STATISTICAL ANALYSIS PLAN

CCD-5633AA1-02

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A MULTICENTER, DOUBLE BLIND, RANDOMIZED, SINGLE DOSE, ACTIVE-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF SYNTHETIC SURFACTANT (CHF 5633) IN COMPARISON TO PORCINE SURFACTANT (PORACTANT ALFA, CUROSURF®) IN THE TREATMENT OF PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME.

Version: Final 1.0

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REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Draft 0.1	07/Dec/2015	[redacted]	New Document
Draft 0.2	03/Feb/2016	[redacted]	Implementation of sponsor comments
Draft 0.3	24/Feb/2016	[redacted]	Incorporated sponsor comments plus refinements.
Draft 0.4	17/Mar/2016	[redacted]	Incorporated sponsor comments and display of protocol deviations and screening failures
Draft 0.5	15/Apr/2016	[redacted]	Incorporated sponsor comments
Draft 0.6	09/May/2018	[redacted]	Updates for Protocol Amendment 4.0 (dated 31/Jan/2018) and sponsor comments
Draft 0.7	29/May/2018	[redacted]	Implementation of sponsor comments
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Draft 0.9	13/Jul/2018	[redacted]	Implementation of sponsor comments
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LIST OF IN-TEXT TABLES / FIGURES

Not applicable.

ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
ADR	Adverse drug reactions
AE	Adverse event
ALT	alanine aminotransferase
AOP	Apnea of prematurity
AST	aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BiPAP	Bi-level positive airway pressure
BPD	Bronchopulmonary dysplasia
bpm	Beats per minute
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CPAP	Continuous Positive Airway Pressure
CS	Clinically significant or Cranial Sonography
CSP	Clinical Study Protocol
CX	Chest X-Ray
DBP	Diastolic blood pressure
eCRF	Electronic Case Report Form
FBC	Full blood count
FiO_2	Fraction of inspired oxygen
GA	Gestational age
GMH	Germinal matrix
H	High (value above upper limit of reference range)
HFNC	High flow nasal cannula
HFOV	High Frequency Oscillatory Ventilation
HL	Hodges-Lehmann
HR	Heart rate
IL1β	Interleukin 1β

Abbreviation / Acronym	Definition / Expansion
IL6	Interleukin 6
IMV	Intermittent Mandatory Ventilation
IRT	Interactive Response Technology
ITT	Intention to treat (population)
IVH	Intraventricular hemorrhage
IVRS	Interactive Voice Response Services
IWRS	Interactive Web Response System
L	Low (value below lower limit of reference range)
MAP	Mean airway pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MOP	Myeloperoxidase
NC	Neonatal Complications of prematurity
NCS	Not clinically significant
NEC	Necrotizing enterocolitis
NHFV	Nasal High frequency ventilation
nIMV	Nasal Intermittent Mandatory Ventilation
NIPPV	Nasal intermittent positive pressure ventilation
NK	Not known
NPSV	Nasal Pressure Support Ventilation
nSIMV	Nasal Synchronized Intermittent Mandatory Ventilation
nSIPPV	Nasal Synchronized Intermittent Positive Pressure Ventilation
OI	Oxygenation index
OR	Odds ratio
OSI	Oxygen saturation index
PaO_2	Partial pressure of oxygen in arterial blood
PDA	Patent ductus arteriosus
PEEP	Positive end-expiratory pressure
PH	Pregnancy history

Abbreviation / Acronym	Definition / Expansion
PIE	Pulmonary interstitial emphysema
PIP	Peak inspiratory pressure
PK	Pharmacokinetic
PMA	post menstrual age
PNA	post-natal age
POC	Proof of Concept
PP	Per protocol
PT	Preferred term
PTV	Patient trigger ventilation
PVL	Periventricular leukomalacia
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of prematurity
RR	Relative risk
RSS	Respiratory severity score
SAE	Serious adverse event
SAF	Safety Population
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SE	Standard error
SIMV	Synchronized intermittent mandatory ventilation
SIPPV	Synchronized intermittent positive pressure ventilation
SOC	System Organ Class
SpO_2	Arterial oxygen saturation
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
TNF-α	Tumor Necrosis Factor-alpha
VS	Ventilatory Support
WHO-DD	World Health Organization - Drug Dictionary
Y/N	Yes/No

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final amended CSP Version 4.0, dated, 31/Jan/2018.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum.

