Statistical Analysis Plan

Sponsor Name:	Liquidia Technologies, Inc.
Protocol Number:	LTI-301
Protocol Title:	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
Protocol Version and Date:	Original (20th October 2017) Amendment 1 (13th November 2017) Amendment 2 (7th January 2019) Amendment 3 (20th March 2019)
Author(s):	Gary Layton
SAP Version:	Final v2.0
SAP Version Date:	23rd July 2020

Signature Page

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I confirm that I have reviewed this document and agree with the content.

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Revision History

Version (Date)	Summary of Changes
1.0 (10th July 2019)	Initial version – The initial version was written for the reporting of data collected through to Month 2.
2.0 (23rd July 2020)	Updated to provide details for final reporting of study data.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
6MWD	Six Minute Walk Distance
AE	Adverse Event
CSR	Clinical Study Report
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MLWHF	Minnesota Living With Heart Failure
MMRM	Mixed Effect Model for Repeated Measures
NT-proBNP	N-Terminal Pro B-Type Natriuretic Peptide
NYHA	New York Health Association
PAH	Pulmonary Arterial Hypertension
PK	Pharmacokinetics
PT	Preferred Term
QID	“quater in die” – 4 Times a Day
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

2. INTRODUCTION

LIQ861 (treprostinil) inhalation powder is a prostacyclin vasodilator for the treatment of pulmonary arterial hypertension (PAH; World Health Organization [WHO] Group 1) in patients with New York Heart Association (NYHA) Class II-III symptoms, to improve exercise ability.

This statistical analysis plan (SAP) is developed based on Protocol Version 3.0 (dated 20th March 2019) and the electronic case report form (eCRF) dated 23rd July 2018. The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are comprehensive and appropriate for the assessment of study objectives specified in the protocol. Any amendments to the SAP will be made prior to database lock. Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report (CSR).

A CSR summarized data collected from Screening up through the Month 2 Visit in order to satisfy the agreement for the regulatory filing. An initial version of the SAP detailed the analyses required for that CSR. This SAP (Version 2.0) details the analyses required for the final reporting of the study.

2.1. RESPONSIBILITIES

Nuventra Pharma Sciences, Inc. will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures.

3. STUDY OVERVIEW

3.1. STUDY OBJECTIVES

The primary objective of this study is to evaluate the long-term safety and tolerability of LIQ86l in patients with PAH.

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

3.2. STUDY DESIGN

Study LTI-301 is a Phase 3, open-label, multicenter study in subjects 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 ("Transition" group) or who are taking no more than 2 approved non-prostacyclin oral PAH therapies ("Add-On" group). A subset of patients on Tyvaso (N=18) will be enrolled in a 1 directional crossover to compare the bioavailability and PK of treprostinil as they transition from Tyvaso to LIQ861.

For all subjects, scheduled study visits to the clinic will occur at Screening (within 28 days prior to Baseline on Day 1), Baseline (Day 1), Week 2, Month 1, Month 2, Month 4, and every 4 months thereafter (e.g., Month 8, Month 12) until termination of the study by the Sponsor, all subjects are transitioned to an extension study or regulatory approval.

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) until the Study Termination Visit.

Unscheduled visits may be conducted at the Investigator's discretion for subject safety monitoring, follow-up of AEs, or other reasons that will be documented.

Subjects 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.

3.3. DETERMINATION OF SAMPLE SIZE

At least 130 PAH subjects were to be enrolled to ensure that at least 100 completed 2 months of treatment to evaluate the long-term safety and tolerability of LIQ861. The study enrolled 121 subjects and 113 had the Month 2 visit.

3.4. TREATMENT ASSIGNMENT AND BLINDING

All subjects will receive open label LIQ861 and doses according to their individualized titration.

3.5. ADMINISTRATION OF STUDY MEDICATION

Tyvaso Transition subjects will receive training on the use of the dry powder inhaler (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 remain in the clinic for safety observation per Investigator discretion. The initial LIQ861 dose will be matched to the comparable prescribed Tyvaso dose at transition as detailed in the study protocol (Appendix 2 of the protocol); 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.

