/terminates prior to completion of the final assessments, then the site will make every effort to conduct a Study Termination Visit.

Unscheduled visits may be conducted at the Investigator's discretion for patient safety monitoring, following up on TEAEs/SAEs, or other reasons that will be documented. Assessments at unscheduled visits will be symptom driven and conducted at the Investigator's discretion.

5. TREATMENTS

5.1. Treatments Administered

LIQ861 will be self-administered by the patients in the study after receiving adequate training by qualified study staff. LIQ861 administration must occur only in accordance with the procedures described in this protocol and detailed instructions that are supplied for distribution to the study patients.

5.2. Identity of Investigational Product(s)

LIQ861 is a capsule containing a pre-loaded amount of a white to off-white dry powder containing treprostinil and excipients (bulk powder), which is intended to be inhaled with the use of the RS00 Model 8 DPI (Figure 1). The bulk powder, which is manufactured by Liquidia Technologies, consists of particles of precise size (1 μm) and shape ("pollen-shaped") that are created from a treprostinil/excipient matrix using Liquidia's PRINT Technology.

5.2.1. LIQ861

The LIQ861 formulation is comprised of treprostinil sodium (drug substance salt) and five excipients: trehalose dihydrate, Polysorbate 80, leucine, sodium citrate, and sodium chloride. The mass proportion of the excipients in the pollen-shaped particles greatly exceeds the strength of treprostinil in the mixture (See Investigator's Brochure). As such, the fill weights of bulk powder are much greater than the dosage strength of active drug substance. Four capsule strengths of LIQ861 have been manufactured for this study:

- The 25 μg treprostinil capsule strength is a capsule that is filled with 5 mg LIQ861 bulk powder.
- The 50 μg treprostinil capsule strength is a capsule that is filled with 10 mg LIQ861 bulk powder.
- The 75 μg treprostinil capsule strength is a capsule that is filled with 15 mg LIQ861 bulk powder.

- The 100 µg treprostinil capsule strength is a capsule that is filled with 20 mg LIQ861 bulk powder.

For dose levels in excess of 100 µg treprostinil, multiple capsules of lower capsule strength may be used in immediate succession to achieve the desired dose of treprostinil. A dose level of 125 µg should be delivered with a combination of a 75 µg and a 50 µg capsule, and a dose level of 150 µg should be delivered with a combination of two 75 µg capsules.

5.2.2. Labeling

Study drug will bear a label that meets applicable laws for an investigational drug, which may include, but is not limited to, the following information:

- Federal law statement
- Lot number
- Box number
- Storage information
- Capsule Strength
- Expiration date
- Name of Sponsor

5.2.3. Storage and Handling

All study drug will be kept in a locked area with limited access and stored at 15°-30°C (59°-86°F). When in the possession of patients, all study drug should be stored in a cool, dry area. Study drug is packaged, per strength, as four capsules per bottle, with eight bottles and two DPIs per box.

5.3. Selection of Doses in the Study

The results of study LTI-101 showed that the observed exposures of treprostinil after inhalation of LIQ861 are proportional to administered dose levels consistent with the capsule strengths selected for this study. Mean Cmax and AUCinf values from the LTI-101 study were compared with mean exposure levels reported in published literature and in the Drug Approval Reviews from the FDA. Commonalities between the exposures observed in the LTI-101 study and those reported for Tyvaso were used to project a Tyvaso Approximate Dose (TAD) for LIQ861. This assessment was the basis of the original dose selection guidance (LTI-301 Protocol Amendment 1, 13-Nov-2017).

Review of interim PK data from crossover patients in LTI-301 has shown that the initial TAD for LIQ861 may be providing lower plasma exposure than originally projected. The estimated treprostinil doses delivered from Tyvaso appear to result in plasma exposures that are more consistent with the estimated emitted doses from LIQ861. The trend of observed plasma exposures from within-patient PK comparisons in interim LTI-301 data review, combined with estimates of expected emitted doses from LIQ861 administration, are the basis of revised initial transition dose selection guidance provided in Table 2 and the directed dose administrations for future PK patients provided in Table 3 (see Appendix 2).

If the patient is not already on Tyvaso, the starting dose will be LIQ861 QID at the 25 µg treprostinil capsule strength. For patients transitioning from Tyvaso, patients should start at doses recommended in the Guidance for LIQ861 Dose Selection and Titration, Appendix 2. For all patients, dosing may be titrated per instructions provided in Appendix 2.

5.4. Selection and Timing of Dose for Each Patient

Patients will receive QID administration of study drug on an outpatient basis until regulatory approval of LIQ861 for the treatment of PAH or until the sponsor decides to amend or terminate the study.

5.5. Prior and Concomitant Therapy

Medications taken within 3 months of screening will be documented in the patient's notes and electronic case report form (eCRF).

Any new or changed concomitant medication (prescriptions and non-prescriptions), including PGI use, will be recorded in the source documents and eCRF throughout the study, including any medication taken between the Screening Visit and initiation of treatment with LIQ861.

5.6. Prohibited Therapy

Patients may not be treated with LIQ861 if concurrently receiving any of the following medications:

- CYP2C8 inhibitors and inducers, listed in Appendix 3
- Oral administered prostacyclin analogues and agonists, such as treprostinil and selexipag

5.7. Dose Modification

When dosing is to exceed 100 µg treprostinil, administration of LIQ861 capsules should be administered as follows to achieve the target dose:

To achieve a target dose of 125 µg treprostinil, the subject should administer one 50 µg treprostinil capsule followed by one 75 µg treprostinil capsule.

To achieve a target dose of 150 µg treprostinil, the subject should administer one 75 µg treprostinil capsule followed by another 75 µg treprostinil capsule.

Based on data from the LTI-101 study, dose levels of up to 150 µg treprostinil in LIQ861 are well-tolerated. Authorization from the Sponsor is required prior to dosing at levels above 150 µg treprostinil.

5.8. Treatment Compliance

Patients will self-administer the study drug at home. At each visit, the patient will receive a sufficient and documented quantity of capsules intended to last through the next visit. Patients should be instructed to return unused study medication at each study visit for product accountability. Sealed investigational product may be re-dispensed to the same patient. Any other returned study medication should be retained for product accountability.

5.8.1. Study Drug Accountability

All study drug will be administered in accordance with the conditions of this protocol. Only authorized site personnel may supply or dispense study drug. In rare instances, a courier may be used to retrieve drug from a study site and deliver it to a patient. Study drug orders, records of study drug receipt, dispensing, and running inventory will be examined and reconciled throughout the study. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Upon the completion of the study, study drug will be

subjected to final reconciliation. At that time, all unused, partially used, and fully used study drug along with a packing slip must be returned to a designated facility.

6. STUDY PROCEDURES

6.1. Study Measurements and Assessments

6.1.1. Assessment of Safety

Safety assessments will include the following:

- AEs and SAEs, both reported and observed
- Adverse device events (ADE)
- Physical examination
- Vital sign measurements
- Venous blood for clinical laboratory tests will include hematology, coagulation, and blood chemistry.

6.1.2. Exploratory Assessments

While this study is not designed to make conclusions on efficacy, exploratory assessments of efficacy endpoints will be made as previously described.

6.2. Study Phases and Procedures

A Time and Events Schedule is provided in Appendix 1.

6.2.1. Screening Phase (Visit 1; Day -28 through Day 1)

The initial Screening Visit may be conducted up to 28 days prior to Baseline on Day 1. The following procedures/assessments will be performed at Screening:

- Informed consent (must be done prior to **any** of the following procedures, including asking patients to discontinue prohibited medications)
- Record medical history and patient demographics
- Documentation of prohibited, prior, and current medications with duration of treatment
- Height, weight, and age
- Vital Signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes
- Serum pregnancy test (for all females of child bearing potential)
- Venous blood for clinical laboratory tests
- Venous blood for infectious disease screen (HIV, hepatitis B, and hepatitis C analysis)
- Six-minute walk test (6MWT)
- Pulmonary function testing (FEV1 and FEV1/FVC ratio), with or without bronchodilator
- NYHA Functional Class Assessment
- Assessment of hepatic and renal impairment (See Appendix 6)
- Full physical examination
- Confirm patient meets all eligibility criteria
- Schedule next study visit (Baseline)

The results of all laboratory assessments must be returned and reviewed prior to enrolling the patient for Day 1 procedures.

