Abbreviated Clinical Study Report Synopsis

A Two Part, Phase 2 Open-label, Multi-Centre, Dose Escalation Hemodynamic Study to Evaluate Dose-Response and Safety of Inhaled LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Subjects

LTI-201

EudraCT No.:	2018-003414-40
ClinicalTrials.gov:	NCT03884465
Investigational product:	LIQ861
Clinical development phase:	Phase 2
Indication:	Pulmonary arterial hypertension (WHO Group 1)
Sponsor:	Liquidia Technologies, Inc 419 Davis Dr. Suite 100 Morrisville, NC, United States of America
Coordinating investigators:	Prof Dr med Ardeschir Ghofrani Universitätsklinikum Giessen Medizinische Klinik II Klinikstr. 33, Giessen, Germany Dr Laurent Savale Hôpital Bicêtre 78, rue Général Leclerc 94270 Le Kremlin-Bicêtre, France
Date of first subject enrolled:	30-Oct-2019
Date of last subject completed:	12-May-2021
Early termination:	12-May-2021
Sponsor's signatory name:	Tushar Shah Liquidia Technologies, Inc
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Report version and date:	Final 1.0 (02-May-2022)

This clinical study was performed in compliance with Good Clinical Practices including the archiving of essential documents.

Synopsis

Name of sponsor/company: Liquidia Technologies, Inc
Name of product: LIQ861
Name of active ingredient: treprostinil

Title of the study:
A two-part, phase 2 open-label, multi-centre dose escalation hemodynamic study to evaluate dose-response and safety of inhaled LIQ861 (treprostinil) in pulmonary arterial hypertension (WHO Group 1) subjects

Clinical trial registry: NCT03884465 (ClinicalTrials.gov), 2018-003414-40 (EudraCT)
Protocol number: LTI-201

Principal investigators and study sites[1]:
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Coordinating investigators:
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Publication (reference): Not applicable

Studied period:
30-Oct-2019 (first subject in) to 12-May-2021 (last subject contact)

Reporting period:
This report describes all clinical data collected from the time of the first subject signing the informed consent (30-Oct-2019) until completion of the safety follow-up after the last LIQ861 administration of all enrolled subjects (12-May-2021).

Clinical phase: Phase 2

Objectives:
The primary objective of this study was to characterize acute hemodynamic dose-response relationship and the chronic hemodynamic response to LIQ861.

The secondary objective of this study was to evaluate the acute and chronic safety and tolerability of LIQ861 in subjects with pulmonary arterial hypertension (PAH).

[1] Sites that screened subjects.

Methodology:

This was a two-part (Parts A and B), open-label, multi-centre, phase 2 dose escalation study to evaluate hemodynamic (HD) and safety of LIQ861 in PAH subjects (WHO Group 1), followed by an open-label extension period.

Part A: Subjects were to be enrolled in 4 dose cohorts with 8 subjects for each cohort. After screening, subjects underwent right heart catheterization (RHC) to assess HD parameters on Day 1 before, during, and after inhalation of nitric oxide (NO) to assess HD response to vasodilators. After post-NO baseline HD measurements, subjects orally inhaled LIQ861 at doses of 25 µg (Cohort 1), 50 µg (Cohort 2), 75 µg (Cohort 3), and 100 µg (Cohort 4) treprostinil.[2] Blood samples for PK measurements were also collected on Day 1. At sites that did not participate in Part B, subjects completed the study with Part A at Day 1.

Once a dose cohort was completed, the available safety, HD and PK data were reviewed by the safety review committee before escalation to next dose. Subject enrollment was to be suspended if either a treatment-related severe adverse event (AE) occurred in 2 or more subjects within a dose cohort or if a treatment-related serious AE (SAE) occurred in any subject.