Add-On subjects will receive training on the use of the 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. Study drug will be administered for Add-On subjects initially at 25 mcg treprostinil in LIQ861 QID, with timing of dose titrations chosen at the Investigator's discretion while maintaining a QID dosing schedule. Alterations to the dosing interval (e.g. 3 times a day or 5 times a day) must be approved by the Sponsor.

Titration to a higher dose of treprostinil in LIQ861 will be governed by a subject's degree of symptomatic relief, not to tolerance of prostacyclin side effects. If there are no symptoms of prostacyclin excess, doses of LIQ861 will be increased in 25 mcg treprostinil strength increments in accordance with the Guidance for LIQ861 Dose Selection and Titration described in the study protocol (Appendix 2 of the protocol) up to the maximum allowed dose of 150 mcg treprostinil strength. Dosing in excess of 150 mcg treprostinil strength, which has not been previously studied, will require consent from the Sponsor.

Two LIQ861 formulations were used during the conduct of the LTI-301 study and, for brevity, are referred to as the "clinical formulation" and the intended "commercial formulation".

Four dose strengths of LIQ861 were used in this study: 25, 50, 75, and 100 mcg treprostinil capsules. For dose levels in excess of 100 mcg treprostinil, 2 capsules of lower strength were used in immediate succession to achieve the desired dose of treprostinil.

It should be noted that when the study was ongoing, the strength of the intended commercial formulation was recalculated, resulting in revised capsule strengths of 26.5, 53, 79.5 and 106 mcg treprostinil. The clinical and intended commercial formulations have been determined to be comparable and clinical differences in strengths were expected to be negligible. For ease of review, the 25, 50, 75, and 100 mcg capsule strength nomenclature will be used throughout the tables, listings, and figures.

4. ENDPOINTS

4.1. PRIMARY ENDPOINT

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

4.2. SAFETY ENDPOINTS

Safety endpoints are as follows:

- Incidence of treatment-emergent drug/device-related adverse events
- Changes from Baseline to Month 2/Study Termination in clinical laboratory and vital signs*

* Changes from Baseline to Month 2 and Month 4 will be summarized. In the absence of data at the relevant visit early termination data may be used if collected within the visit window (see Section 6.4).

4.3. PHARMACOKINETIC ENDPOINTS

The details for these endpoints can be found in the protocol and the PK SAP. As PK data have already been reported no further details will be provided in this SAP.

4.4. 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.

5. ANALYSIS POPULATIONS

As data through Month 2 have already been reported for Study LTI301 the participants have already been classified for each population. The same classifications will be used for these analyses.

5.1. SCREENED POPULATION

The Screened Population includes all subjects who signed the informed consent.

This population includes 146 subjects.

5.2. SAFETY POPULATION

The Safety Population includes all subjects who received at least 1 inhalation of LIQ861.

This population includes 121 subjects (55 Transition and 66 Add-On).

5.3. EFFICACY POPULATION

The Efficacy Population includes all subjects who received at least 1 inhalation of LIQ861 and provided at least 1 post-Baseline efficacy assessment.

This population includes 120 subjects (55 Transition and 65 Add-On).

5.4. MODIFIED INTENT TO TREAT POPULATION

The Modified Intent-to-Treat (mITT) Population includes all subjects who received at least 1 inhalation of LIQ861 and were identified as WHO Group 1, based upon adjudication by a panel of PAH experts (refer to Study LTI-301 Adjudication Committee Charter).

This population includes 106 subjects (46 Transition and 60 Add-On).

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

Subjects differ by treatment history prior to entry to Study LTI-301 - the two groups will be referred to as the Transition and Add-On Groups. For all summary tables data will be presented for all subjects (Overall) and by group.

Continuous variables will be summarized using the number of non-missing observations (n), mean, standard deviation (SD), standard error (SE), median, minimum and maximum. Categorical variables will be summarized using frequencies and percentages.

Categorical shift tables will include marginal totals.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more decimal place than the original values, and SD and SE should be printed out to 2 more decimal places than the original values. The minimum and maximum should report the same number of decimal places as the original values.

Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer. The number of subjects in the analysis population will be the denominator.

