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 B of the Study

Version: 1

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Date: March 16, 2015

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APPENDICES

1. INTRODUCTION

This document describes the planned data summaries and statistical analyses for Part B of 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.

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

1.1. 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.

1.2. Study Objectives

The objectives for Part B of the study are:

- *The secondary objectives of this study are to evaluate the developmental progress of patients with PPHN treated with IV sildenafil or placebo, 12 and 24 months after the end of study treatment.*

2. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

There is no interim analysis planned for the study.

The study will be un-masked after the last subject completed the Part A of the study and the database for Part A of the study is locked.

3. HYPOTHESES AND DECISION RULES

3.1. Statistical Hypotheses

There are no formal statistical hypotheses for Part B of the study.

3.2. Statistical Decision Rules

Not applicable.

4. ANALYSIS SETS

All subjects enrolled in Part B of the study will be included for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety.

5. ENDPOINTS

Part B:

Long-term Assessments*: Monitored at 12 and 24 months after completion of study treatment:*

- *Developmental progress, audiological and visual acuity assessments;*
- *Safety, assessed by adverse events, and survival.*

5.1. Efficacy Endpoint(s)

There are no efficacy endpoints evaluated in Part B of the study.

5.2. Safety Endpoints

Adverse events (AE), including serious adverse events (SAE) and death.

Survival rates at Month 12 and 24 after completion of study treatment.

5.3. Other Endpoints

5.3.1. Developmental Progress

1. Measurement from Bayley Scales of Infant Development at Month 12 and Month 24
    - Cognitive;
    - Language;
    - Motor.
2. Measurements from Bayley Scales of Infant Development - Parent at Month 24
    - Social-emotional;
    - Adaptive behavior.

5.3.2. Audiological Assessment

1. Measurements from pure tone audiometry at Month 12 and Month 24:
    - Behavior hearing assessment results;
    - Results by air conduction via phones/headphones; or
    - Results by air conduction via soundfield;
    - Results by bone conduction, when indicated.
2. Measurements from immitance audiometry at Month 12 and Month 24:
    - Results of tympanometry;
    - Results of ipsilateral stapedial reflex.
3. Measurements from otoacoustic emissions assessment at Month 12 and Month 24:
    - Results from transient evoked emission; or
    - Results from distortion product.

5.3.3. Neurological Assessment

Measurements from Hammersmith Infant Neurological Exam at Month 12 and Month 24:

- Cranial nerves score;
- Posture score;
- Movement score;
- Tone score;
- Reflexes and reaction score;
- Neurological exam global score.

5.3.4. Ophthalmological Assessment

Ophthalmological assessment at Month 12 and 24:

- Visual acuity;
- Results from eye examination –anterior segment;
- Results from eye examination – posterior segment.

6. HANDLING OF MISSING VALUES

No imputation is planned for missing data in data analyses.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. Statistical Methods

For continuous variables, summary statistics of n, mean, standard deviation, median, minimum and maximum will be tabulated by treatment group (iNO+ sildenafil vs. iNO alone in Part A of the study.

For categorical variables, n (%) of subjects in each category will be tabulated by treatment group (iNO+ sildenafil vs. iNO alone) in Part A of the study.

For subjects with multiple records in a given visit, the one with assessment date closest to the target visit day (see Appendix) will be selected for tabulation; for two observations with equal distance from the target visit day, the one assessed at a later time will be selected for tabulation.

All observations will be included in data listings for the endpoints listed below.

7.2. Statistical Analyses

7.2.1. Analysis of Safety Endpoints

All adverse events will be coded and grouped by system organ class. The incidence of each adverse event will be tabulated by treatment group. Tabulations by maximum severity and treatment group will also be included.

Data listings will be provided for adverse events, serious adverse events and death.

The duration of overall survival will be summarized graphically using Kaplan-Meier plots for each treatment group. Tabular summaries of the Kaplan-Meier curves giving the median, quartiles, mean, standard error of the mean and range of overall survival will also be provided for each treatment group. Number of deaths and survival rate at Month 12 and 24 will be tabulated by treatment group.