The 24-months assessment analysis will be described in a separate SAP.

1. STUDY OBJECTIVES

This trial is a multicenter, double-blind, randomized, single dose, active-controlled, Proof of Concept (POC)/Phase II study to investigate the efficacy and safety of synthetic surfactant (CHF 5633) in comparison to porcine surfactant (Poractant alfa, Curosurf ®) in the treatment of preterm neonates with Respiratory Distress Syndrome (RDS).

1.1 Primary Objectives

Main objectives of this study are:

- to investigate the short term efficacy profile of CHF 5633 vs. porcine surfactant (Poractant Alfa, Curosurf®) in terms of reduced oxygen requirement and ventilatory support (VS)
- to evaluate the mid-term efficacy profile in terms of reduced incidence of bronchopulmonary dysplasia (BPD) and mortality/BPD rate at 36 weeks post menstrual age (PMA), mortality rate at 28 days post-natal age (PNA) and 36 weeks PMA, RDS-associated mortality through 14 days of age and other major co-morbidities of prematurity.

1.2 Secondary Objectives

Other objectives of the present study are:

- to evaluate the need for re-dosing in the two treatment groups according the pre-defined criteria;
- to evaluate the inflammatory status through the measurements of specific biomarkers of inflammation in tracheal aspirates (in a subgroup of babies who require endotracheal intubation for mechanical ventilation when feasible);
- to assess immunogenicity through the measurement of antibodies to SP-B analogue (CHF 5736.03) and SP-C analogue (CHF 4902.03) contained in CHF 5633;
- to perform the evaluation of oxygenation status through invasive measurements [in a subgroup of babies who have an arterial (umbilical, peripheral) access, when feasible];
- to evaluate the safety profile in the two treatment groups in terms of adverse events (AEs) and adverse drug reactions (ADRs), vital signs, hematology and biochemistry values.

2. STUDY DESIGN

The Schedule of Assessments is presented in Appendix 1.

3. STUDY POPULATION

A total number of 126 (63 in each treatment group) preterm neonates with a gestational age of 24^{+0} weeks up to 29^{+6} weeks with RDS, will be randomized in the study. Detailed lists of inclusion and exclusion criteria are shown in Sections 4.2 and 4.3 of the CSP.

4. STATISTICAL BASIS FOR SAMPLE SIZE

According to the exploratory nature of this study, no formal sample size calculation was performed. A maximum number of sixty-three randomized neonates per treatment group (126 in total) is deemed sufficient to describe the efficacy and safety of CHF5633 compared to Poractant Alfa.

5. RANDOMIZATION

A dynamic randomization method was used to balance the treatment groups by investigational site and gestational age group (i.e. from 24^{+0} to 26^{+6} weeks and from 27^{+0} to 29^{+6} weeks). Patients will be centrally assigned to one of the two treatment arms on admission through an IRT system (Interactive Response Technology, combination of voice and web response system and also referred as IVRS/IWRS).

The IRT will allocate the patient to a certain treatment group using the Pocock and Simon minimization algorithm (2) and assign the study medication kit number corresponding to the patients' treatment group. IRT specification will be fully described in a specific document, created separately.

Patients will be identified by a unique number of six digits (country in first digit, investigational site in subsequent two digits and followed by three digits with the progressive numbering of patient in each site.

For more information refer to section 6.5 of the CSP.

6. STATISTICAL ANALYSIS CONVENTIONS

6.1 Collected Data

The study schedule is enclosed as Appendix 1.

6.1.1 Disposition data

The following disposition information will be recorded and listed:

- Screen Date.
- Enrolled Date.
- Failed Date.
- Discontinued Date.
- Reason for Failure / Early withdrawal
- Completed Date.
- Parental Informed Consent Date.

