# Protocol A1481316

**A MULTI-CENTRE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, TWO-ARMED, PARALLEL GROUP STUDY TO EVALUATE EFFICACY AND SAFETY OF IV SILDENAFIL IN THE TREATMENT OF NEONATES WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN) OR HYPOXIC RESPIRATORY FAILURE AND AT RISK FOR PPHN, WITH A LONG TERM FOLLOW-UP INVESTIGATION OF DEVELOPMENTAL PROGRESS 12 AND 24 MONTHS AFTER COMPLETION OF STUDY TREATMENT**

# STATISTICAL ANALYSIS PLAN (SAP) FOR PART A OF THE STUDY



**Version**: 3.0

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## APPENDICES

## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

This Statistical Analysis Plan (SAP) for study A1481316 is based on the protocol Amendment 3 dated April 16, 2015.

This is the second revision to the initial version of the document.

The following changes were made to the initial version in the first revision:

- *Figure 1* (Study Design Part A) was updated with the one in the latest protocol amendment 3 dated April 16, 2015.
- Treatment unblinding (Section 3): To ensure the data integrity of Part B of the study, treatment unblinding will only be made to the study team members after the database lock of Part A of the study. Treatment unblinding to the investigators and the subjects will be done after the database lock for Part B of the study.
- ANCOVA model for time on iNO for subjects without treatment failure after initiation of IV study drug treatment: The covariate is revised from 'time on iNO prior to randomization' to 'time on iNO prior to the initiation of IV study drug treatment', as IV study drug treatment may not be initiated immediately after the randomization.
- Calculation of total time on iNO for subjects with multiple iNO treatment: The following sentence was added in Section 8.1: "If there are gaps in between consecutive iNO treatments, those gaps will be included in the calculation of total time on iNO".
- Algorithms for calculation of duration of hospital stay and duration of stay in intensive unit care were added in Section 6.1.
- ANCOVA model for the endpoints for oxygenation parameters was specified in Section 8.1.
- Definition of Day 1 of the study was put in Appendix 1. Definition of Day 0 and visit window for Day 14 were deleted from Appendix 1 as they are not applicable to the study.
- Minor editorial changes were made throughout this document to correct grammatical errors or increase clarity.

The following changes were made to the first revision in the second revision:

- Specifying this SAP is for the planned data summaries and statistical analyses for Part A of the study.

[redacted]

- Treatment unblinding (Section 3): Treatment unblindning to the investigators will be done after the Clinical Study Report (CSR) for Part A of the study is completed. Treatment unblinding to the investigators will be done after the Clinical Study Report (CSR) for Part A of the study is completed. For subjects who are still ongoing for Part B of the study, they and the specialists who conduct study assessments should remain blinded until completion and database lock for Part B of the study.

- Clarify the definition of Per-Protocol population in Section 5.2 as: Per-protocol population (PP) will consist of all randomized patients who are treated in Part A of the study according to the protocol without any major violations that could potentially affect the evaluation of the primary endpoints.

- Specifying major protocol deviations that could potentially affect the evaluation of the primary endpoints which lead to exclusion of subjects from PP analyses. (Section 5.6).

- Adding more details to the assessment time of efficacy endpoints in Section 6.1, specifically for the co-primary endpoints, time on iNO will be assessed at 336 hours (14 days) from the IV study drug initiation, or hospital discharge, whichever occurs first; treatment failure rate will be assessed at the date of 336 hours (14 days) from the study drug initiation, or hospital discharge, whichever occurs first, as only dates not time are collected for initiation of ECMO and death.

- Adding patient profile to be created for subjects with treatment failures (Section 8.5).

- Minor editorial changes were made to increase clarity.

## 2. INTRODUCTION

This document describes the planned data summaries and statistical analyses for Part A of the study for Protocol A1481316, entitled "A Multi-centre, Randomized, placebo-controlled, double-blind, two-armed, parallel group study to evaluate efficacy and safety of iv sildenafil in the treatment of neonates with persistent pulmonary hypertension of the newborn (PPHN) or hypoxic respiratory failure and at risk for PPHN, with a long term follow-up investigation of developmental progress 12 and 24 months after completion of study treatment". It is meant to supplement the study protocol which should be referred to for details regarding the objectives and design of the study. Any deviation to this analysis plan will be described in the Clinical Study Report.

The planned data summaries and statistical analyses for Part B of the study will be documented in a separate statistical analysis plan.