Part B started immediately after the conclusion of the Part A assessments to assess the 16-week HD and chronic use safety and tolerability of LIQ861. Subjects continued therapy at the dose they had received in Part A by self-administration four times daily (QID) on Day 1 until Week 16. The dose could be up or down titrated by no more than 25 µg per week (titration schedule) to relieve symptoms or reduce side effects. Part B dosing (the second LIQ861 administration on Day 1) could be started at 25 µg before following the titration schedule. Visits had to be performed at Weeks 2, 4, 8, and 16. At the Week 16 visit, RHC and HD assessments including blood sampling for PK analysis as performed on Day 1 of Part A were repeated. At all visits of Part B, the six-minute walk distance (6MWD) by using the six-minute walk test (6MWT), the New York Heart Association (NYHA) Functional Class status, the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, and the PAH symptoms using the patient global impression of severity (PGI-S) were assessed. The registry to evaluate early and long-term PAH disease (REVEAL) registry risk score and European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk score were determined.

During the study, safety monitoring (physical examination, electrocardiogram (ECG), heart monitoring, and assessment of vital signs and clinical laboratory) and AE documentation were performed.

[2] During the LIQ861development, a change in the IMP strengths to account accurately for treprostinil content, resulted in modification of capsule strength nomenclature from 25, 50, 75, and 100 µg (used in protocol v3.0 and v4.0, and product labels) to 26.5, 53, 79.5, and 106 µg treprostinil, respectively. In protocol v5.0, the nomenclature was updated. The bulk LIQ861 inhalation powder composition or treprostinil content was not changed. In this study report (including Tables, Figures, and Listings), the dosing nomenclature originally used for capsule strength (25, 50, 75, 100 µg) was used to remain consistent with data presentations provided in other documents (eg, Study LTI301 clinical study report and new drug application) and to allow assessment of efficacy and safety within and between studies for each corresponding strength.

Subjects who completed Part B were offered to continue therapy QID until Week 126 in the **open-label extension period**. The titration schedule had to be followed. Visits were planned at Weeks 32, 48, 74, 100, and 126 for safety and exploratory assessments.

The study was prematurely terminated due to the impact of COVID on recruitment and sponsor's decision not to pursue development and approval of LIQ861 in the EU at this time. Due to the early termination, only the first two cohorts were enrolled and the LIQ861 dose of subjects in Part B was gradually down titrated at the discretion of the investigator until treatment was discontinued and a study termination visit within 30 days after the last LIQ861 administration was performed.

Number of subjects (total and for each treatment) planned and analyzed:

- A sample size of 32 treated subjects was planned, 8 subjects per dose cohort.
- Because of the premature study termination and dose-escalation in 2 dose cohorts only, 15 subjects were treated and analyzed.

An overview of the number of subjects enrolled and analyzed is given in the table below.

	Screened set	Safety set	EXP	HDA	HDB
LIQ861 dose Part A: 25 µg	8	8	7	8	6
LIQ861 dose Part A: 50 µg	7	7	7	7	-
Not dosed	2	-	-	-	-
Total	17	15	14	15	6

N = 0 is shown as '-'.
EXP = exploratory set, HDA= hemodynamic set Part A , HDB = hemodynamic set Part A, N = number of subjects in the set.

Diagnosis and main criteria for inclusion and exclusion[3]:

Requirements for inclusion were:

1. An Institutional Review Board approved informed consent was signed and dated by the subject prior to any study-related activities.
2. The subject was 18 years of age or older.
3. If the subject was a female of childbearing potential, then the subject had to have a negative pregnancy test at the Day 1 Visit (tests performed within 2 days before Day 1 were accepted) and agreed to practice a highly effective (failure rate of less than 1% per year when used consistently and correctly) method of birth control until 24 hours after completion of all study assessments defined in Appendix 1 of the protocol. If the subject was postmenopausal or had documented surgical sterilization, a pregnancy test and birth control was not necessary. It was the investigator's responsibility for determining whether the subject had adequate birth control for study participation.

[3] Based on the protocol version v5.0 (09-Jul-2020). The inclusion and exclusion criteria have not been changed since V3.0 (07-Aug-2019).