6.1.2 Demographic and Background Data

The following demographic and anthropometric information will be recorded and listed:

Neonate information

- Date/Time of Birth
- Gestational Age (Weeks)
- Gestational Age (Days)
  GA in weeks will be derived using the following formula:
  GA (weeks) + [GA(Days) / 7]
  Derived value will be shown in the table. Both original and derived values will be listed.
- Sex
- Birth Weight (grams)
- Race ([blank], white, black or African American, Asian, American Indian or Alaska native, native Hawaiian or other pacific islander, other)
- Ethnicity ([blank], not Hispanic or Latino, Hispanic or Latino, not reported)
- APGAR score (Score Range: 1-10, [blank] possible)
- Any respiratory support in the delivery room? (Y/N)
  If yes, which method
- Chest X-Ray (CX) performed? (Y/N), performed if deemed appropriate, at screening and at Day1 24h post with
  - Date/Time performed
  - Findings (Normal/Abnormal NCS/Abnormal CS)
  - Specification of findings (if abnormal)
- Complications of Prematurity (NC) with
  - Specification of complication ([Blank], Pneumothorax, Pneumopericardium, Pneumoperitoneum, Pneumomediastinum, Apnea of prematurity AOP, Necrotizing enterocolitis NEC, Patent ductus arteriosus PDA, Pneumonia, Pulmonary interstitial emphysema PIE, Pulmonary hemorrhage, Germinal matrix/Intraventricular hemorrhage (GMH/IVH,), Cerebral parenchymal hemorrhage (CPH), Neonatal jaundice, Periventricular leukomalacia (PVL,), Retinopathy of prematurity (ROP,), Bacterial sepsis and/or meningitis, Hypoglycemia, Hyperglycemia, Hypocalcemia, Hypercalcemia, Hyponatremia, Hypernatremia, Hypokalemia, Hyperkalemia)
  - Grade of Interventricular Hemorrhage

- Start/End Date and Time
- Ongoing (Y/N)

Mother information

- Mother Medical/Surgical History (only entered if clinically significant) conditions with
  - Medical Disease
  - Start/End Date
  - Ongoing (Y/N)
- Mother Previous and Concomitant Medications with
  - Has the Subject`s mother taken any Medication during the pregnancy or the delivery? (Y/N)
  - Trade or Generic Name
  - Start/End Date (Day, Month, Year entered separately)
  - Ongoing (Y/N)
  - Indication
- Pregnancy History (PH).
  - Type of the delivery ([blank], spontaneous, C-section with labor, C-section without labor, emergency C-section).
  - Antibiotic intake during the pregnancy (Y/N).
  - Steroid intake for fetal lung maturation (Y/N) and if yes, with information how the course was ([blank], complete, incomplete).
  - Complications (verbatim, trimester ([blank], first, second, third) and treatment given or in progress(Y/N).
  - Intrapartum complication (verbatim and treatment given (Y/N).
- Cranial Sonography (CS) with
  - Was Cranial Sonography performed? (Y/N).
  - Date/Time of sonography (Day, Month, Year entered separately).
  - Findings (Normal/Abnormal NCS/Abnormal CS).
  - Was Germinal Matrix Hemorrhage (GMH) / Intraventricular Hemorrhage (IVH) present? (Y/N) with district ([blank], right, left, bilateral) if answered YES.
  - IVH Grade ([blank] or grade 1-4 possible).
  - Was Periventricular Leukomalacia (PVL) present? (Y/N).

- Was Cerebral Parenchymal Hemorrhage present? (Y/N).

For Cranial Sonography all values measured will be listed. Screening results will be tabulated with descriptive statistics in addition.
All medical history will be coded using Version 18.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

Mother previous and concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO-DD) (Version **MAR2015**) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

6.1.3 Safety Data

6.1.3.1 Adverse Events and Adverse Drug Reactions

6.1.3.1.1 Adverse Events

An AE is, "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment." An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not considered related to the medicinal (investigational or non-investigational) product. All AEs will be coded using the latest available version (Version 18.0) of the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity during or after first intake of the study drug has been administered.

A pre-treatment AE is defined as an AE that begins before first intake of the study drug.

Any AEs with incomplete start and end dates/times will be treated as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first

dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

- DD-UK-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

Missing start/end time (where UK and UKN indicate unknown or missing day and month respectively):

- Adverse events with unknown start and/end times (but where the date is known) will be imputed with a time of 00:00 h (start) / 23:59 h (end) for the tabulations but will be shown as UK:UK in the listings (where UK = unknown). If the date is the date of treatment start will be imputed as time of start of treatment following a worst case approach.

- Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as UK in the listings.

AE Duration (days) will be computed as follows:

- When both dates are completely known and AE is resolved:

  Duration (days) = AE end date – AE onset date + 1

- When the AE onset date is fully known but the AE is not resolved at the end of the trial:

  Duration (days) = date of completion/discontinuation – AE onset date + 1

  In this case the duration will be presented as ">x days" in the listings rather than "x days"

When the AE onset date is incomplete or unknown or when the AE has resolved but with an incomplete or unknown end date, the AE duration will not be calculated, unless otherwise specified.

AE Relative Day of Onset will be computed as follows

- Relative day of onset for pre-treatment AE:

  Relative Day of Onset = AE onset date – reference date

- Relative day of onset for TEAE:

  Relative Day of Onset = AE onset date – reference date + 1

where reference date is treatment date/time.

6.1.3.1.2 Adverse Drug Reactions

An ADR is an, "untoward and unintended response to an investigational medicinal product related to any dose administered."

For further information please refer to Section 10 of the CSP.

6.1.3.1.3 Neonatal Morbidities

The incidence of major neonatal morbidities will be monitored (for the list of neonatal morbidities and complications of prematurity see section 10.8 of the CSP). These include:

- Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum);
- anemia of prematurity;
- apnea of prematurity;
- necrotizing enterocolitis (NEC);
- patent ductus arteriosus (PDA),
- pneumonia;
- pulmonary interstitial emphysema (PIE);
- pulmonary hemorrhage;
- germinal matrix/intraventricular hemorrhage (GMH/IVH);
- cerebral parenchymal hemorrhage;
- neonatal jaundice;
- periventricular leukomalacia (PVL);
- sepsis and/or meningitis;
- Presence of the following abnormal laboratory values:

- hypoglycemia
- hyperglycemia
- hypocalcaemia
- hypercalcemia
- hyponatremia
- hypernatremia
- hypokalemia
- hyperkalemia.

6.1.3.2 Clinical Laboratory Tests

The following safety laboratory parameters will be measured:

- **Biochemistry:** urea, creatinine and electrolytes (sodium, potassium, calcium, phosphorus), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, C-reactive protein.
- **Hematology:** full blood count (FBC).

6.1.3.3 Vital Signs

The following vital signs measurements will be obtained:

- Systolic blood pressure (SBP) [mmHg];
- Diastolic blood pressure (DBP) [mmHg],
- Heart rate (bpm);
- SpO2 during administration [%].

6.1.3.4 Physical Examination

Not applicable.

6.1.3.5 Neonatal Concomitant Medications

Any concomitant medication required for the normal care of preterm neonates will be permitted during the study. Concomitant medication will be coded using the World Health Organization-Drug

Dictionary (WHO-DD) (Version **SEP2015**) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

6.1.3.6 Surgical/ Medical Procedures

Any Surgical/ Medical Procedure required for the normal care of preterm neonates during the study conduct will be documented with:

- Has the Subject undergone any Surgical/Medical procedures? (Y/N), if answered yes with:
  - Name of the Procedure;
  - Start/End Date and Time;
  - Adverse Event Number (assigned);
  - Indication: Complication (with number and specification if other mentioned.)

and coded.

6.1.3.7 Immunogenicity Assessment

Immunogenicity assessment will be carried out in one blood sample collected prior to study treatment administration and approximately at 5 weeks after administration (with a window from 3 to 6 weeks). The measure of anti-SP-B and anti-SP-C antibodies will be evaluated by a titration versus a positive control serum (GP). Further details are given in section 7.2.1 of the CSP.

6.1.4 Pharmacodynamic/Efficacy Data

6.1.4.1 Ratio of arterial oxygen saturation (SpO_2/FiO_2)

Ratio of arterial oxygen saturation determined by pulse oximetry and fraction of inspired oxygen (SpO_2/FiO_2) will be determined in the first 7 days post-treatment (at 30 minutes, at 1, 3, 6, 12, 18, 24 hours, at Days 2, 3, 5 and 7), at Day 28±2 PNA, at discharge home and at 36 weeks PMA.