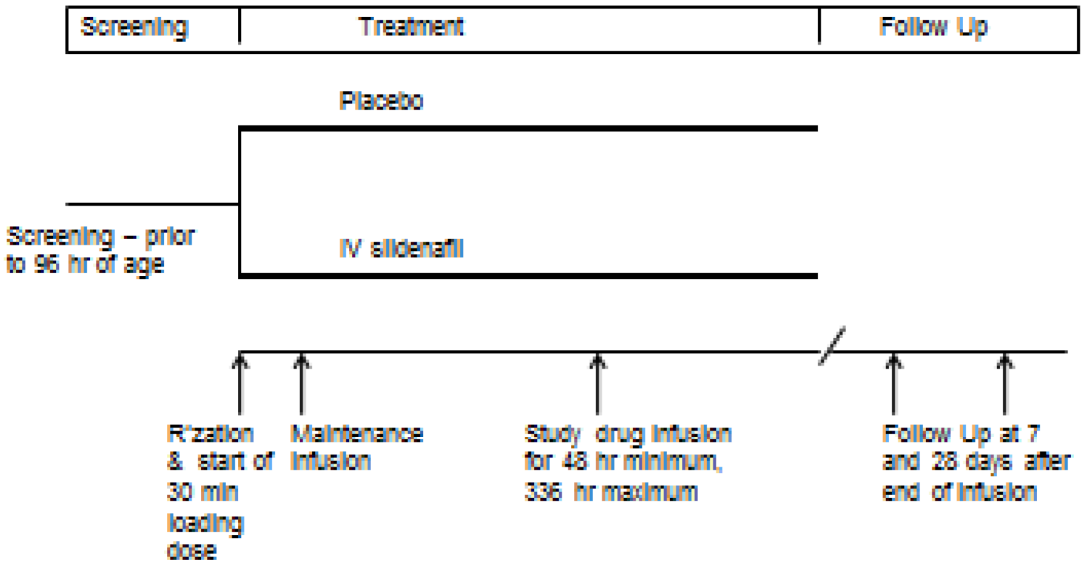
Note: in this document any text taken directly from the protocol is ***italicised***.

## 2.1. Study Design

*This study will be conducted in two parts. Part A is the double-blind phase to assess the efficacy and safety of IV sildenafil versus placebo when added to iNO for no more than 14 days, during the acute phase of the disease, with follow-up at 7 and 28 days after the end of study drug infusion. Part B is the long-term, non-interventional phase, during which all subjects will be encouraged to return at 12 and 24 months after the end of study drug infusion, to take part in developmental assessments, hearing and ophthalmology tests.*

*Analysis of the double-blind phase of the study (Part A) will be performed when all subjects have completed or discontinued from the double-blind phase, and a study report will be written. Analysis of the non-interventional phase of the study (Part B) will be performed when all subjects have completed or discontinued from the 2-year follow-up visit, and a final study report will be written.*

***Figure 1. Study Design Part A***




## 2.2. Study Objectives

Primary Objectives:

- *The primary objectives of this study are to evaluate the efficacy and safety of IV sildenafil when added to iNO for the treatment of neonates with PPHN or hypoxic respiratory failure and at risk for PPHN.*

Secondary Objectives:

- *To monitor the developmental progress of patients with PPHN treated with IV sildenafil or placebo, at 12 and 24 months after the end of study treatment.*

- *Pharmacokinetics (PK): To further characterize the PK of sildenafil and UK-103,320 in neonates with PPHN or HRF and at risk of developing PPHN.*

## 3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

*A PK interim analysis is planned for this study (See Section* 7.9 of the final protocol*)). There is no efficacy or safety interim analysis planned for this study.*

*An interim analysis will be performed by an unblinded PK analyst after a minimum of 10 subjects in Part A have completed the study. Observed sildenafil concentration-time data will be evaluated to determine whether PK sampling should occur during all three proposed sampling windows (4-8 hrs; 18-24 hrs; and 40-48 hrs) following the stop of infusion.*

Treatment unblinding to the study team members and analyses for Part A of the study will be done after the database lock for Part A of the study. Treatment unblinding to the investigators will be done after the Clinical Study Report (CSR) for Part A of the study is completed. For subjects who are still ongoing for Part B of the study, they and the specialists who conduct study assessments should remain blinded until completion and database lock for Part B of the study.

## 4. HYPOTHESES AND DECISION RULES

### 4.1. Statistical Hypotheses

*The primary statistical objective is to test for the superiority of iNO + sildenafil over iNO + placebo for time on iNO treatment after initiation of IV study drug treatment for subjects without treatment failures and for treatment failure rate.*

Using $\mu_1$ and $\mu_2$ to represent the true time on iNO for iNO + placebo and iNO + sildenafil respectively for subjects without treatment failures, the hypotheses are:

$H_0$: $\mu_1-\mu_2 =0$;

$H_1$: $\mu_1-\mu_2 \neq 0$.