4. The subject diagnosed with PAH belonged to one of the following subgroups of the updated Nice Clinical Classification Group 1, which includes:
    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), human immunodeficiency virus (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 subject was NYHA Functional Class II - IV at Screening and:
    a) had not previously been treated for PAH, or
    b) had documented stable doses of no more than 2 approved non-prostacyclin PAH-disease specific therapies for at least 3 months prior to Screening, was willing and able to add LIQ861 to their treatment regimen and was willing to withhold the dosing of these therapies for at least 12 hours prior to study-mandated RHC procedures.
6. The subject had to complete a baseline 6MWD ≥150 m.
7. The subject had to have evidence of Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC) ≥60% of predicted values and FEV1/FVC ratio ≥60% during the 6-month period prior to consent.

Subjects with any of the following were to be excluded from study participation:

1. The subject's clinical condition was such that, in the opinion of the investigator, they were not expected to remain clinically stable for the duration of the study.
2. Subjects with pulmonary hypertension (PH) in the Updated Nice Classification Groups 2-5, or PAH Group 1 subgroups were not covered by the inclusion criteria (eg, associated with portal hypertension [1.4.3] or with schistosomiasis [1.4.5]).
3. The subject was currently taking prostacyclin analogues or agonists, including treprostinil, iloprost, epoprostenol or selexipag.
4. The subject discontinued any medication (except for anticoagulants, but otherwise including but not limited to oxygen, a different class of vasodilator, diuretic, digoxin, and digitalis) for PH within 14 days prior to Day 1.
5. The subject had a new type of therapy (including but not limited to oxygen, a different class of vasodilator, diuretic, digoxin, and digitalis) for PH added within 30 days prior to Day 1.

6. The subject had uncontrolled systemic hypertension as evidenced by systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg at the time of screening.
7. The subject had 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 symptomatic coronary artery disease.
8. The subject had an atrial septostomy.
9. The subject had a history of prolongation of QT interval on ECG as follows: Male subjects with a corrected QT interval using Fridericia's formula (QTcF) >450 msec and female subjects with QTcF >470 msec.
10. The subject had any serious or life-threatening disease other than conditions associated with PAH.
11. The subject took any excluded medications listed in the Investigator's Brochure, namely inhibitors and inducers of CYP2C8 (see Appendix 3 of the protocol v5.0, Appendix 11.1.1).
12. The subject had a hypersensitivity or allergy to any of the ingredients of LIQ861, NO, or other clinically relevant allergies (clinical relevance per investigator judgment).
13. The subject had an acute pulmonary embolus within 6 months prior to Baseline.
14. The subject had a stroke or transient ischemic attack within 6 months prior to Baseline.
15. The subject had evidence of an active uncontrolled sepsis or systemic infection in the period after informed consent up to Baseline.
16. The subject was pregnant or lactating.
17. The subject had any musculoskeletal disease or any other disease that limits evaluation of 6MWD.
18. The subject has participated in an investigational product or device study within the 30 days prior to Baseline.
19. The subject had current evidence of drug abuse in the opinion of the investigator.
20. The subject had severe hepatic impairment as evidenced by any history of ascites AND encephalopathy.
21. The subject had severe renal impairment (estimated glomerular filtration rate <35 mL/min utilizing the Modification of Diet in Renal Disease study equation or requires dialytic support.
22. The subject was an employee or an immediate family member to an employee of the sponsor or the investigator.
23. The subject was not a member or beneficiary of a social security scheme.

24. The subject lacked a legal protection measure.
25. The subject had been deprived of their liberty by a judicial or administrative decision.
26. The subject had a known Hepatitis B or Hepatitis C infection with active viral replication.
27. The subject had a known HIV infection with CD4 count less than 200 and more than undetectable viral load, defined as less than 50 copies/mL.
28. The subject required use of intravenous inotropes including, but not limited to, Levosimendan, Dopamine, Dobutamine, Dopexamine, Epinephrine, Isoprenaline (isoproterenol), Norepinephrine (noradrenaline), Milrinone, or Amrinone, within 30 days prior to Baseline.
29. The subject required intravenous diuretic therapy within 30 days prior to Baseline.
30. Subjects was taking vitamin K antagonist therapy with a known international normalized ratio ≥3.5 (assessed per local care standards) at the time of screening assessments or at Baseline.