6.2.2. Baseline – (Visit 2; Day 1)

The description of assessments in this section is intended for patients that are **NOT** enrolled in the PK Sub-Study. Patients who are enrolled in the PK Sub-Study should follow the assessments described in Section 6.2.3.

The following assessments are to be completed at Baseline and prior to dose administration:

- Eligibility re-assessment
- Brief physical examination
- Vital signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes
- Weight
- Venous blood for clinical laboratory tests, including NT-proBNP
- Urine pregnancy test (for all females of child bearing potential, Day 1 only)
- 6MWT
- NYHA Functional Class Assessment
- MLWHF questionnaire
- Assessment of PAH Symptoms
- Device training
- Prior medications
- Record time of last dose of inhaled treprostinil
- Administer first dose of LIQ861 (after all other predose assessments)
    - Note that for Tyvaso transition patients, the time of LIQ861 administration should be at least 4 hours after the last dose of Tyvaso

The following assessments are to be completed after dose administration:

- Inhalation Device User Survey
    - The Inhalation Device User Survey should only be administered to Tyvaso Transition patients.
- Concomitant medications
- Treatment-Emergent Adverse Events
- Study Drug Dispensation
- Schedule Next Visit

6.2.3. Baseline – PK Sub-Study (Visit 2; Day 1 & Day 2)

The description of assessments in this section is intended **ONLY** for patients that are enrolled in the PK Sub-Study. Patients that are **NOT** enrolled in the PK Sub-Study should follow the assessments described in Section 6.2.2.

Day 1

The following assessments are to be completed at Baseline and prior to Tyvaso administration on Day 1:

- Eligibility re-assessment

- Brief physical examination
- Vital signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes
- Weight
- Venous blood for clinical laboratory tests, including NT-proBNP
- Urine pregnancy test (for all females of child bearing potential, Day 1 only)
- 6MWT
- NYHA Functional Class Assessment
- Assessment of PAH Symptoms
- Prior medications
- Record time of last dose of inhaled treprostinil
- Plasma for baseline PK measurement (must be taken before Tyvaso administration, within 30 minutes of dose administration)
- Final dose of Tyvaso (after all other predose assessments)
    - Note that this must be the first dose of the day. If the subject has taken Tyvaso prior to arrival at the clinic, the PK sub-study should not be conducted or the visit should be rescheduled.

The following assessments are to be completed after Tyvaso administration on Day 1, but before the first dose of LIQ861 is administered:

- Plasma for PK measurements at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 180 minutes and 4 hours after Tyvaso administration. Actual times of blood collection for each timepoint must be recorded.
- Adverse Events
- Concomitant medications
- Venous blood for clinical laboratory tests at 4 hours after Tyvaso administration
- MLWHF questionnaire
- DPI Training

The second treprostinil dose of the day should be the first administration of LIQ861. The following assessments are to be completed after the first dose of LIQ861 is administered:

- Treatment-Emergent Adverse Events
- Concomitant medications
- Inhalation Device User Survey
- Study Drug Dispensation
- Schedule Next Visit

Day 2

The following assessments are to be completed at Baseline and prior to study drug administration on Day 2:

- Treatment-Emergent Adverse Events
- Eligibility re-assessment
- Brief physical examination
- Vital signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes

- Weight
- Venous blood for clinical laboratory tests, including NT-proBNP
- DPI re-training
- Concomitant medications
- Record time of last dose of inhaled treprostinil
- Plasma for baseline PK measurement (must be taken before LIQ861 administration, within 30 minutes of dose administration)
- Administer dose of LIQ861 (after all other predose assessments)
    - Note that this should be the first dose of the day. If the subject has taken LIQ861 prior to arrival at the clinic, then Day 2 of the PK sub-study should be rescheduled.

The following assessments are to be completed after the first study drug administration on Day 2:

- Plasma for PK measurements at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 180 minutes and at 4 hours after study drug administration. Actual times of blood collection for each timepoint must be recorded.
- Concomitant medications
- Venous blood for clinical laboratory tests at 4 hours after study drug administration
- Study Drug Dispensation
- Schedule next visit
- Treatment-Emergent Adverse Events
- Inhalation Device User Survey

6.2.4. Visit 3 (Week 2)

Visit 3 should be scheduled approximately 2 weeks ± 2 days from the first administration of LIQ861.

The following assessments may be conducted before or after study drug administration at Visit 3:

- NYHA Functional Class Assessment
- Collect unused study drug
- Study drug accountability
- Study drug dispensation
- Schedule next visit
- Assess PAH Symptoms
- Consider dosing adjustments and record any prescribed changes

The following assessments will be conducted prior to study drug administration at Visit 3:

- Vital signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes
- Venous blood for clinical laboratory tests, including NT-proBNP
- DPI re-training
- Concomitant medications
- Treatment-Emergent Adverse Events
- Record time of last dose of inhaled treprostinil
- Administration of study drug

- Note that the time of LIQ861 administration should be at least 4 hours after the last dose of LIQ861.

The following assessments will be conducted after study drug administration at Visit 3:

- 6MWT (within 15 to 60 minutes after administration of LIQ861)
- Concomitant medications
- Treatment-Emergent Adverse Events
- Inhalation Device User Survey
  - The Inhalation Device User Survey should only be administered to Tyvaso Transition patients.

6.2.5. Visits 4 & 5 (Month 1 & Month 2)

Visits 4 and 5 should be scheduled approximately 1 and 2 months ± 3 days from the first administration of LIQ861, respectively.

The following assessments may be done before or after study drug administration at Visits 4 & 5:

- Brief Physical Examination (Visit 5 only)
- NYHA Functional Class Assessment
- Collect unused study drug
- Study drug accountability
- Study drug dispensation
- Schedule next visit
- Assess PAH Symptoms
- Consider dosing adjustments and record any prescribed changes

The following assessments will be conducted prior to study drug administration at Visits 4 & 5:

- Vital signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes
- Venous blood for clinical laboratory tests, including NT-proBNP
- DPI re-training
- Concomitant medications
- Treatment-Emergent Adverse Events
- Record time of last dose of inhaled treprostinil
- Administration of study drug
  - Note that the time of LIQ861 administration should be at least 4 hours after the last dose of LIQ861

The following assessments will be conducted after study drug administration at Visits 4 & 5:

- 6MWT (within 15 to 60 minutes after administration of LIQ861)
- MLWHF questionnaire (Visit 5 only)
- Concomitant medications
- Treatment-Emergent Adverse Events

6.2.6. Visits 6+ (Month 4)

6.2.6.1. In Clinic at Month 4 and Every 4 Months thereafter until Study Termination Visit

Visit 6 should be scheduled approximately 4 months ± 7 days from the first administration of LIQ861 and in-clinic follow-up visits should be scheduled every 4 months ± 7 days thereafter.

The following assessments may be done before or after study drug administration at Visit 6 and all subsequent in clinic follow-up visits:

- Full Physical Examination (at Visit 6 and every 12 months thereafter)
- NYHA Functional Class Assessment
- Collect unused study drug
- Study drug accountability
- Assess PAH Symptoms
- Consider dosing adjustments and record any prescribed changes
- Study drug dispensation
- Schedule next visit
- Schedule telephone follow-up visit for 8 weeks from the current visit to assess AEs, concomitant medications, PAH symptoms, and dose adjustment.

The following assessments will be conducted prior to study drug administration at Visit 6 and all subsequent in clinic follow-up visits:

- Vital signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes (at Visit 6 and every 12 months thereafter)
- Weight (at Visit 6 and every 12 months thereafter)
- Venous blood for clinical laboratory tests
    - NT-proBNP collected at every 4 month visit
    - Hematology and Blood Chemistry collected at Visit 6 and every 12 months thereafter
- DPI re-training
- Concomitant medications
- Treatment-Emergent Adverse Events
- Record time of last dose of inhaled treprostinil
- Administration of study drug
    - Note that the time of LIQ861 administration should be at least 4 hours after the last dose of LIQ861

The following assessments will be conducted <u>after</u> study drug administration at Visit 6 and all subsequent in clinic follow-up visits:

- 6MWT (within 15 to 60 minutes after administration of LIQ861)
- Inhalation Device User Survey (at Visit 6 and every 12 months thereafter)
    - The Inhalation Device User Survey should only be administered to Tyvaso Transition patients.
- MLWHF questionnaire (at Visit 6 and every 12 months thereafter)
- Concomitant medications

- Treatment-Emergent Adverse Events

6.2.6.2. Phone Visits (every 4 months starting at Month 6)

Phone visits (conducted by telephone call) should be scheduled approximately every 4 months ± 3 days starting at Month 6.