Using $\rho_1$ and $\rho_2$ to represent the true treatment failure rate for iNO + placebo and iNO + sildenafil respectively, the hypotheses are:

$H_0$: $\rho_1- \rho_2 =0$;

$H_1$: $\rho_1- \rho_2 \neq 0$.

### 4.2. Statistical Decision Rules

For time on iNO for subjects without treatment failures, treatment comparison will be conducted using analysis of covariance (ANCOVA) adjusting for time on iNO treatment prior to the initiation of IV study drug treatment.

For treatment failure rate, treatment comparison will be conducted using either Chi-square test or Fisher's exact test whichever is appropriate.

If p-values are <0.05(2-sided) from both analyses in favor of iNO + sildenafil treatment, superiority of iNO + sildenafil over iNO + placebo can be concluded at 5% (2-sided) significance level.

## 5. ANALYSIS SETS

*Efficacy analysis will only be conducted for Part A of the study.*

### 5.1. Full Analysis Set

*The intent-to-treat population (ITT) will consist of all randomized patients treated with study treatment.* The full analysis set of this study will include all ITT subjects.

### 5.2. 'Per Protocol' Analysis Set

Per-protocol population (PP) will consist of all randomized patients who are treated in Part A of the study according to the protocol without any major violations that could potentially affect the evaluation of the primary endpoints. *The primary efficacy analysis will be conducted using ITT population. If PP population is <90% of the ITT population, then efficacy analyses will also be conducted using PP population as sensitivity analyses.*

### 5.3. Safety Analysis Set

The safety analysis set will include all subjects treated with study treatment.

### 5.4. PK Analysis Sets

The PK analysis set is defined as all subjects randomized and treated who had at least 1 concentration during whole treatment period.

### 5.5. Treatment Misallocations

If a subject is:

- Randomized but not treated, then they will be reported under their randomized treatment group, but will not be included in the efficacy analyses and safety analyses as actual treatment is missing.

- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing, but will be reported under the treatment they actually received for all safety analyses.

- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses, but will reported under the treatment they actually received for all safety analyses.

### 5.6. Protocol Deviations

Major protocol deviations that could potentially affect the evaluation of the primary endpoints which lead to exclusion of subjects from PP analyses will include but may not be limited to the following. The list will be finalized before database lock.

- Meet Exclusion Criterion 12  Apgar score of less than 3 at 5 minutes after birth.
- Dosing or Administration Error where Accidental dosing gaps in study drug infusion occur.
- OI less than 15 at both 30 minutes and at 0 hour prior to randomization.

## 6. ENDPOINTS AND COVARIATES

### 6.1. Efficacy Endpoint(s)

Efficacy endpoints will only be assessed for Part A of the study.

Co-primary endpoints (assessed at 14 days from the initiation of IV study drug or hospital discharge, whichever occurs first):

- *Time on iNO treatment after initiation of IV study drug for subjects without treatment failure;*

*And*

- *Treatment failure rate, defined as need for additional treatment targeting PPHN, need for ECMO, or death during the study*.

For the co-primary endpoints, time on iNO will be assessed at 336 hours (14 days) from the IV study drug initiation, or hospital discharge, whichever occurs first; treatment failure rate will be assessed at the date of 336 hours (14 days) from the study drug initiation, or hospital discharge, whichever occurs first, as only dates not time are collected for initiation of ECMO and death.

Secondary efficacy endpoints (assessed at 14 days [336 hours] from the initiation of IV study drug or hospital discharge, whichever occurs first):

- *Time to final weaning of mechanical ventilation for PPHN;*
- *Time from initiation of study drug to treatment failure (additional drug treatment targeting PPHN, ECMO, or death); each component will also be evaluated separately;*
- *Proportion of subjects with individual components of treatment failure (needing additional treatment targeting PPHN, needing ECMO, or who die);*
- *Change in OI at 6, 12, and 24 hours from baseline;*
- *Change in differential saturation (pre- and post-ductal) at 6, 12, and 24 hours from baseline;*
- *Change in P/F ratio at 6, 12, and 24 hours from baseline.*

*Other efficacy endpoints* CCI

[redacted]



## 6.2. Safety Endpoints

Part A:

*Safety parameters: Incidence and severity of adverse events and abnormal laboratory parameters*.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (See Section 8.3). Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan:

- Vision disorders (HLGT);

- Hearing losses (HLT);
- Erection increased (PT).

Tier-2 events: These are events that are not tier-1 and are not uncommon in this patient population, in any treatment group.

- Hypotension;
- Collapse of lung;
- Atelectasis;
- Hypoxia.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

Part B:

*Monitored at 12 and 24 months after completion of study treatment:*

- *Developmental progress, hearing, and visual acuity assessments;*

*Safety, assessed by adverse events, and survival.*

### 6.3. PK Endpoints

Sildenafil and UK-103,320 plasma concentrations and the corresponding PK parameters obtained from a population PK analysis.