Test product, dose, mode of administration, batch number:

- LIQ861, active ingredient: treprostinil
- Doses: 25 µg, 50 µg, 75 µg, and 100 µg treprostinil[4]
- Mode of administration: dry powder inhalation by using the RS00 Model 8 dry-powder inhaler
- Batch number: 190025, 190029, 190030, 190031, 190032, 200009, 200010, 200085

Duration of treatment: once in Part A, QID for 16 weeks in Part B and for 126 weeks in the open-label extension period, if applicable

Criteria for evaluation[5]:

Safety

Primary endpoint:

- Incidence and severity of treatment-emergent AEs (TEAEs) and SAEs

[4] During the LIQ861development, a change in the IMP strengths to account accurately for treprostinil content, resulted in modification of capsule strength nomenclature from 25, 50, 75, and 100 µg (used in protocol v3.0 and v4.0, and product labels) to 26.5, 53, 79.5, and 106 µg treprostinil, respectively. In protocol v5.0, the nomenclature was updated. The bulk LIQ861 inhalation powder composition or treprostinil content was not changed. In this study report (including Tables, Figures, and Listings), the dosing nomenclature originally used for capsule strength (25, 50, 75, 100 µg) was used to remain consistent with data presentations provided in other documents (eg, Study LTI301 clinical study report and new drug application) and to allow assessment of efficacy and safety within and between studies for each corresponding strength.

[5] Based on statistical analysis plan v2.0 (03-Sep-2021).

Secondary endpoints:

- Secondary acute safety endpoints (on Day 1 and at Week 16 RHC day[6]):
    - Change from baseline measurements to 240 minutes in vital signs
- Secondary chronic safety endpoints:
    - Incidence of drug-related TEAEs
    - Changes from Day 1 (Baseline) measurements to Week 16/Early Termination/Week 126 in vital signs, clinical laboratory, and physical examination findings

The following HD and explorative variables were analyzed and only a short summary of the data is given in the report:

Primary HD endpoint:

- Maximum response in pulmonary vascular resistance (PVR; termed eMAX) from Baseline (Day 1, pre-dose), post dosing with LIQ861, on Day 1 and at Week 16, respectively; ie, the maximum reduction in PVR from baseline value after taking LIQ861

Secondary HD endpoints:

- Changes from Baseline (pre-dose) and the percentage changes from Baseline calculated for measurements prior to NO at Week 16, and post both NO and LIQ861 on both HD assessment days for the following HD parameters:
    - PVR
    - pulmonary vascular resistance index (PVRI)
    - pulmonary arterial pressure (PAP; systolic, diastolic and mean)
    - pulmonary capillary wedge pressure
    - right atrial pressure/central venous pressure[7]
    - pulmonary arterial compliance[8]
    - CO
    - cardiac index (CI)
    - systemic vascular resistance (SVR)
    - systemic vascular resistance index (SVRI)
    - mixed venous oxygen saturation
    - systemic arterial oxygen saturation
    - pulmonary artery oxygen saturation

[6] The protocol did not specify that acute safety endpoints were to be assessed at Day 1 and Week 16. The incidence of drug-related TEAEs within 4 hours of dosing and the change from baseline measurements to 120 minutes in ECG/heart monitor assessments were not analyzed.

[7] Right atrial pressure and central venous pressure are interchangeable in the context of this study. Therefore, the term right atrial pressure/central venous pressure was used.

[8] Pulmonary arterial compliance was not included in the protocol and was added to the list of parameters in SAP.