The following assessments should be conducted during the Phone Visit:

- Concomitant medications.
- Treatment-Emergent Adverse Events.
- Assess PAH Symptoms.
- Consider dosing adjustments and record any prescribed changes.
- Confirm date of next in clinic follow-up visit.

6.2.6.3. Study Termination Visit

Study termination visits will occur when a patient is discontinued from the study or once the Sponsor has decided to terminate the study.

The following assessments should be conducted during the Study Termination Visit:

- Full Physical Examination
- Weight and height
- Vital Signs (temperature, blood pressure, respiratory rate, and heart rate) collected after the patient has been upright and rested for at least 5 minutes
- Venous blood for clinical laboratory tests, including NT-proBNP
- 6MWT
- NYHA Functional Class Assessment
- Assess PAH Symptoms
- Inhalation Device User Survey
    - The Inhalation Device User Survey should only be administered to Tyvaso Transition patients.
- MLWHF questionnaire
- Record time of last dose of LIQ861
- Treatment-Emergent Adverse Events
- Concomitant medications
- Collect unused study drug
- Study drug accountability

At the Study Termination Visit, Study Drug Dispensation will not be performed and future visits should only be scheduled for follow-up visits in the event of an Early Termination. All remaining supply of Study Drug should be collected and reconciled.

6.2.7. Follow-up for Withdrawn Patients

Follow-up should occur for all patients that are removed from the study (Early Termination) for at least 4 months after receiving the last dose of LIQ861 or until all TEAEs are resolved or stabilized. If the patient was withdrawn from treatment with the study drug for clinical worsening, follow-up visits should be scheduled at the discretion of the investigator for the longer of the following periods:

- at least 4 months from receiving the last dose of LIQ861,
- until, in the opinion of the investigator, the patient is no longer clinically worsened from his or her baseline state, or
- until, in the opinion of the investigator, clinical worsening from baseline state is no longer attributed to treatment with LIQ861.

Follow-up visits may be conducted as telephone calls or in person visits at the Investigational site. At a minimum, follow-up visits should occur at approximately 2 weeks ± 2 days, and at 2 months and 4 months after receiving the last dose of LIQ861 and include the following assessments:

- Treatment-Emergent Adverse Events
- Concomitant medications

If the patient was withdrawn from treatment with the study drug for clinical worsening, additional assessments for the signs and symptoms that lead to judgement of clinical worsening should be made at all follow-up visits within 4 months of Early Termination or until the signs and symptoms that lead to judgement of clinical worsening are resolved.

6.3. Unscheduled Visits

Unscheduled visits, including telephone calls, may be conducted as needed based on the Investigator's medical judgment. At a minimum, the following safety assessments should be recorded at any unscheduled visits:

- Treatment-Emergent Adverse Events.
- Concomitant medications.
- Dose adjustments.

The following safety assessments may also be recorded at unscheduled visits:

- Physical examination findings.
- Clinical laboratory tests as indicated per Investigator judgment.
- PAH symptoms.

6.4. Pharmacokinetic Assessments

Blood samples for noncompartmental pharmacokinetic analysis will be collected during the PK Sub-Study only as outlined in the Time and Events Schedule in Appendix 1. Approximately 3 mL of whole blood will be collected from an indwelling catheter for each blood draw to yield approximately 1.5 mL of plasma collected for bioanalytical analysis.

Blood samples will be collected in lavender-top tubes with potassium (K_2) EDTA at the following nominal time points defined in the time and events schedule (actual blood sampling times must be recorded in the source and eCRF): predose (within 30 minutes of dose administration) and at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 180 minutes and 4 hours after the start of Tyvaso or LIQ861 inhalation.

Collecting, Processing, and Shipping Pharmacokinetic Samples

Blood samples will be drawn and processed for plasma as described in Appendix 4. The yield of plasma will be subdivided into 2 samples (~0.75 mL each) and frozen at -20°C within 60 minutes of sample collection. One set of these samples will be shipped to the bioanalytical lab for analysis,

as described in Appendix 4, and the other set will be stored at -20°C at the site until disposition instructions are communicated by Liquidia or designee.

6.5. Clinical Laboratory Tests

All routine samples will be analyzed by a licensed clinical laboratory. The clinical laboratory tests are as follows:

- **Hematology/Coagulation**: hemoglobin, hematocrit, white blood cell count with differential, and red blood cell count
- **Blood Chemistry**: Alanine aminotransferase (ALT; SGPT) and Aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), creatinine, alkaline phosphatase, sodium, potassium, magnesium, calcium, chloride, and uric acid.
- **Biomarkers:** NT-proBNP
- **Serum pregnancy test**: βhCG test for females of childbearing potential
- **Urine pregnancy test**: hCG test for females of childbearing potential (Baseline Visit only)

Blood for clinical labs should be collected at predose and at 4 hours post-dose on Day 1 and on Day 2 for patients in the PK sub-study. For all other visits, blood should be collected only at predose.

The Investigator is responsible for determining if out of range laboratory values are clinically significant or not. All clinically significant values will be recorded as AEs in the eCRF and followed until stabilization, resolution, or loss to follow up. Once resolved, the appropriate AE/SAE eCRF page(s) will be updated.

Details on sample collection and processing procedures will be provided in a separate laboratory manual.

6.6. Physical Examinations

A full physical exam (PE) will consist of assessments of the following: skin, ears, nose, throat, head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, neurologic, and lymphatic.

A brief physical exam includes all the body systems of the full PE, except for eyes, musculoskeletal, and neurologic.

All physical exam findings must be assessed as not clinically significant or clinically significant by the Investigator and recorded in the source document and eCRF. Clinically significant changes noted in PE findings should be recorded as an AE.

6.7. Vital Signs

Vital signs will be obtained per site standard of care to include oral temperature (°F or °C, with units indicated), blood pressure (mmHg), respiratory rate (breaths per minute), and heart rate (beats per minute [bpm]). Blood pressure, respiratory rate, and heart rate will be obtained after the patient has been upright and rested for at least 5 minutes.

6.8. Six-Minute Walk Test (6MWT)

The 6MWT should be performed as described by the guidelines from the American Thoracic Society (ATS 2002). Required equipment, detailed instructions, and a worksheet for data collection is provided in Appendix 7.

6.9. Assessment Windows

The actual time of the assessments must be recorded. At the Baseline visit, 6MWT should be performed prior to administration of inhaled treprostinil (Tyvaso or LIQ861), and the actual start and end time should be recorded. At all subsequent visits, 6MWT should be performed between 15 and 60 minutes after administration of LIQ861, and the actual start and end time should be recorded.

Collection of PK samples should occur as close to the nominal timepoint as possible. The actual time of PK sample collection will be recorded. All other assessments should be scheduled around the collection of PK samples at their nominal timepoints.

6.10. Patient Questionnaires

For all patients, the MLWHF questionnaire (Rector and Cohn 1992)will be administered at Baseline (Day 1), Visit 5 (Month 2), Visit 6 (Month 4), and every 12 months thereafter.

For all Tyvaso Transition patients, responses to the Inhalation Device User Survey (Appendix 5) will be collected at Baseline (Day 1), Visit 3 (Week 2), Visit 6 (Month 4), and every 12 months thereafter.

7. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. Only Treatment-Emergent AEs (TEAEs) and SAEs (occurring after the first inhalation of LIQ861, or Tyvaso in the PK sub-study, through the appropriate follow-up period) will be recorded in this study.

Definitions and terminology relevant to IND Safety Reports, as referenced in the U.S. Code of Federal Regulations, are addressed below.

7.1. Definition of a Treatment-Emergent Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. All AEs that occur after the time of treatment with the investigational product will be considered a Treatment Emergent AE (TEAE).

A TEAE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

A TEAE **does** include any:

- Exacerbation of a pre-existing illness.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.

- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments (e.g., change in physical examination), if they represent a clinically relevant finding, that were not present at Baseline or worsened during the course of the study.
- Laboratory test abnormalities, if they represent a clinically relevant finding, symptomatic or not, which were not present at Baseline or worsened during the course of the study.

A TEAE **does not** include a/an:

- Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions).
- Overdose of either study drug or concurrent medication without any signs or symptoms.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.

7.1.1. Definition of a Suspected Adverse Reaction

Suspected adverse reaction means any TEAE for which there is a reasonable possibility that the drug caused the TEAE. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the TEAE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

The following examples are the types of evidence that would suggest a causal relationship between the drug and the TEAE and would justify the consideration of an event as a suspected adverse reaction:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, throat irritation).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report them, is the need to evaluate the available evidence and render judgment about the likelihood that the drug actually caused the adverse event. FDA considers the definition of suspected adverse reaction and the application of the reasonable possibility of causality standard to be consistent with the concepts and discussion about causality in the International Conference on Harmonization (ICH) E2A guidance.

7.1.2. Definition of an Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.1.3. Definition of Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. "Unexpected," as used in this definition, also refers to TEAEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs, or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the Angiotensin-Converting Enzyme (ACE) inhibitor class and angioedema would be described in the Investigator's Brochure as a class, the first case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes.

This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the Investigator's Brochure as the basis for determining if newly acquired information generated from clinical trials or reported from other sources is unexpected. The suspected adverse reactions listed in the Investigator's Brochure (i.e., "expected") are those observed with the investigational drug and for which a causal relationship between the event and the drug is suspected or confirmed.

7.1.4. Definition of a Serious Adverse Event or Serious Suspected Adverse Reaction

A TEAE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

a. Death.

b. A life-threatening TEAE.

   - *A TEAE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include a TEAE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.*

c. Inpatient hospitalization or prolongation of existing hospitalization.

   - *Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered a TEAE.*
   - *Complications that occur during hospitalization are TEAEs. If a complication prolongs hospitalization, the event is an SAE.*
   - *"Inpatient" hospitalization means the patient has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.*

d. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

   - *This is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental*

trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. A congenital anomaly in the offspring of a patient who received drug.

f. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

- Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe (e.g., an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious). Similarly, a severe AE is not necessarily serious (e.g., nausea lasting for several hours may be rated as severe but may not be considered serious).

7.2. Adverse Device Effect and Serious Adverse Device Effect

An Adverse Device Event (ADE) is defined as any untoward and unintended response to a medical device. In this case, an ADE would refer to any untoward and unintended response to the RS00 Model 8 DPI.

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

A device event may also be a SAE if the product involved a participant in the clinical trial. A test article (device) that malfunctioned prior to use in a clinical research participant would not be a SAE for the participant. However, if the device malfunctioned or broke once use was attempted by the participant; it would be reportable as an AE, or as a SAE if serious criteria were met.

7.2.1. Unanticipated Adverse Device Effects

Unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

All unanticipated adverse device effects must be reported by the Investigator to the Sponsor within 3 days from identification or awareness of the event. Investigators are responsible for preparing and submitting complete, accurate, and timely reports to the reviewing IRB of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event, later than 10 working days after they first learn of the effect.

Any device that is associated with an unanticipated adverse device effect should be collected from the patient in accordance with the same procedures as any other used device (i.e., device accountability and marked for destruction).

If the Sponsor determines that an unanticipated adverse device effect, as reported by an Investigator, presents an unreasonable risk to the subject, the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible.

7.3. Severity of TEAEs/SAEs

The severity (mild, moderate, or severe) of each TEAE/SAE must be assessed by the Investigator, or designee. The following criteria should be considered when assessing severity:

- Mild — The symptom is barely noticeable to the patient and does not influence performance or functioning.
- Moderate — The symptom is of sufficient severity to make the patient uncomfortable, and performance of daily activities is influenced. Treatment for the symptom may be needed.
- Severe — The symptom causes severe discomfort. Treatment for the symptom may be necessary.

7.4. Assessment of Relatedness to Study Drug or Device

The Investigator will assess each TEAE and ADE for causality based on their medical judgment and the observed symptoms associated with the event. Each TEAE and ADE will be assessed as related or unrelated to study drug based on the following criteria:

- Unrelated — This category applies to those TEAEs and ADEs that the Investigator determines are most likely due to extraneous causes (disease, environment, etc.) and does not follow a reasonable temporal relationship.
- Related — This category applies to those TEAEs and ADEs that the Investigator determines are most likely due to test drug or device.

7.5. Method, Frequency, and Time Period for Detecting Adverse Events and Serious Adverse Events

At appropriate intervals (e.g., at every study visit and telephone contact), patients should be assessed for TEAEs and SAEs. After the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about TEAEs by asking a non-leading question such as the following:

1. “How are you feeling?”
2. “Have you had any medical problems since your last assessment/visit?”
3. “Have you taken any new medicines since your last assessment/visit?”

7.6. Reporting AEs and SAEs

7.6.1. Reporting Adverse Events

AEs occurring from when the patient signs the Informed Consent Form (ICF) until the last study event will be recorded. All AEs and SAEs occurring prior to the first inhalation of LIQ861 will be recorded in the medical history. Also, any sign, symptom, or disease present before the first inhalation of LIQ861 are considered AEs only if they have worsened after the first inhalation of LIQ861.

If the investigator detects an AE in a study patient after the last scheduled follow-up visit and considers the event related to treatment with LIQ861, the investigator should report it to the Sponsor's Medical Monitor.

The investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term (e.g., "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in terms of severity (Section 7.3) and relatedness (Section 7.4).

7.6.2. Timeframes for Reporting SAEs/SADEs

Prompt notification of the Sponsor regarding SAEs/SADEs is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. The Investigator must report SAEs/SADEs according to the following time frames:

- **Death or Life-Threatening Event:**
    - *Initial notification* must be provided to the Sponsor's Medical Monitor, or designee, **within 24 hours** of the Investigational site learning of the death or life-threatening event (regardless of causality).
    - *Complete SAE/SADE information* (i.e., all SAE/SADE pages) must be sent to the Sponsor's Medical Monitor or designee and the Sponsor's clinical operations lead, or designee, **within 24 hours** of receipt of the information by the Investigational site.
    - *Follow-up information* must be sent to the Sponsor's Medical Monitor, or designee, **within 24 hours** of receipt of the information by the Investigational site.
- **All other SAEs**
    - Complete SAE information (i.e., all SAE pages) must be sent to the Sponsor's Medical Monitor, or designee, **within 24 hours** of receipt of the information by the Investigational site.
    - Follow-up information must be sent to the Sponsor's Medical Monitor, or designee, and the Sponsor's clinical operations lead, or designee, **within 24 hours** of receipt of the information by the Investigational site.

7.6.3. SAE/SADE Information to Report

At a minimum, initial SAE/SADE reports must contain the site name and number, patient ID, patient demographic information, details of study drug administration, the serious adverse event

term, onset date, severity, relationship to study drug, and a brief narrative of the event. If the patient died, the report should include the cause of death and whether or not the death was related to the study drug, as well as any autopsy findings, if available. Please note that **relationship to study drug/causality is very important** and must be included in the initial report as it may impact expedited regulatory reporting requirements for the event. Do not, however, delay reporting of an SAE in order to obtain additional information. Additional information may be reported as a follow-up report as described in Section 7.6.8.

Complete SAE/SADE information should be reported in compliance with the Sponsor's Safety Management Plan for this study.

There may be instances when copies of medical records for certain cases are requested. **However, it is not acceptable for the Investigator to send photocopies of the patients' medical records in lieu of completion of the appropriate AE/SAE pages**. If medical records are submitted, all patient personal identifiers must be completely and thoroughly redacted prior to submission.

7.6.4. SAE/SADE Reporting Contact Information

Individual sites should report SAEs to NorthAmerica_Medical@parexel.com based on the timeframes given in Section 7.6.2.

7.6.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as TEAEs and SAEs

The Investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically relevant.

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., vital signs) that are judged by the Investigator as clinically relevant must be recorded in the medical history or as TEAEs or SAEs if they meet the definition of an adverse event. Clinically relevant abnormal laboratory findings or other abnormal assessments that are detected after the first inhalation of LIQ861, or that are present before administration of LIQ861 but worsen after the first inhalation of LIQ861, should be assessed for AE criteria.