Unless stated otherwise, baseline will be taken as the last available non-missing assessment prior to study drug administration (Day 1).

In by-visit summary tables, the baseline will be summarized using all available data, but also for each visit using only the baseline data from subjects with available data at the visit; hence the mean change from baseline will equal the mean visit value – mean baseline value.

Throughout this document 'change from baseline' refers to the actual change from baseline (i.e. visit value – baseline value).

All data will be listed separately for each group. Data listings will present study days in addition to dates, where study day is derived as (assessment date – first day of dosing + 1).

Since there is no formal hypothesis testing, no adjustment for multiplicity will be made for inferential statistical comparisons within or between groups.

Programming of analyses, tables and listings will be performed using R Version 3.4.0 or higher (R Foundation for Statistical Computing, Vienna, Austria) or SAS® Version 9.3 or higher (Cary, North Carolina, US).

6.2. MISSING DATA

All possible efforts will be made to minimize missing data. No imputation of missing data will be performed unless specifically mentioned.

The original data will always be presented in the listings.

6.2.1. MISSING BASELINE

Unless specified otherwise, screen values or pre-dose unscheduled measurements may be used as a baseline value in the event of missing Day 1 pre-dose measurements.

6.2.2. ADVERSE EVENT CLASSIFICATIONS

AEs with missing classifications will be assumed to be the following:

- missing causality will be taken as treatment related
- missing seriousness will be taken as serious
- missing severity will be taken as severe

6.2.3. PARTIAL OR MISSING DATES

For missing or partial dates for adverse events and medications the following rules will be applied to impute the date:

If the start date is incomplete, then it will be imputed as follows:

- If the start date is completely missing, the start date will be equal to the first dose date (Day 1). However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.

- If the start day is missing: check if month is same as month of first dose date of study treatment. If yes, impute to first dose date of study treatment; else impute first day of the month. However, if the stop date is not missing, is the same month as the start day and is before the first dose of study treatment, then the stop date will be used instead.

- If the start day and month are missing: check if year is same as the year of the first dose date of study treatment. If yes, impute to first dose date of study treatment; else impute to first day of the first month (January). However, if the stop date is not missing, is the same year as the start day and is before the date of the first dose of study treatment, then the stop date will be used instead.

If the stop date is incomplete, then it will be imputed as follows:

- If the stop date is completely missing and the medication/event is not ongoing, the stop date will be imputed as the date of study withdrawal.

- If the stop day is missing, the last day of the month will be used. If resulted imputed stop date is after the date of study withdrawal, then the date of study withdrawal will be used.

- If the stop day and month are missing, then the last day of the last month (31st December) will be used. If resulted imputed stop date is after the date of study withdrawal, then the date of study withdrawal will be used.

The original reported partial dates will be provided in listings, but study days and derived variables (e.g. durations) will be use the imputed dates.

6.2.4. LABORATORY VALUES

If laboratory parameters are reported as out of assay range, e.g. < x or > y the limit of quantification will be used in the calculation of summary statistics. However, the listing will present the data as originally reported (e.g. < x).

6.2.5. SUMMARY TABLE PRESENTATIONS

In summaries for continuous data, the number of missing values will be presented. The missing count will not include subjects who have discontinued at earlier visits or not had the potential to reach the visit (i.e. subject transitioned to extension study prior to reaching the visit).

In summaries for categorical data the following categories will be included:

- No potential to reach the visit
- Withdrew prior to the visit
- Missing

6.3. SUBGROUPS

The following subgroups will be used:

- Age (< 65 years of age, ≥ 65 years of age)
- Age (<75 years of age, ≥ 75 years of age) – NT-proBNP only
- Sex (Female, Male)
- Race (Asian, Black, White, Other)
- Number of PAH specific medications at baseline (none, 1, 2)
- Duration since diagnosis (≤ 5 years, > 5 years)

6.4. VISIT WINDOWS

Data will be assigned to visits using windowing (see table below). If more than one assessment (including the early termination or unscheduled assessments) falls within the same defined window, the assessment closest to the target day with non-missing data will be considered for analysis; however, with the exception of laboratory and vital sign data, the visit must be within 7 days of the final dose of study treatment. For laboratory and vital sign data the assessment must be no more than 1 day after the final dose of study treatment. If two qualifying assessment dates are at the same distance from the target day, the latest assessment with non-missing data will be taken for analysis.