6.1.4.2 Fraction of inspired oxygen (FiO_2)

FiO_2 will be measured in the first 7 days post treatment (at 30 minutes, at 1, 3, 6, 12, 18, 24 hours, at Days 2, 3, 5 and 7), at Day 28±2 PNA, at discharge home and at 36 weeks PMA.

6.1.4.3 Arterial oxygen saturation (SpO2)

SpO_2 will be measured in the first 7 days post treatment (at 30 minutes, at 1, 3, 6, 12, 18, 24 hours, at Days 2, 3, 5 and 7), at Day 28±2 PNA, at discharge home and at 36 weeks PMA.

6.1.4.4 Respiratory Severity Score (RSS)

Respiratory Severity Score (RSS) [FiO_2 corrected by mean airway pressure (MAP)] will be calculated at each timepoint (i.e., at 30 minutes, at 1, 3, 6, 12, 18, 24 hours and on Day 2) as FiO_2 x MAP.

6.1.4.5 Oxygen Saturation Index (OSI)

Oxygen Saturation Index (OSI) will be calculated at each timepoint (i.e., at 30 minutes, at 1, 3, 6, 12, 18, 24 hours and on Day 2) as

$$FiO_2 \times MAP \times 100/SpO_2.$$

6.1.4.6 Ventilator Settings

MAP (cmH_20), PIP (cmH_20) and PEEP (cmH_20) will be determined in the first 7 days post-treatment (at 30 minutes, at 1, 3, 6, 12, 18, 24 hours, at Days 2, 3, 5 and 7), at Day 28±2 PNA, at discharge home and at 36 weeks PMA.

6.1.4.7 Biomarkers of inflammation

CXCL8, Interleukin 1β (IL1β), Interleukin 6 (IL6), Tumor Necrosis Factor-alpha (TNF-α), myeloperoxidase (MPO) will be collected prior to study drug administration, at 24±1 hours and on day 2 (48±1 hours) in a subgroup of babies who require endotracheal intubation for mechanical ventilation, when feasible. Additionally, total proteins concentration and CXCL8/total protein, IL1β/total protein, IL6/total protein, TNF-α/total protein, MPO /total protein will also be provided.

6.1.4.8 Mortality and BPD

Mortality

The mortality incidence at 36-week PMA and at Day 28 will be compared by treatment as for Mortality/BPD incidence.

RDS-Mortality

The RDS-associated Mortality incidence through 14 days of age will be surveyed in the corresponding treatment group. Patients with reasons for discontinuation='RDS RELATED DEATH" and died within 14 days of age will be considered in the counts.

Bronchopulmonary Dysplasia (BPD)

BPD is defined according to the diagnostic criteria recently proposed by the NICHD / NHLBI / ORD Workshop [4].

The patients will be diagnosed with BPD and included in the analysis if the following applies:

Has the baby been treated with oxygen >21% for at least 28 days? ='Yes' and 'Did the patient have a diagnosis of BPD?='Yes'.

In addition, if:

1) there is no requirement for supplemental oxygen and ventilatory support (i.e. "Is there a requirement for supplemental oxygen?" = "No" and "Is there a requirement for ventilatory support?"="No", BPD will classified as 'Mild'

2) if there is requirement for supplemental oxygen (i.e. 'Is there a requirement for supplemental oxygen?" = "Yes") and oxygen value <30% then BPD will be classified as 'Moderate';

3) if there is requirement for supplemental oxygen (i.e. 'Is there a requirement for supplemental oxygen?" = "Yes") with an oxygen value ≥30% and/or positive pressure ("Is there a requirement for ventilatory support?"="Yes") then BPD will be classified as 'Severe'

Note: if "Is there a requirement for ventilatory support?"="Yes" but ventilatory support used is Low Flow Nasal Cannula, this shouldn't be considered as positive pressure use. Please refer to Data Review report for additional details.

Mortality/BPD incidence

The mortality/BPD incidence at 36-week PMA will be defined as:

Incidence of neonates dead within 36-week PMA or alive at 36-week PMA with a diagnosis of BPD.