7.6.6. Documenting SAEs/SADEs

A separate set of SAE pages should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE page.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the TEAE and/or SAE term.

7.6.7. Regulatory/Ethics reporting requirement

The Investigator must comply with the applicable local regulatory requirements related to the reporting of SAEs to the Sponsor. Additionally, the Investigator will be responsible for submitting SAE reports to the IRB/EC.

The Sponsor, or designee, will be responsible for submitting SAE reports to applicable regulatory authorities.

7.6.8. Follow-up of TEAEs and SAEs

All TEAEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts. TEAEs and SAEs will be followed until resolution, until the condition stabilizes, or until the patient is lost to follow-up. Once resolved, the appropriate TEAE/SAE eCRF page(s) will be updated. If a patient dies during participation in the study or during a recognized follow-up period, a copy of any post-mortem findings, including histopathology, should be obtained, if available, and forwarded to the Sponsor, or designee. New or updated information will be recorded on the originally completed SAE Report Form with all changes signed and dated by the Investigator, or designee.

8. STATISTICS

An integrated statistical and PK analysis plan (SAP) will provide details of planned analyses and summary documents, such as tables, listings and figures. An overview of the planned analyses is provided here. However, final analyses may not be limited to the summaries described herein.

8.1. Determination of Sample Size

Safety Study: Approximately 130 patients will be enrolled in the Main Study to ensure that at least 100 patients are evaluated for safety.

PK Sub-Study: The PK Sub-Study will enroll at least 18 PAH patients to evaluate the comparative bioavailability of treprostinil from LIQ861 to treprostinil from Tyvaso. The number of patients enrolled is sufficient to support such pharmacokinetic analyses.

8.2. Analysis Populations

The analysis populations are defined as follows:

- **Safety Population** will include all patients who receive at least one inhalation of LIQ861 and provide at least one post-Baseline safety assessment.

- **Pharmacokinetic Population (PK Population)** will include all patients in the PK Sub-Study who have not had any adverse events or protocol violations deemed to impact the PK, and have sufficient quantifiable samples collected for estimation of pharmacokinetic parameters from Day 1 of the crossover.

Safety endpoints will be reported for patients in the Safety Population. PK analyses will be performed on patients in the PK population. Inclusion of various populations in specific exploratory analyses will be defined in the SAP.

8.3. Baseline Characteristics and Patient Disposition

Overall Baseline and demographic data will be summarized using descriptive statistics. Patient disposition (e.g., the number of patients enrolled, completed, and discontinued) will be summarized and medical history data will be listed.

8.4. Hypothesis

No formal hypothesis testing is planned.

8.5. Exploratory Analyses

All analyses for the exploratory endpoints described in Section 3.2.4 will be described in the SAP.

8.6. Noncompartmental Pharmacokinetic Analyses (PK sub-study)

Treprostinil concentrations will be summarized, by treatment, using descriptive statistics (including sample size (N), mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum) for each treatment. Concentrations below the limit of quantification (BLQ) will be treated as zero for the computation of descriptive statistics and for construction of mean concentration-time profiles. Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics.

For pharmacokinetic analysis, treprostinil concentrations below the limit of quantification (BLQ) will be assigned a value of zero when they precede quantifiable samples in the initial portion of the profile. Following Cmax, BLQ values embedded between two quantifiable data points will be treated as missing when calculating area under the curve. BLQ values occurring at the end of the collection interval (after the last quantifiable concentration) will be treated as missing data. When consecutive BLQ concentrations follow quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile.

The PK parameters in Table 1 will be estimated by noncompartmental methods from plasma samples. Actual elapsed time from dosing will be used to estimate all individual PK parameters. The final list of PK parameters reported will be described in the SAP.

Table 1. Pharmacokinetic Parameters

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum concentration (h), obtained directly from the observed concentration versus time data.
AUClast	Area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration
AUCinf	Area under the plasma concentration-time curve from 0- time extrapolated to infinity
AUCext	The percentage of the AUC that is extrapolated beyond the last measurable concentration
λ_z	Apparent plasma terminal-phase elimination rate constant
$t_{½}$	Terminal-phase half life
Vz/F	Apparent volume of distribution, terminal phase
CL/F	Apparent systemic clearance
MRT	Mean residence time
Frel	Relative Bioavailability in %

Derived plasma PK descriptive statistics will be tabulated by treatment and reported with summary statistics. Descriptive statistics for PK parameters (Cmax, Tmax, AUClast, AUCinf, λ_z, $t_{1/2}$, Vz/F, CL/F, Frel) will include the arithmetic and geometric mean (for Cmax, AUClast, and AUCinf, only), CV%, SD of the arithmetic mean, median, minimum, maximum, and N.

Relative bioavailability (Frel) will be calculated for all patients that complete both days of the PK sub-study assessments using the following formula:

$$Frel = \frac{AUCinf_{LIQ861}}{AUCinf_{Tyvaso}} \times \frac{Dose_{Tyvaso}}{Dose_{LIQ861}}$$

8.7. Safety Analyses

Extent of Exposure, Adverse Events, Adverse Device Effects, Clinical Laboratory Assessments, and Vital Signs will be summarized with descriptive statistics.

8.7.1. Prior and Concomitant Medications

Medications taken after the patient receives study drug through Study Termination or Follow-up to Early Termination will be listed by treatment, dose level, and patient.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki", ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study patient. For studies conducted under a United States IND, such as this study, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50 and 21 CFR, part 56 are adhered to. The PK sub-study study is also subject to and will be conducted in compliance with 21 CFR, part 320, "Retention of Bioavailability and Bioequivalence Testing Samples."

9.1.2. Institutional Review Board (IRB)/Ethics Committee (EC) Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be reviewed and approved by the governing IRB/EC of the participating center prior to study initiation. Approval from the IRB/EC should be documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

Any modifications or amendment to documents originally submitted for review must also be submitted to the IRB/EC for approval prior to implementation. Additionally, the IRB/EC must be informed of any serious or unexpected AEs, new information that may adversely affect the safety of the patients or the conduct of the study, annual updates and/or requests for re-approval, and when the study has been completed.

9.1.3. Informed Consent

It is the responsibility of the Investigator or designee to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The Investigator, or designee, must utilize an IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient

and the person obtaining consent. A copy of the signed consent form will be provided to the patient and the original will be maintained with the patient's records.

9.1.4. Conflicts of Interest

The Investigator will be paid by the Sponsor of this study for study-related expenses, but will not profit from results, whether positive or negative, with regard to the product being evaluated. The Investigator will disclose any financial conflicts of interest to the Sponsor, should they arise, as required in 21 CFR part 54.

9.1.5. Confidentiality

The Investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials and an identification code (i.e., not names) should be recorded on any form submitted to the sponsor and IRB. The Investigator must keep a patient log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

9.1.6. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories (although not limited to) the following (1) Investigator's study file, and (2) patient clinical source documents.

The Investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/EC approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents can include (although is not limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram (ECG), electroencephalogram (EEG), X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

All clinical study documents must be retained by the Investigator until at least two years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, until two years after the IND is discontinued and regulatory authorities have been notified. The Investigator must notify the Sponsor prior to destroying any clinical study records.

Should the Investigator wish to move study records to another location, arrangements must be made to store these in sealed containers so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

9.1.7. Case Report Forms

For each patient who receives study drug, an eCRF must be completed and signed by the principal Investigator or sub-Investigator within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because

of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

9.1.8. Drug Accountability

The Investigator, or designee (i.e., pharmacist), is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), inventory at the site, distribution to, collection from, use by patient, and the destruction or return of unused study medication to the Sponsor. Dispensing records will document quantities received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication. The Investigator will assure that the study medication and records described in this section will be stored in a locked cabinet suitable for storage of pharmaceutical products and in accordance with the conditions specified in the Investigator's Brochure. Investigators must also assure that study medication and records will be available for examination by the study monitor during periodic visits.