7.2.2. Analysis of Development Progress

For Bayley Scales of Infant Development, summary statistics of composite score and percentile rank will be tabulated by subtest (cognitive, language and motor) and treatment group at Month 12 and Month 24.

For Bayley Scales of Infant Development-Parent, summary statistics of composite score and percentile rank will be tabulated by subtest (social-emotional and adaptive behavior) and treatment group at Month 24.

7.2.3. Analysis of Audiological Assessment

1. Measurements from pure tone audiometry

    - Behavior hearing assessment results: n (%) of subjects with results of normal, abnormal, incomplete/inconclusive and missing will be tabulated by treatment group at Month 12 and Month 24.

- Results by air conduction via phones/headphones: n (%) of subjects in each category of response (<=20 DB HL, 21-40 DB HL, 41-70 DB HL, 71-90 DB HL, no response, or could not test) will be tabulated by ear (right or left), frequency and treatment group at Month 12 and Month 24.

- Results by air conduction -soundfield: n (%) of subjects in each category of response (<=20 DB HL, 21-40 DB HL, 41-70 DB HL, 71-90 DB HL, no response, or could not test) will be tabulated by frequency and treatment group at Month 12 and Month 24.

- Results by bone conduction: n (%) of subjects with bone conduction, and n (%) of subjects in each type of hearing loss (sensorineural, conductive, mixed, neural or unspecified) will be tabulated by treatment group at Month 12 and Month 24.

2. Measurements from immitance audiometry

    - Results of tympanometry: summary statistics will be tabulated for peak pressure (sign of + or -) and static acoustic admittance by ear and treatment group at Month 12 and Month 24

    - Results of ipsilateral stapedial reflex: n (%) of subjects in each category of assessment (present, absent, undetermined or not assessed) will be tabulated by ear, frequency and treatment group at Month 12 and Month 24.

Measurements from otoacoustic emissions assessment at Month 12 and Month 24

- For each assessment method (transient evoked emission, distort product etc.), n (%) of subjects in each category of assessment (present, absent, undetermined or not assessed) will be tabulated by ear, frequency and treatment group at Month 12 and Month 24.

7.2.4. Analysis of Neurological Assessment

For scores from each subtest (cranial nerves, posture, movement, tone, and reflexes and reaction), and neurological global exam score, summary statistics will be tabulated by treatment group at Month 12 and Month 24.

7.2.5. Analysis of Ophthalmological Assessment

For visual acuity, the following data analyses will be conducted:

1. n (%) of subjects with amblyopia, strabismus, or nystagmus will be tabulated by eye (right or left) and treatment group at Month 12 and Month 24.

2. For verbal child, n (%) of subjects with visual assessment category of visual acuity chart, counting finger, hand motion, light perception, no light perception will be tabulated by eye and treatment group at Month 12 and Month 24.

3. For verbal child with visual acuity assessed by visual acuity chart, summary statistics of LogMAR visual acuity value will be tabulated by eye and treatment group at Month 12 and Month 24.

   LogMAR values will be derived from Snellen scores (or equivalent) by converting to the decimal notation (dividing the numerator of the Snellen fraction by the denominator) and then taking the negative of the logarithm. For example, 20/40 = 0.5 and –log0.5 is 0.3.

For eye examinations for anterior and posterior segment, n (%) subjects with results of normal, abnormal and not done will be tabulated by eye (right or left) and treatment group at Month 12 and Month 24.

7.2.6. Other Analyses

Summary tables with descriptive statistics and data listings will also be provided for medical history, physical examination, and subject disposition (based on CRF of End of Study – Subject Summary).

8. APPENDIX

Appendix 1. DEFINITION AND USE OF VISIT WINDOWS IN REPORTING

Visit Label	Definition [Day window]
Month 12	Date of Assessment – Date of Last Day on Study Treatment in Part A of the Study: [1 to 540] with target day of 360
Month 24	Date of Assessment – Date of Last Day on Study Treatment in Part A of the Study: >= 541 with target day of 720