6.1.4.9 Rescue medication

The percentage of patients requiring at least one rescue surfactant dose at any time during the study and within 48 hrs since last dose will be determined by treatment group. Patients with pulmonary hemorrhage during the study (displayed as adverse event with corresponding preferred term 'Pulmonary haemorrhage') will be excluded from this summary.

6.1.4.10 Respiratory Support and Related Duration of Ventilation (Invasive and Non-invasive)

Any respiratory Support given for the normal care of preterm neonates during the study conduct will be documented with:

- Was any respiratory support provided? (Y/N), if answered yes with:
- Method of Ventilation (and specification if other had been mentioned);
- Start/End Date and Time.

Non-invasive ventilation will include the use of at least one of the following ventilatory supports:

- Continuous Positive Airway Pressure (CPAP)
- Bi-level Positive Airway Pressure (BiPAP)
- Nasal Intermittent Positive Pressure Ventilation (NIPPV)
- High Flow Nasal Cannula (HFNC)
- Other: Nasal Synchronized Intermittent Positive Pressure Ventilation (nSIPPV)
- Other: Nasal Synchronized Intermittent Mandatory Ventilation (nSIMV)
- Other: Nasal Intermittent Mandatory Ventilation (nIMV)
- Other: Nasal High frequency ventilation (NHFV)
- Other: Nasal Pressure Support Ventilation (NPSV)

- Other: NIPPV-NAVAMODE
- Other: NON-INVNAVA
- Other (refer to Data Review Report for exhaustive list)

Invasive ventilation will include the use of at least one the following ventilatory support:

- High Frequency Oscillatory Ventilation (HFOV)
- HFOV/NAVAMODE
- Synchronized Intermittent Mandatory Ventilation (SIMV)
- Patient Trigger Ventilation (PTV)
- Synchronized Intermittent Positive Pressure Ventilation (SIPPV)
- Other: Intermittent Mandatory Ventilation (IMV)
- Other: A/C (assist/control)
- Other: Pressure Support Ventilation (PSV)
- Other: PPVTHRUETTUBE
- Other: SIMV/NAVA,
- Other: IMV/NAVAMODE
- Other (refer to Data Review Report for exhaustive list).

Note: Low Flow Nasal Cannula use will be summarized under “Oxygen alone”.

Duration of non-invasive and invasive ventilation will be defined as total number of days when neonates received non-invasive and invasive mechanical ventilation, respectively.

Duration of ventilation (invasive and non-invasive) will be calculated as the sum of each period of received ventilation which will be calculated as ventilation end date/time minus ventilation started date/time. A review of these data will be performed during BDRM to specify whether specific adaptations of the algorithm have to be implemented.

To account for missing time in date/time when deriving duration variables, the following approaches will be used:

- Time points with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h or treatment administration time (1st treatment Day 1 only) for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).

6.1.4.11 Oxygen Use and Related Duration

Any Oxygen given alone for the normal care of preterm neonates during the study conduct will be documented with:

- Was the subject given Oxygen alone? (Y/N), if answered yes with:
    - Start/End Date and Time.

In addition, all the cases of "Low Flow Nasal Cannula" as reported in the ventilatory parameters pages will be summarized under Oxygen use.

Duration of oxygen use will be calculated as sum of oxygen use/LFNC end date/time minus oxygen/ LFNC use started date/time.

To account for missing time in date/time when deriving duration variables, the following approaches will be used:

- Time points with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h or treatment administration time (1st treatment Day 1 only) for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).

6.1.4.12 Normal breathing (i.e. at room air) patients within 24 hours

Percentage of patients with at least one reading of FiO_2 equal to 0.21 (i.e. at room air) within 24 hours from first intake will be taken as estimation of normal breathing.

Additionally the median duration time to reach FiO_2 equal to 0.21 (normal breathing) will be determined.

6.1.4.13 Alveolar–Arterial Gradient

The alveolar–arterial gradient ($A\text{-}aO_2$) is used in determining the source of hypoxemia is derived on the eCRF as difference of alveolar PO_2 (PaO_2) and arterial PO_2.

Values in the first 48 hours after the first surfactant intake (i.e., at 3, 6, 12, 18, 24 hours and on day 2) will be collected, given the challenges to placing arterial catheters in pre-term neonates.