Visit	Target Day	Analysis Window	Interval
Baseline[a]	1[b]	Day -30 to Day 1	
Week 2	14	2 -22	21
Month 1	30	23 – 45	23
Month 2	60	46 – 90	45

Visit	Target Day	Analysis Window	Interval
Month 4	120	91 – 150	60
Month 8	240	211 – 270	60
Month 12	360	331 – 390	60
Month 16	480	451 – 510	60
Month m	30m	(30m - 29) – (30m + 30)	60

[a] Baseline is the last assessment taken prior to the start of study treatment.

[b] Day 1 represents the first day of study treatment.

Please note that telephone visits are not included as only log data will be collected at those visits (e.g. AEs and concomitant medications).

These visit windows will be reviewed and may be updated prior to reporting. Any assessments that fall outside of these windows will be reviewed on a case-by-case basis, and decisions on their handling will be fully documented prior to reporting. Data collected outside these windows will only be listed.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. PATIENT DISPOSITION AND WITHDRAWALS

For all subjects screened the following will be presented:

- Number of subjects screened
- Number (%) of subjects who failed screening
- Number (%) of subjects who met the eligibility criteria, but didn't enter the study treatment phase (with reasons)

The above information will only be presented in the 'Overall' column and percentages will use the number of subjects screened (i.e. Screened population) as the denominator.

For the Safety population the following will be presented:

- Number of subjects dosed (Enrolled)
- Number (%) of subjects who withdrew from the study (along with reasons)
- Number (%) of subjects who completed the study
- Number (%) of subjects who chose to enter the extension study (Study LTI-302)

- Number (%) of subjects in each analysis population

Percentages will use the number of subjects dosed (i.e. Safety population) as the denominator.

A Kaplan-Meier plot will present the time to study drug discontinuation. Subjects who transition to Study LTI-302 will be censored on the day of their transition.

For each scheduled visit the following will be presented using the Safety population:

- Number (%) of subjects who had the potential to reach the visit
- Number (%) of subjects who attended the visit (including only clinic visits)
- Number (%) of subjects who withdrew from the study prior to the visit
- Number (%) of subjects who missed the visit

Their potential to reach a visit is based on the duration of time they could have been in the study, from their first dosing date till their date of transitioning to Study LTI-302 or, for those subjects who withdraw from LTI-301, the date when subjects started transitioning to LTI-302 (18th July 2019).
The algorithm will be:

1. Did they have the visit within 7 days of their last dose of study treatment?
    a. If yes, then **Yes to Potential and Attended Visit**
    b. If no, go to 2
2. Did they have the potential to have the visit?
    a. If yes, then go to 3
    b. If no, then **No to Potential**
3. Did they withdraw prior to the visit?
    a. If yes, then **Yes to Potential and Withdrew prior to the visit**
    b. If no, then **Yes to Potential and Missing**

7.2. DEMOGRAPHIC CHARACTERISTICS

These data were reported in the Month 2 clinical study report. The outputs will be repeated for this final study report.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

These data were reported in the Month 2 clinical study report. The outputs will be repeated for this final study report.

7.4. PRIOR AND CONCOMITANT MEDICATIONS

Prior medications will be defined as those medications started prior to the administration of study drug on Day 1. Concomitant medications will be defined as those medications taken following administration of study drug on Day 1. Hence medications started before receiving the study dose,but continuing after will be considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

Prior medications (PAH and non-PAH) were reported in the Month 2 clinical study report. The outputs will be repeated for this final study report.

Concomitant medications will be presented for the Safety population by therapeutic class and preferred term (PT), using the WHO-Drug Dictionary (WHO-Drug; March, 2017), with frequencies and percentages. A subject who took the same medication more than once will be counted only once. Separate summaries will be presented for PAH disease specific medications and non-PAH disease specific medications.