  - systemic blood pressure (systolic, diastolic and mean)
  - heart rate (HR)
- eMAX from Baseline (Day 1, pre-dose), post dosing with LIQ861, on Day 1 and at Week 16, respectively, in PAP (systolic, diastolic and mean), PVRI, CO, CI, SVR, and SVRI (ie, maximum reduction for PAP, PVRI, SVR, and SVRI, and maximum increase for CO and CI)

Exploratory endpoints:

- Changes from Baseline (Day 1) in 6MWD, HR, dyspnea, fatigue, and oxygen saturation
- Changes from Baseline (Day 1) in NYHA Functional Class status
- Changes from Baseline (Day 1) in NT-proBNP levels
- Changes from Baseline (Day 1) to Week 16 in the REVEAL registry risk score
- Changes from Baseline (Day 1) to Week 16 in the risk levels (ESC/ERS risk score)
- Changes from Baseline (Day 1) in PGI-S

Statistical methods:

No formal statistical testing was done. All variables were analyzed descriptively, ie, continuous variables by summary statistics and categorical variables by frequency tables using number and percentage of subjects.

All enrolled subjects (written informed consent and screened) were included in the screened set. All enrolled subjects who received at least 1 inhalation of LIQ861 were included in the safety set. Subjects in the safety set who received at least 1 inhalation of LIQ861 in Part B were included in the exploratory set. Subjects in the safety set who had at least 1 evaluable post-LIQ861 HD measurement were included in the HD set Part A. Subjects in the safety set who had at least 1 evaluable post-LIQ861 HD measurement at Week 16 were included in the HD set Part B.

No interim analysis after completion of Parts A and B were performed. All analyzed safety data were reported in this clinical study report.

SUMMARY - CONCLUSIONS

Subject disposition

15 of 17 subjects who were screened for study participation were treated at least once with LIQ861 and included in the safety analysis. In Part A, 8 subjects (Cohort 1) were treated with 25 µg and 7 subjects (Cohort 2) with 50 µg. All but 1 subject discontinued the study prematurely: 12 subjects due to early study termination by the sponsor and 2 subjects because of an AE. 1 subject of Cohort 1 completed the study in Part A and was not enrolled in Part B due to an AE. The other (14) subjects entered in Part B but none in Cohort 2 completed Part B. 7 subjects of Cohort 1 continued LIQ861 treatment in the extension period. The maximum dose

taken QID during the study was 150 µg in 3 subjects, 125 µg in 1 subject, 75 µg in 7 subjects, 50 µg in 2 subjects, and 25 µg in 1 subject.

Demographics and baseline characteristics

The study population included 9 women and 6 men with a median age of 57 years (range 36 to 77 years) and a body mass index between 23.7 and 38.0 kg/m². PAH was diagnosed 0.2 to 31 years ago. 60% of subjects were NYHA Functional Class II and 40% Class III. The majority of subjects (≥60%) had idiopathic PAH and a FEV1 of ≥80%. Most of them had 2 PAH-disease specific therapies (53% of subjects) and took a medication combination of endothelin receptor antagonists and phosphodiesterase type 5 inhibitors (33% of subjects).

Safety results

Overview of treatment-emergent adverse events (safety set, N = 15)

	Part A dose cohort					
	25 µg (N = 8)		50 µg (N = 7)		Total (N = 15)	
	n'	n (%)[a]	n'	n (%)[a]	n'	n (%)[a]
Any TEAE	27	7 (87.5)	15	6 (85.7)	42	13 (86.7)
Any TEAE related to IMP	15	7 (87.5)	10	5 (71.4)	25	12 (80.0)
Any SAE	1	1 (12.5)	-		1	1 (6.7)
Any SAE related to IMP	1	1 (12.5)	-		1	1 (6.7)
Any TEAE leading to IMP discontinuation	2	1 (12.5)	2	1 (14.3)	4	2 (13.3)

n' = 0 is shown as '-'.

[a] Percentages are based on the total number of subjects per group.

IMP = investigational medicinal product, N = number of subjects, n' = number of events, n = number of subjects with events, SAE = treatment-related serious adverse event, TEAE = treatment-emergent adverse event.

13 of 15 subjects (87%) had a total of 42 TEAEs during the study of which 25 were considered related to the investigational medicinal product (IMP) and 1 was qualified as serious TEAE.

The most frequent reported TEAEs were cough (33% of subjects), throat irritation (27% of subjects), and headache (20% of subjects). These events were considered related to the IMP by the investigator. All other events occurred in less than 3 subjects.