6.1.4.14 Oxygenation Index

The Oxygenation Index (OI) is a calculation used in intensive care medicine to measure the fraction of inspired oxygen (FiO_2) and its usage within the body according to the following formula (lower oxygenation index is better):

$OI = FiO_2 * MAP / PaO_2$.

Values in the first 48 hours after the first surfactant intake (i.e., at 3, 6, 12, 18, 24 hours and on day 2) will be collected.

6.2 Analysis Populations

6.2.1 Safety Population

The safety population consists of all randomized patients who took at least one dose of study medication.

The safety population (SAF) will be used in the analysis of all safety variables.

In case of deviation between as-randomized treatment and treatment actually received, the treatment actually received will be used in the safety analyses (i.e. an "as-treated" analysis will be performed).

6.2.2 Intention-to-Treat Population

The Intention-to-Treat population (ITT) consists of all randomized patients who received at least one dose of study medication and with at least one available evaluation of efficacy after the baseline.

The efficacy analyses will be performed based on the ITT population.

6.2.3 Per Protocol Population

Considering the exploratory nature of the study, no Per Protocol (PP) analysis is planned. Hence, the need to repeat efficacy analysis on a PP population for specific efficacy parameters has been discussed during the BDRM before database lock based on the amount and kind of major protocol violations.

The PP Population will then consist of subjects in the ITT population with no major protocol deviations. FiO2 and SpO2/FiO2 analyses will be repeated in the PP population.

6.3 Statistical Analysis Methods

6.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed and described using summary statistics. Frequency counts (number of neonates [n] and percentages) will be made for each qualitative variable. General descriptive statistics for numeric variables will include the n (number of observed values), the mean, the standard deviation, the median, the minimum, and the maximum values. For categorical variables, the number and percent of subjects with a specific level of the variable will be presented (if not stated otherwise).

All listings will include unscheduled measurements, i.e. all measured values will be listed. Listings are to be sorted by patient number and then by visit/week/day/timepoint (where applicable).

- All listings will be presented for the randomized population. Screened neonates will be used for disposition listing.
- Randomized treatment and actual treatment will be displayed in 'Listing 16.1.7 – Randomization Schedule' and misallocations, if any, will be identified with a flag (§). The actual treatment will be presented in all safety listings, while the randomized treatment will be presented in the efficacy listings.
- In case of values excluded from the analysis, specific flags will be presented.

All descriptive statistics will be presented by treatment.

6.3.2 Statistical Significance Level

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated.

6.3.3 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.2 or later.

6.3.4 Missing Data

Generally there will be no imputation of missing data. Hence critical missing data, if any, will be discussed during the BDRM before database lock. Decisions will be fully documented in the BDRM Report.

6.3.5 Interim Analysis

Not applicable.

6.3.6 Protocol Deviations

Protocol deviations detected during the study will be collected in a log file list and discussed within [redacted] (physician, Data Manager, Biostatistician, PK Scientist/Analyst and Medical Writer). The Sponsor will evaluate the protocol deviations at the BDRM before database lock in order to estimate their influence (major, minor) on study results and to decide whether these deviations may warrant exclusion of a subject from the statistical analyses. Major protocol violations will be listed and summarized by treatment.

6.3.7 Patients disposition

Reason for screening failures will be presented with a breakdown of the reasons for discontinuation.

Disposition of patients and reason for discontinuations will be presented for the randomized patients population by treatment and overall.

6.3.8 Demographic Data

All demographic data will be presented using the ITT and safety population. Data listings and summary tables will be provided.

6.3.9 Mother and Neonatal Concomitant Medication

Any concomitant medication given for the normal care of preterm neonates or used by the neonates' mother during the study will be listed and displayed in a frequency table.

Tables will be presented by Anatomical Main Group (1st level of ATC), Therapeutic Subgroup (2nd level of ATC), Chemical Subgroup (4th level of ATC) and preferred drug name, alphabetically sorted. Code and decode will be displayed as follow:

- R, Respiratory System
  - R03, Drugs for Obstructive Airway Diseases
    - R03CC, Selective Beta-2-Adrenoreceptor Agonists
      - Salbutamol.

In the summaries, subjects experiencing more than one medication classified in the same category (previous medications, concomitant medications) within the same anatomical main group, therapeutic subgroups, chemical subgroup and preferred name will be counted only once.