In the summary tables, classes/PTs will be presented by decreasing frequency of subjects overall. In cases of classes/PTs with equal frequencies, medications will be sorted alphabetically.

The PAH disease specific medications ongoing on Day 1 will be summarized. The summary will include the number and percentage of subjects on 0, 1 or 2 medications, and also the number and percentage of subjects on each combination. Shift from baseline tables will also be presented (for number [0, 1 or 2] and combinations) at Months 4, 8 and 12.

The shift table will also be presented to the subject's end of the study, but will be split by those who completed LTI-301 and those who withdrew from LTI-301. Please note, for those who withdrew from LTI-301 the intention is to only consider medications taken before study drug discontinuation and not additional medications taken afterwards.

7.5. EXTENT OF EXPOSURE

The duration of treatment will be summarized as both a continuous variable using descriptive statistics and as a categorical variable (e.g., <2 months, 2 to < 4months, 4 to < 8 months..). Duration of treatment is defined as (date of last dose – date of first dose +1). The duration will be summarized for each dose and overall.

For these summaries a month will be taken to be 28 days in duration.

At Months 2, 4 and 8 (Study Days 56, 112 and 224) the average daily dose (mcg) will be summarized. Summaries will be generated for all subjects who had the potential to reach the visit (taking dose as 0 for those who have withdrawn prior to the visit) and for all subjects

still ongoing in the study at the visit.

Dose shifts from baseline will also be presented by visit.

The number and percentage of Transition subjects with sustained transition treatment through the end of Month 2 will be tabulated by initial dose and overall, where sustained transition treatment is defined as:

- treatment with LIQ861 through at least 2 months beyond transition from Tyvaso
- no interruptions to study treatment totaling more than 7 days prior to the end of Month 2
- no treatment with any prostacyclin or prostacyclin analogs apart from administration of LIQ861

The number and percentage of subjects on each dose of LIQ861 will also be tabulated against the previous Tyvaso dose for Transition subjects at Months 2, 4, 8 and 12.

7.6. STUDY TREATMENT COMPLIANCE

Compliance will be assessed using subject data recorded in the drug accountability form of the eCRF. The compliance rate for each subject will be computed as 100% x (actual number of capsules taken over the study period)/ (designated total number of capsules that should have been taken over the study period). Study period is defined as the number of days from Day 1 till their last day of dosing. The number of dosing days will take account of dose interruptions due to AEs. If a subject fails to return study medication compliance will be provided as a range, assuming that either all or none of the unreturned medication was returned.

8. SAFETY ENDPOINTS

All safety evaluation will be performed using the Safety population. The mITT population will only be used where specifically mentioned.

8.1. ADVERSE EVENTS

AEs will be coded using MedDRA version 20.1.

AEs will be considered TEAE unless there is clear indication that the event occurred prior to the first dose of study drug. AEs present prior to study drug administration that increased in severity or relationship to study drug afterwards will also be classed as TEAEs.

All AEs that occur after the first dose of study drug will be considered to be 'treatment-

emergent' with the exception of AEs that occur more than 7 days after the last dose of study drug.

Events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent (see Section 6.2).

Only TEAEs will be included in the summary tables.

An overall summary will present the number of subjects with:

- any TEAE*
- any TEAE considered as related to study drug (evaluated by the investigator as Related or severity not reported)*
- any serious TEAE*
- any serious TEAE considered as related to study drug*
- Maximum severity TEAEs of mild, moderate or severe; i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity
- Maximum severity TEAEs considered as related to study drug of mild, moderate or severe; i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity
- any TEAE leading to study drug discontinuation (i.e. TEAEs reported as having either an action taken as 'Drug Withdrawn') and/or Study Discontinuation*
- any TEAE considered as related study drug discontinuation (i.e. TEAEs reported as having either an action taken as 'Drug Withdrawn') and/or Study Discontinuation *
- any TEAE leading to death*

The table will also include the total number of TEAEs reported for those flagged (*). The total number of unique terms within subjects will also be presented for those flagged (*), counting each TEAE PT only once within each subject.

This overall summary will be presented for both the Safety and mITT populations.