During the study, the investigator will be notified of any expiry dates or retest date extensions of study drug supplies. If an expiry date notification is received during the study, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for destruction or return to the Sponsor or its designee.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with study requirements. Accountability records and inventory will be inspected during periodic visits throughout the study. Drug reconciliation may also be performed by a monitor during periodic visits, and the site may return used drug kits after reconciliation has been completed. At the Study Termination Visit, following final drug reconciliation by the monitor, the study site will be instructed by the Sponsor or its designee to return all unused study drug supplies, including empty containers.

9.1.9. Inspections

The Investigator will provide access to source documents and all study records for this trial to appropriately qualified personnel from the Sponsor, or its representatives, and to regulatory authority inspectors.

9.2. Sponsor Responsibilities

9.2.1. Study Materials and Instructions

It is the sponsor's responsibility to ensure that the Investigator is provided with the documents and other study materials necessary to conduct the study. Examples of those materials include, but are not limited to: protocol, Investigator's Brochure, study drug, eCRF, SAE collection forms, logs, etc. The sponsor will also provide training and oversight through site and medical monitoring.

9.2.2. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, will be made by Sponsor-initiated amendment. IRB/EC approval must be obtained before changes can be implemented.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

In accordance with International Conference on Harmonization Good Clinical Practice (ICH E6 (R2)) guidelines, study monitors must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitors, both central and field monitors, are responsible for routine review of the eCRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitors should have access to any patient records needed to verify the entries on the eCRFs. The Investigator agrees to cooperate with the monitors to ensure that any problems detected in the course of these monitoring activities are resolved.

9.3.2. Study Discontinuation

Both the sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/ECs. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

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APPENDIX 1. TIME AND EVENTS SCHEDULES

TIME AND EVENTS SCHEDULE FOR THE STUDY							
	Screening	Baseline [a]	Treatment		Follow-ups		
	Visit 1	Visit 2	Visit 3	Visits 4 & 5	Visits 6+		
Event	Day –28 to 1	Baseline Day 1	Week 2 (± 2 day)	Months 1 & 2 (± 3 days)	In Clinic at Month 4 and Every 4 Months thereafter until Study Termination Visit [b] (± 7 days)	Phone Visits at Month 6 and Every 4 Months thereafter until Study Termination Visit [b] (± 3 days)	Study Termination Visit [c]
Informed Consent	X						
Confirmation of eligibility	X	X					
Medical History & Demographics	X						
Physical Examination [d]	X	X		X [e]	X [f]		X [c]
Weight/Height Measurement	X	X [g]			X [f]		X
Vital Signs [h]	X	X	X	X	X [f]		X
Clinical Labs (blood) [i]	X	X	X	X	X [f]		X
NT-proBNP (blood) [i]	X	X	X	X	X		X
Serum Pregnancy Test for Females [j]	X						
Urine Pregnancy Test for Females [j]		X					
Infectious Disease Screen	X						
6MWT & Functional Class	X	X	X	X	X		X
Pulmonary Function Testing	X						
Inhalation Device User Survey [k]		X	X		X [f]		X
MLWHF questionnaire		X		X [e]	X [f]		X
Patient DPI Training [l]		X	X	X	X		
Record Last Dose of Inhaled Treprostinil		X	X	X	X		X
LIQ861 Administration [m]		X	X	X	X		
Treatment-Emergent Adverse Events [n]		X	X	X	X	X	X
Prior Medication Assessment	X	X					
Concomitant Medications		X	X	X	X	X	X
Assess PAH Symptoms		X	X	X	X	X	X
Consider and Record Dose Adjustments			X	X	X	X	
Collect Unused Study Drug			X	X	X		X
Dispense Study Drug		X	X	X	X [o]		
Schedule Next Visit	X	X	X	X	X [o]	X	

a. This table is for assessments for all subjects not participation in the PK Sub-Study. For Day 1 and Day 2 assessments in the PK Sub-Study see the PK Sub-Study T&E Table (below).
b. Patients will continue on 4-month periodic follow-up visits from the completion of Visit 6 until the Study Termination Visit.
c. Study Termination Visit should be completed within 1 month of drug approval or study termination or when a patient is discontinued from the study.

d. A full PE will be conducted at Visit 1, at Visit 6 and every 12 months thereafter, and at Study Termination; a brief PE will be conducted during Visit 2 & Visit 5.
e. Assessment is to be conducted at Visit 5 (Month 2) only.
f. Assessment is to be conducted at Visit 6 and every 12 months thereafter.
g. Height does not need to be assessed at Visit 2.
h. Vital signs, temperature, blood pressure, respiratory rate, and heart rate (blood pressure, respiratory rate, and heart rate will be measured after the patient has been upright and rested for at least 5 minutes).
i. Obtain venous blood for clinical laboratory tests before study drug administration.
j. Females of childbearing potential only.
k. The Inhalation Device User Survey should only be administered to Tyvaso Transition patients.
l. Patients should receive device training prior to the first dose of LIQ861. Patients should be retrained at each remaining visit until the Study Termination Visit.
m. Refer to instructions for use. For Tyvaso transition patients at Baseline, and all patients at post-Baseline visits, time of LIQ861 administration should be at least 4 hours after the last dose of inhaled treprostinil (Tyvaso or LIQ861).
n. Only treatment-emergent AEs will be collected.
o. The next Phone Visit and In Clinic Follow-up Visit should both be scheduled before the end of an in-clinic visit. During Phone Visits, the timing of the following In Clinic Follow-up visit should be confirmed.

TIME AND EVENTS SCHEDULE FOR THE PK SUB-STUDY

	Screening	Baseline [a]						Treatment						Treatment through Follow-Up
	Visit 1	Visit 2												Visits 3+
		Day 1 (Starting Hour)						Day 2 (Starting Hour)						
Event	Day –28 to 0	-1	0	1	2	3	4	-1	0	1	2	3	4	Week 1 through Follow-Up
Informed Consent	X													
Confirmation of eligibility	X	X						X						
Medical History & Demographics	X													
Physical Examination [b]	X	X						X						
Weight/Height Measurement [c]	X	X						X						
Vital Signs [d]	X	X						X						
Clinical Labs (blood) [e]	X	X					X [f]	X					X [f]	
NT-proBNP	X	X						X						
Serum Pregnancy Test for Females [g]	X													
Urine Pregnancy Test for Females [g]		X												
Infectious Disease Screen	X													
6MWT & Functional Class	X	X												
Pulmonary Function Testing	X													**Proceed to Visit 3 in Main Study T&E Table (above)**
Inhalation Device User Survey [h]							X					X		
MLWHF questionnaire						X								
Patient DPI Training [i]						X		X						
Record Last Dose of Inhaled Treprostinil		X						X						
Tyvaso Administration			X											
LIQ861 Administration							X		X				X	
Plasma for Pharmacokinetics [j]		X	X	X	X	X	X [f]	X	X	X	X	X	X [f]	
Treatment-Emergent Adverse Events [k]							X	← Continuous →						
Prior Medication Assessment	X	X												
Concomitant Medications			← Continuous →					← Continuous →						
Assess PAH Symptoms		X												
Dispense Study Drug							X						X	
Schedule Next Visit	X						X						X	

a. This table is for assessments in the PK Sub-Study. For Day 1 assessments for patients that are not in the PK Sub-Study, see the Study T&E Table (above)
b. A full PE will be conducted on Visit 1; a brief PE will be conducted during Visit 2.
c. Height does not need to be assessed at Visit 2.
d. Vital signs, temperature, blood pressure, respiratory rate, and heart rate (blood pressure, respiratory rate, and heart rate will be measured after the patient has been upright and rested for at least 5 minutes).
e. Obtain venous blood for clinical laboratory tests at predose and 4 hours post-dose on Day 1 and Day 2.
f. Blood for clinical labs and PK collected in the 4th hour after dosing should be obtained prior to administration of the first dose of LIQ861 on Day 1 and prior to administration of the second dose of LIQ861 on Day 2.
g. Females of childbearing potential only.
h. The Inhalation Device User Survey should be administered after administration of LIQ861.
i. Patients should receive device training prior to the first dose of LIQ861 on Day 1 and Day 2. Timing in relation to dose administration is not critical.

j. For PK sub-study only: Collect blood for measurement of treprostinil concentrations predose (within 30 minutes before dosing), and at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 180 minutes and 4 hours after study drug administration. Record actual times of blood collection for each timepoint.
k. Adverse events will be collected after administration of Tyvaso.