Most (39) TEAEs were mild or moderate with an onset in Part B (21 TEAEs), required no action, and had resolved at the end of the study. In 4 subjects, at least 1 mild or moderate TEAE (ie, palpitations, brain natriuretic peptide increased, dizziness, headache, diabetic neuropathy, or iron deficiency) was not resolved; all but headache was not considered related to the IMP. Only, 3 TEAEs that occurred in 2 subjects of Cohort 1 were severe and considered related to the IMP: nausea (onset in Part B) and headache (onset in extension period) in 1 subject, and hypoxia (onset in Part A) in another subject. In 2 subjects, the LIQ861 dose was reduced because of moderate cough or swelling face.

2 subjects discontinued the trial prematurely due to severe nausea and headache during the extension period or due to moderate throat irritation and mild vomiting during Part B.

1 SAE (severe hypoxia) considered related to the IMP occurred in Part A in a subject who had received a LIQ861 dose of 25 µg. After medication therapy, the subject had recovered at the same day and terminated the study after Part A.

No subject died during the study.

No clinically relevant trend over time was observed in laboratory values, body temperature, blood pressure, heart rate, respiratory rate, ECG, or physical examination findings.

Hemodynamic results

PVR and mean pulmonary arterial pressure (mPAP) data are highlighted as these are typically most responsive to prostacyclin therapy.

In Cohort 1 (25 µg treprostinil) and Cohort 2 (50 µg treprostinil) on Day 1, treatment with NO and inhaled LIQ861 showed an expected reduction in PVR (by a mean of 33.1% and 18.1%) and mPAP (approximately 15%). Following inhaled LIQ861, the maximum effect was seen after 15-30 minutes and returned to the baseline value after around 90 minutes. There was no evidence of a dose response between the 25 µg and 50 µg doses of inhaled LIQ861.

At Week 16, 6 of the 8 subjects in Cohort 1 had a repeat HD assessment. The subjects had titrated from 25 µg to doses ranging from 75-150 µg with a mean dose of 117 µg. Baseline PVR and mPAP at Week 16 were improved relative to the Day 1 baseline, shown by a reduction in mean values. Treatment with NO and LIQ861 was associated with further improvement in PVR and mPAP from Week 16 baseline, shown by a reduction in mean values. Despite the baseline value being lower at Week 16, the magnitude of the reduction was comparable to the effect observed on Day 1. At Week 16, a meaningful reduction was still observed at 90 minutes following LIQ861 dosing with a maximum effect after 15-60 minutes.

Exploratory efficacy results

While this was an open-label safety study, the following efficacy measures were evaluated during the 16 weeks of chronic administration of LIQ861: 6MWT, NT-proBNP, PGI-S, NYHA Functional Class, and PAH risk scores. 6 of the 8 subjects in Cohort 1 completed the 16 weeks of therapy and titrated to doses of 75-150 µg LIQ861 (mean = 117 µg). 4 of the 7 subjects in Cohort 2 were treated for 4 weeks. Their LIQ861 therapy was discontinued due to study termination. These subjects achieved doses of 50 µg.

With chronic LIQ861 administration, improvement in 6MWT (mean change approximately 20 m) and reduction in NT-proBNP (mean change approximately 70 pg/mL) were observed. From the screening visit to the last pre-dose measure prior to the 6MWT, PGI-S scores improved or remained stable during the study for all but 1 subject. Post the 6MWT, no discernable changes were observed. The NYHA Functional Class assessment remained stable with LIQ861 treatment whereas the PAH risk scores improved in all but 1 subject during the study.

Pharmacokinetic results

Pharmacokinetic (PK) results are reported in a separate PK report.

Conclusions:

- LIQ861 administrated by inhaler up to a QID dose of 150 µg treprostinil in PAH subjects was safe and well tolerated
- Expected HD changes (improvements in PVR and mPAP) were observed following acute and chronic LIQ861 administration
- With chronic therapy, subjects clinical course seemed to improve or remain stable following 16 weeks of LIQ861 treatment

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