This summary will also be produced using the Safety population for the following:

- the subgroups in Section 6.3
- those TEAEs with an onset up to the Month 2 visit (inclusive) and those with an onset after the Month 2 visit separately.

The number and percentage of subjects with TEAEs will be presented by system organ class (SOC) and PT for both the Safety and mITT populations. Subjects with multiple TEAEs within a SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination.

A similar summary will be presented for the Safety population of TEAEs considered as study drug related.

The 'all causality' summary will also be produced using the Safety population for the following:

- the subgroups in Section 6.3
- those TEAEs with an onset up to the Month 2 visit (inclusive) and those with an onset after the Month 2 visit separately.

SOC and PT summaries of TEAEs by maximum severity (mild, moderate or severe) will be presented for all TEAEs and also for those considered as related to study drug.

All summaries will be ordered by descending frequency of total number of subjects within each SOC and then similarly by decreasing frequency of total number of subjects within each PT, in the overall column. In cases of SOCs or PTs with equal frequencies, AEs will be sorted alphabetically.

All TEAEs will be listed by subject and AE onset day. AE duration (stop date/time – start date/time) will be included in the listing; where applicable imputed data will be used for the calculation of AE duration, but the original date information will be presented in the listing.

The following separate listings will also be provided:

- serious AEs
- TEAEs leading to study drug discontinuation (i.e. TEAEs reported as having either an action taken as 'Drug Withdrawn') and/or Study Discontinuation

If there are any deaths a listing will include the date of death and the adverse event(s) associated with death.

8.2. LABORATORY EVALUATIONS

Laboratory safety parameters are to be assessed at Screening, Baseline, Week 2 and Months 1, 2, 4 and every 12 months thereafter.

Observed and change from baseline clinical laboratory data (including hematology and blood chemistry parameters) will be summarized using descriptive statistics, for Months 2 and 4.

A shift from baseline table for Months 2 and 4 will be presented. Normal, abnormal low, abnormal high and missing records will be summarized, with marginal totals, using frequencies and percentages.

In addition to summarizing by visit the last 'on-treatment' measurements will also be summarized. The last 'on-treatment' measurement must be after Day 1 and within 1 day of the final dose of LIQ861.

All individual laboratory results will be listed. The listing will include change from baseline values and values outside the laboratory reference range will be flagged.

All pregnancy laboratory results (serum and urine) will be listed.

8.3. VITAL SIGNS

Vital signs are to be assessed at Screening, Baseline, Week 2 and Months 1, 2, 4 and every 12 months thereafter.

Observed and change from baseline data will be summarized using descriptive statistics for Months 2 and 4.

In addition to summarizing by visit the last 'on-treatment' measurements will also be summarized. The last 'on-treatment' measurement must be after Day 1 and within 1 day of the final dose of LIQ861.

Vital signs data will be listed, with changes from baseline values included.

8.4. PHYSICAL EXAMINATION

All abnormal findings at Baseline will be recorded on the Medical History/Concomitant Diagnoses page (or equivalent) of the case report form. New abnormal findings or a worsening of baseline conditions detected at follow-up physical examinations will be recorded as AEs on the eCRF.

Physical examination data will be listed.

9. EXPLORATORY ENDPOINTS

9.1. SIX-MINUTE WALK DISTANCE

Six-minute walk distance is to be assessed at Screening, Baseline, Week 2 and Months 1, 2, 4 and every 4 months thereafter.

6MWD and changes from baseline will be summarized by visit (Week 2 and Months 2, 4 and 8). For the changes from baseline the 95% confidence intervals for the mean changes will also be presented. Mean changes from baseline and 95% CIs will be plotted against visit for each Group.

The changes from baseline in 6MWD to Month 8 will be analyzed using a mixed effect model for repeated measures (MMRM) with group, visit and group-by-visit interaction as fixed effects and baseline as a covariate. An unstructured covariance will be attempted, but alternative structures will be explored if the unstructured structure isn't suitable. The Kenward-Roger method will be used to adjust the degrees of freedom. Comparisons of the least square means for the interaction term, group-by-visit, will provide inferential statistics for comparisons between groups at Months 2, 4 and 8.