APPENDIX 2. GUIDANCE FOR LIQ861 DOSE SELECTION AND TITRATION

Dose Titration

Titration to a higher dose of treprostinil in LIQ861 should be governed by patient's degree of symptomatic relief, not to tolerance of PGI_2 side effects. If there are no symptoms of PGI_2 excess, doses of LIQ861 may be increased in 25 µg treprostinil strength increments according to the following guidelines up to the Maximum Allowed Dose of 150 µg treprostinil strength.

Dosing in excess of 150 µg treprostinil strength has not been previously studied and should not be implemented without consent from the sponsor.

Selection of Initial Dose in LIQ861 Add-on Patients

Start the patient on LIQ861 QID at the 25 µg treprostinil capsule strength.

1. After initial administration of LIQ861, supervise the patient's condition for a minimum post-dose observation period of 1 hour and discharge at the discretion of the Investigator.
2. Patients should be called between Day 5 and Day 7 post-dose to assess symptomatic relief and tolerance of LIQ861 therapy and a decision should be made whether to maintain the patient at the same dose or to increase to 50 µg LIQ861, administered as a single capsule QID.
3. At the Week 2 Visit, or after 2 weeks of stable LIQ861 QID administration, if the patient is experiencing sufficient symptomatic relief AND is tolerating the treatment, that dose should be maintained unless symptoms worsen.
    a. If the patient is not experiencing sufficient symptomatic relief OR is not tolerating the treatment, LIQ861 may be increased or decreased by 25 µg treprostinil strength increments, respectively.
4. Additional dosing increases may be implemented at 25 µg increments per week, however dose escalations are limited to a maximum of 150 µg as dosing in excess of 150 µg treprostinil strength has not been previously studied and should not be implemented without consent of the Sponsor. Prior to any dose titration the Investigator should contact the patient by phone to assess degree of symptomatic relief and tolerance and need/desire to adjust the LIQ861 dose.

Selection of Initial Dose in Tyvaso Transition Patients

If the patient is transitioning from Tyvaso, determine the appropriate LIQ861 starting dose from Table 2 below:

Table 2. Starting LIQ861 dose based upon Tyvaso Dose

Tyvaso Dose[1]		Starting LIQ861 Dose
Estimated Treprostinil	**Breaths of Tyvaso**	**Capsule Strength**
≤ 30 µg	≤ 5	25 µg
≥ 36 µg and ≤ 48 µg	≥ 6 and ≤ 8	50 µg
≥ 54 µg and ≤ 66 µg	≥ 9 and ≤ 11	75 µg
≥ 72 µg and ≤ 84 µg	≥ 12 and ≤ 14	100 µg
≥ 90 µg and ≤ 102 µg	≥ 15 and ≤ 17	125 µg
≥ 108 µg	≥ 18	150 µg

[1]Tyvaso doses up to 54 µg are consistent with the label. However, it is understood that physicians may choose to dose in excess of 54 µg and it is important to explore transitioning these patients given that LIQ861 was well tolerated up to 150 µg in healthy volunteers.

After initial administration of LIQ861 on Day 1, supervise the patient's condition for a minimum post-dose observation period of 4 hours.

For the second and third dose on Day 1, titrate LIQ861 dose in increments of 25 µg treprostinil strength based on clinical observations, patient feedback, and Investigator discretion. The patient should be observed for a minimum of 1 hour after the second dose of LIQ861 and may be discharged at the discretion of the Investigator.

At the Week 2 Visit, or after 2 weeks of QID administration of LIQ861, if the patient is experiencing sufficient symptomatic relief AND is tolerating the treatment, that dose should be maintained unless symptoms worsen.

a. If the patient is <u>not</u> experiencing sufficient symptomatic relief OR is <u>not</u> tolerating the treatment, LIQ861 may be increased or decreased by 25 µg treprostinil strength increments, respectively.

Additional dosing increases may be implemented at 25 µg increments per week, however dose escalations are limited to a maximum of 150 µg, unless agreed to by the Sponsor. Prior to any dose titration the Investigator should contact the patient by phone to assess degree of symptomatic relief and tolerance and need/desire to adjust the LIQ861 dose.

<u>Tyvaso Transition Patients – PK Sub-Study Procedures</u>

If the patient is transitioning from Tyvaso and is enrolled in the PK Sub-Study, the patient's final dose of Tyvaso on Day 1 of the study, and the starting dose for LIQ861 should be administered as described in Table 3. In the event that a patient's prescribed Tyvaso dose is not a multiple of 3 breaths, the dose administered on Day 1 for PK assessments will be selected as described in Table 3.

Table 3. Tyvaso and LIQ861 Dosing for Patients in the PK Sub-Study

Prescribed Tyvaso Dose[1]		PK Sub-Study Dosing	
Estimated Treprostinil	**Breaths of Tyvaso**	**Day 1: Breaths of Tyvaso**	**Day 2: LIQ861 Capsule**
≤ 30 µg	≤ 5	3	25 µg
≥ 36 µg and ≤ 48 µg	≥ 6 and ≤ 8	6	50 µg
≥ 54 µg and ≤ 66 µg	≥ 9 and ≤ 11	9	75 µg
≥ 72 µg and ≤ 84 µg	≥ 12 and ≤ 14	12	100 µg
≥ 90 µg and ≤ 102 µg	≥ 15 and ≤ 17	15	125 µg
≥ 108 µg	≥ 18	18	150 µg

[1]Prescribed Tyvaso Dose is the dose on which the patient has been stable in concordance with the study eligibility criteria.

Day 1

1. PK samplings will be collected over a 4 hour period after administration of the final Tyvaso dose. LIQ861 should be administered at the appropriate starting dose beginning with the second dose on Day 1.
    a. If the starting dose of LIQ861 is not tolerated, the next dose of LIQ861 may be decreased by 25 µg treprostinil strength.
    b. If the starting dose does not appear to be providing similar efficacy to the patient's Tyvaso treatment, the next dose of LIQ861 may be increased by 25 µg and the patient should be observed for at least an hour after the increase prior to discharge from the clinic at the Investigator's discretion.

Day 2

1. For the first dose on Day 2, LIQ861 should be administered at the same dose as the last tolerated dose taken on Day 1, and PK samples should be collected over a 4 hour period. After completion of the PK sampling, the patient may be discharged at the discretion of the Investigator.
2. At the Week 2 Visit, or after 2 weeks of QID administration of LIQ861, if the patient is experiencing sufficient symptomatic relief AND is tolerating the treatment, that dose should be maintained unless symptoms worsen.
    b. If the patient is not experiencing sufficient symptomatic relief OR is not tolerating the treatment, LIQ861 may be increased or decreased by 25 µg treprostinil strength increments, respectively.
3. Additional dosing increases may be implemented at 25 µg increments per week up to a maximum of 150 µg. Prior to any dose titration the Investigator should contact the patient by

phone to assess degree of symptomatic relief and tolerance and need/desire to adjust the LIQ861 dose.

Management of Side Effects

If symptoms of PGI_2 excess are observed, further dose increases of LIQ861 should be avoided until these symptoms subside.

If side effects cannot be tolerated or medically managed, one or more of the following strategies may be employed:

- Reduction of LIQ861 in 25 µg treprostinil strength increments until symptoms subside
- Discontinuation of LIQ861

Employment of any of the above strategies for mitigation of non-tolerated side effects should be documented in the eCRFs.