PK endpoints will only be measured in Part A of the study.

### 6.4. Covariates

The covariates are study treatment group and time on iNO treatment prior to the initiation of IV study drug treatment.

## 7. HANDLING OF MISSING VALUES

*As the study will be conducted while subjects are treated in the hospitals, the chance of having missing data on primary endpoint is minimal***.**

No imputation is planned for missing data for efficacy and safety data analyses.

# 8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

## 8.1. Primary Efficacy Analyses

*Time on iNO for subjects without treatment failures will be summarized for each treatment. If multiple iNO treatments are given to a subject, total time on iNO will be calculated for this endpoint for that subject.* If there are gaps in between consecutive iNO treatments, those gaps will be included in the calculation of total time on iNO. *Mean treatment difference, its 95% confidence interval and p-value will be calculated.*

The following SAS codes will be used for statistical analyses:

```
PROC GLM;
 CLASS TX;
 MODEL TIME_ON_iNO = PRIOR_iNO TX;
 LSMEANS TX/PDIFF TDIFF;
 RUN;
```

Where,
TX=treatment group
TIME_ON_iNO= time on iNO (hours)
PRIOR_iNO= time on iNO treatment prior to the initiation of IV study drug treatment (hours).

*Treatment failure rate and its 95% confidence interval will be calculated for each treatment group. Treatment comparison will be conducted using either Chi-square test or Fisher's exact test whichever is appropriate. Estimated treatment difference in rates, its 95% confidence interval and p-value will be calculated*.

The following SAS codes will be used for statistical analyses:

```
PROC FREQ;
 TABLES TX*RESPONSE/CHISQ FISHER RISKDIFF;
 EXACT RISKDIFF;
 RUN;
```

Where,
TX=treatment group
RESPONSE=treatment response (failure vs. non-failure).

## 8.2. Secondary Efficacy Analyses

- *For continuous endpoints* (other than composite benefit score)*, similar analyses (ANCOVA) conducted for time on iNO or 2-sample t-test (no adjustment for baseline values) will be used.* For the endpoints for oxygenation parameters (OI, differential saturation and P/F ratio), the ANCOVA model will be adjusted for baseline value which will be results measured during Screening.

- *For categorical endpoints, similar analyses conducted for treatment failure rate will be used.*

- *For time-to-event endpoints, time-to results will be summarized using Kaplan-Meier estimates and log-rank test will be used for treatment comparisons.* The following SAS codes will be used for statistical analyses:

```
PROC LIFETEST;
  PLOTS=(SURVIVAL);
  TIME TIME_TO*CENSOR(1);
  STRATA TX;
    RUN;
```

Where,
TIME_TO=time to endpoint
CENSOR= censoring variable, 1=censored, 0=event.

**8.3. Safety Analyses**

*Safety analyses will be carried out for the ITT population only for both Part A and Part B of the study. All adverse events will be coded and grouped by system organ class. The incidence of each treatment emergent adverse event will be tabulated by treatment. Tabulations by maximum severity and relationship to study treatment will also be included.*

The following data will be summarized by treatment and in accordance with the current Pfizer data standards:

Demographics, subject disposition, study duration, adverse events, laboratory data, vital signs, ECG and concomitant medication data.

For adverse events, for tier-1 and tier-2 event, similar analyses conducted for treatment failure rate will be used. No p-values will be calculated for tier-2 event. For summary tables, footnotes will be added stating p-values and confidence intervals are not adjusted for multiplicity and should be used for screening purpose only.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

### 8.4. PK and PK/PD Analyses

A population PK analysis will be conducted combining the PK data from this study and the study A1481157, a previous completed sildenafil study in PPHN patient population. A separate population PK analysis plan will be developed, and the corresponding population PK analysis report will be issued separately from the main clinical study report. The plasma concentration listings with patient ID and sampling time relative to sildenafil dosing time will be reported in the study report. CCI [redacted]

### 8.5. Other Analyses

Patient profile will be created for subjects with treatment failures including the following data:

- Demographics;
- Medical history;
- Age (hours) at starting therapy, first dose date/time, last dose date/time, subject disposition;
- Primary diagnosis;
- Treatment failure;
- Additional PPHN treatment;
- Oxygenation index;
- Mechanical ventilator;
- Oscillator ventilator;
- Concomitant treatment including iNO, inotropes and other vasoactive medicines;
- Adverse events.

## Appendix 1. Definition of Day 1

| Scheduled Study Visit | Definition |
|---|---|
| Day 1 | the day of initiation of IV study drug treatment |

[redacted]