9.2. NYHA FUNCTIONAL CLASS

NYHA functional class will be assessed at Screening, Baseline, Week 2 and Months 1, 2, 4 and every 4 months thereafter.

NYHA Functional Class will be summarized categorically at each Visit (Week 2 and Months, 2, 4, 8 and 12). A shift table for changes from baseline will also be presented.

The proportion of subjects who improve their functional class will be estimated for each group at each visit (Week 2 and Months 2, 4, 8 and 12) along with its 95% 2-sided binomial confidence interval. Those subjects who didn't have the potential to reach the visit will be taken as missing, but those who withdrew will be taken as not improving.

9.3. NT-proBNP

NT-proBNP will be assessed at Screening, Baseline, Week 2 and Months 1, 2, 4 and every 4 months thereafter.

Values and changes from baseline will be summarized by visit (Week 2 and Months 2, 4 and 8). Geometric means will be included for the absolute values and the ratio to baseline from back-transforming the mean changes from baseline for natural log data will be presented for the changes from baseline. The 95% confidence intervals will also be presented for the ratios. The ratios and 95% CIs will be plotted against visit for each group.

Values and changes from changes from baseline will also be summarized for the age sub-groups (<75 years of age and ≥ 75 years of age).

The change from baseline in NT-proBNP to Month 8 will be analyzed using an MMRM analysis with group, visit and group-by-visit interaction as fixed effects and baseline as a covariate An unstructured covariance will be attempted, but alternative structures will be explored if the unstructured structure isn't suitable. The Kenward-Roger method will be used to adjust the degrees of freedom. Comparisons of the least square means for the interaction term, group by visit, will provide inferential statistics for comparisons between groups at Months 2, 4 and 8. Given that the data are skewed with some subjects having very high values, a natural log transformation will be applied to the data prior to analysis. Consequently back-transformed LS means will provide ratio comparisons of the groups.

9.4. MLWHF QUALITY OF LIFE QUESTIONNAIRE

The MLWHF Quality of Life Questionnaire will be assessed at Baseline, Month 2, Month 4 and every 12 months thereafter. The Questionnaire has 21 items, each scored within the range 0 to 5. Two domains and 1 total score will be derived:

- Physical Dimension (Range 0 to 40)
- Emotional dimension (Range 0 to 25)
- Total Score (Range 0 to 105)

Higher scores denote poorer quality of life. The scores are provided by the site in the eCRF. The scores will be used as provided, even if answers to some of the individual questions are missing.

Scores and changes from baseline will be summarized by visit (Months 2, 4 and 8).

The changes from baseline to Month 8 will be analyzed using an MMRM analysis with group, visit and group-by-visit interaction as fixed effects and baseline as a covariate. An unstructured covariance will be attempted, but alternative structures will be explored if the unstructured structure isn't suitable. The Kenward-Roger method will be used to adjust the degrees of freedom. Comparisons of the least square means for the interaction term, group-by-visit, will provide inferential statistics for comparisons between groups at Months 2, 4 and 8.

9.5. DEVICE SATISFACTION (TYVASO TRANSITION SUBJECTS ONLY)

Patient satisfaction with the LIQ861 DPI compared to the inhalation device from which they transitioned will be assessed using a simple device preference questionnaire at Week 2, Month 4 and every 12 months thereafter. The number and percentage of subjects with each response will be presented for Months 2 and 4.

9.6. RISK ASSESSMENT

Subject's risk assessment according to the 2015 ESC/ERS Pulmonary Hypertension Guidelines will be summarized at Baseline and Month 2, Month 4, Month 8 and Month 12:

Assessment	Low Risk	Medium Risk	High Risk
6MWD (m)	>440	165-440	<165
NYHA Functional Class	I/II	III	IV
NT-proBNP (pg/mL)	<300	300-1400	>1400

The number and percentage of subjects with each risk level will be presented for each Assessment by visit.

Additionally, the number and percentage of subjects with 0, 1, 2 or 3 low risk categories will be presented by visit for each group. The different combinations of low risk assessments will also be presented.