APPENDIX 3. INHIBITORS AND INDUCERS OF CYP2C8

In addition to any medications listed in the Investigator's Brochure that are excluded from concomitant use, the following inhibitors and inducers of CYP2C8 should not be taken by patients receiving LIQ861:

CYP2C8 Inhibitors

- Gemfibrozil
- Ketoconazole
- Trimethoprim
- Clopidogrel
- Deferasirox
- Teriflunomide
- Telithromycin
- Phenelzine
- Montelukast
- Quercetin

CYP2C8 Inducers

- Rifampin

APPENDIX 4. PK SAMPLE COLLECTION, PROCESSING, AND SHIPMENT

Sample Collection and Processing

- One (1) 3 mL Vacutainer tube containing (K_2) EDTA (lavender-top blood collection tubes, 13 x 75 mm, BD Vacutainer catalog # 367856 or equivalent) will be collected for PK analysis at each of the time points specified in Section 6.4 of the protocol. Fill tube as completely as possible to ensure sufficient sample volume for the required tests.
- Immediately after the sample is drawn, gently invert the tube 5 to 10 times to thoroughly mix the anticoagulant and place the tube at room temperature. Samples can be stored at room temperature for up to 60 minutes prior to completing the processing procedure.
- Centrifuge the sample at room temperature at 2500 to 3000 rpm (approximately 650 to 1450 x g) for 10 to 15 minutes to achieve a clear plasma layer over the red cells. The speed and time may be varied according to the make and model of centrifuge used.
- Immediately transfer (approximately) equal portions of the plasma to two (2) properly labeled polypropylene sample storage tubes (Sarstedt 3.5 mL tubes, P/N 60.549 or equivalent), cap and freeze samples at -20°C until shipment.

Note: Use of gel separation blood collection tubes is not recommended for PK sample analysis, as drug may be absorbed by the barrier gel.

Sample Collection and Processing

- All sample shipments should be preceded by a phone call or fax prior to their receipt. All HIV positive or other known infectious sample shipments must be preceded by a phone call or facsimile prior to their receipt.
- Detailed sample inventory information must accompany the samples. Lack of paperwork or illegible information will delay sample login and project initiation. Samples that are unclearly or incompletely labeled may be subject to additional handling fees. Submission of sample inventory information in electronic form is encouraged.
- Frozen samples should be shipped via overnight courier with an adequate amount of dry ice Monday through Wednesday to the following:

  ACM Global Laboratory
  Attn: Clinical Trials Specimen Management
  150 Elmgrove Park
  Rochester, NY 14624

- Notify ACM by e-mail, facsimile, or telephone that a shipment is leaving your location. Upon arrival, the shipment will be unpacked and the contents verified and documented. If requested, the individual responsible at the shipment point of origin will be notified of sample disposition.
- Backup samples should be stored frozen at the Investigational site until successful receipt of initial shipment is confirmed by ACM.

APPENDIX 5. INHALATION DEVICE USER SURVEY

Inhalation Device User Survey

1. How long have you been using the RS00 Model 8 Dry Powder Inhaler (DPI) with LIQ861 (circle the most accurate)?

Less than 1 week	Less than 1 month	Less than 6 months	Less than 1 year	More than 1 year

2. How would you rate the RS00 Model 8 DPI compared to the Tyvaso Inhalation System you were previously using (circle 1)?

0 Strongly Prefer the Old Device	1 Prefer the Old Device	2 No Preference	3 Prefer the New Device	4 Strongly Prefer the New Device

For Investigational Site Personnel Only:			
Site Number	Patient ID	Date Administered	Investigator/Coordinator Initials

APPENDIX 6. ASSESSMENT OF HEPATIC AND RENAL IMPAIRMENT

Evidence of severe hepatic impairment will be assessed by simply documenting the patient's history or presence of ascites and encephalopathy. A patient will be considered to have severe hepatic impairment if the patient both:

- has evidence of ascites, AND
- has been diagnosed with or has evidence of encephalopathy grade of 1 or higher based on the West Haven Criteria.

Any patient fitting this profile should be excluded from the study.

Renal impairment will be assessed by calculating estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD) equation (CDER 2010):

$$\text{eGFR} = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742, if\ female) \times (1.212, if\ African\ American)$$

Where Serum Creatinine is measured in mg/dL, Age is measured in years, and eGFR is measured in mL/min/1.73m^2. Subjects with eGFR less than 45 will be excluded from the PK sub-study and subjects with eGFR of less than 30 will be excluded altogether.

APPENDIX 7. 6MWT INSTRUCTIONS AND WORKSHEET

The following instructions on performing a 6MWT are reproduced from the guidelines published by the American Thoracic Society (ATS 2002). A sample data collection worksheet and Borg Scale are provided at the end of the instructions (below).

Safety Considerations

Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.

Supplies that must be available include:

- oxygen,
- sublingual nitroglycerine,
- aspirin, and
- albuterol (metered dose inhaler or nebulizer).

A telephone or other means should be in place to enable a call for help.

The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.

Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.

If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following:

- chest pain,
- intolerable dyspnea,
- leg cramps,
- staggering,
- diaphoresis, and
- pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician:

- blood pressure,
- pulse rate,
- oxygen saturation, and

- physician evaluation.

Oxygen should be administered as appropriate.

Technical Requirements and Equipment

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length; a 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

The following equipment is required to conduct the assessment:

- Countdown timer (or stopwatch)
- Mechanical lap counter
- Two small cones to mark the turnaround points
- A chair that can be easily moved along the walking course
- Worksheets on a clipboard
- A source of oxygen
- Sphygmomanometer
- Telephone
- Automated electronic defibrillator

In preparation for the assessment, patients should:

- Wear comfortable clothing and appropriate shoes for walking,
- Use their usual walking aids, such as a cane or walker,
- Continue their usual medical regimen
- Not have exercised vigorously within 2 hours of the beginning of the test.

Additionally, a light meal is acceptable before early morning or early afternoon exams.

Instructions for Conducting the 6MWT

1. Repeat testing should be performed about the same time of day to minimize intraday variability.

A “warm-up” period before the test should not be performed.

The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the Patient Information portion of the data collection worksheet (below).

Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

a. The SpO_2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO_2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected.

Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale provided below.

Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.

Instruct the patient as follows:

> "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.
>
> You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

> "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.
>
> Start now, or whenever you are ready."

Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

> After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."
>
> When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."
>
> When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."
>
> When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient: “You are doing well. You have only 1 minute to go.”

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: “You can lean against the wall if you would like; then continue walking whenever you feel able.” Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: “In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you.”

When the timer rings (or buzzes), say this: “Stop!” Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

When the timer is 15 seconds from completion, say this: “In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you.”

When the timer rings (or buzzes), say this: “Stop!” Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

After the test record the postwalk Borg dyspnea and fatigue levels and ask this: “What, if anything, kept you from walking farther?”

If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.

Record the number of laps from the counter (or tick marks on the worksheet).

Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

Congratulate the patient on good effort and offer a drink of water.

Data Collection Worksheet for Conducting a Six-Minute Walk Test

Lap Counter: _	Date:
	Technician ID:
	Walk #:

Patient Information

Patient Name:		Race: ☐ White ☐ Black or African American ☐ Asian ☐ Native Hawaiian or Other Pacific Islander ☐ American Indian or Alaska Native	Medications Before Test (Medication, Dose, Time)
Patient ID #:			
Age:	____years		
Height:	____ft ____in, ____ meters		
Weight:	____ lbs, ____ kg		
Blood Pressure:	____ / ____	Ethnicity: ☐ Hispanic ☐ Not Hispanic	

Test Information

	Baseline	End of Test		
Time:	___:___	___:___	Stopped or Paused before 6 minutes?	☐ No ☐ Yes, Reason?
Heart Rate:	___	___		
Dyspnea[a]:	___ (Borg)	___ (Borg)	Other symptoms at end of test?	☐ Angina ☐ Dizziness ☐ Hip, Leg, or Calf Pain
Fatigue[b]:	___ (Borg)	___ (Borg)		
SpO_2[c]:	___%	___%		

Lap Distance: ____ meters
Total Laps: ____ laps
Final Partial Lap: ____ meters
6MWD[d]: ____ meters
Predicted distance: ___ meters
Percent predicted: ___ %

Technician Comments and Interpretation (including comparison with a pre-LIQ861 6MWD):

a. The patient should rate baseline dyspnea using the Borg Scale (below). At the end of the test, the patient should be reminded of their baseline score before recording the End of Test score.
b. The patient should rate baseline fatigue using the Borg Scale (below). At the end of the test, the patient should be reminded of their baseline score before recording the End of Test score.
c. Collection of SpO_2 is optional. If recorded, the device must be lightweight (less than 2 lbs) and should not be continuously monitored.
d. 6MWD = (Total Laps × Lap Distance) + Final Partial Lap

The Borg Scale

0 Nothing at All
0.5 Very, Very slight (just noticeable)
1 Very slight
2 Slight (light)
3 Moderate
4 Somewhat severe
5 Severe (heavy)
6
7 Very Severe
8
9
10 Very, very severe (maximal)