6.3.10 Exposure to the Investigational Medicinal Product

Drug dosing (both initial and re-dosing) information (dosing date/time, volume administered, calculated dose administered), if available, will be presented in a listing (Appendix 16.2.5).

First and cumulative dose as well as total dose administered (mg/kg) will be summarized by treatment. Number and percentage of neonates receiving additional study drug doses will be summarized by treatment, overall and by number of additional doses (1 or 2).

Time since birth to first dose (h) and to each of the additional doses (h) will be summarized by treatment.

6.3.11 Safety Analysis

The analysis of the safety variables will be based on the safety population.

6.3.11.1 Adverse Events

An overall summary of number and percentage of subjects with at least one treatment-emergent AEs, SAEs, ADRs, serious ADRs and AEs leading to death will be presented by treatment. The number of events will be also displayed.

The number and percentage of patients with at least one AE and the number of AEs will be presented by treatment for treatment-emergent AEs, SAEs, ADRs, and AEs leading to death. The summary results will be presented in alphabetic order for the SOC. Within each SOC, the PTs will be presented sorted by decreasing overall frequency (not explicitly displayed).

The following listings will be produced:

- Pre-treatment AEs;
- TEAEs
- ADRs;
- SAEs;
- TEAEs leading to death.

6.3.11.2 Clinical Safety Laboratory Tests (hematology, biochemistry)

Laboratory values (hematology, biochemistry) will be listed by neonates and study time point.

All values outside the clinical reference ranges, if available, will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. Clinical significance (NCS or CS), if available, will be listed as well.

6.3.11.3 Vital Signs

Vital signs data (SBP, DBP, HR, SpO_2 during administration) taken on Day -1 will be listed by patient.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute and change from baseline values will be presented by treatment at each time point. SpO_2 during administration will be summarized as well.

Time curve of the mean change from baseline in the first week of life will be presented by treatment group.

6.3.11.4 Immunogenicity data

The levels of antibodies in serum will be listed.

'Not reliable' immunogenicity values as defined during Blind Data Review meeting will be flagged in the listing.

6.3.12 Efficacy Variables

The efficacy analysis will be based on the ITT population.

The efficacy parameters will be listed by treatment and time point and will include both absolute values and changes from baseline, where applicable.

The baseline for each of these parameters will be the last pre-dose measurement taken on Day -1 (including unscheduled measurements, if available). If no assessment exists before treatment but a measurement is taken exactly at the same time of treatment, this will be used as baseline measurement and mentioned for corresponding outputs. The latest won't apply to SpO2 since value collected at time 0 is not part of efficacy assessment (See Section 9 of CSP). If measurements at date of treatment have no time information included, it is assumed as taken before treatment time since recorded under screening assessment.

Descriptive statistics of the absolute values and changes from baseline will also be presented.

Post-treatment unscheduled assessment won't be used in the analysis unless original assessment is not available.

6.3.12.1 Statistical Analysis

6.3.12.1.1 SpO_2/FiO_2 Ratio

SpO_2/FiO_2 will be analyzed using a linear mixed model for repeated measures (MMRM) including treatment, time point, treatment by time point interaction, investigational site and gestational age group as fixed effects and pre-dose ratio as covariate. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) at each time point and averaged over the first 24 hours will be estimated by the model. The following SAS code will be used:

```
Proc Mixed data= …(WHERE=(time LE 24));
Class treatment time site agegrp subject;
Model var=treatment time treatment*time site agegrp baseline baseline*time / ddfm=kr;
REPEATED time / subject=subject type=UN;
Lsmeans treatment*time / PDIFF CL alpha=0.05;
Lsmeans treatment / PDIFF CL alpha=0.05; * for overall;
Estimate 'CHF5633 - Curosurf: 30 min' treatment 1 -1 treatment*time 1 0 0 0 0 0 0 -1 0 0 0 0 0 0 /CL alpha=0.05;
Estimate 'CHF5633 - Curosurf: 1 hr' treatment 1 -1 treatment*time  0 1 0 0 0 0 0 0 -1 0 0 0 0 0 /CL alpha=0.05;
Estimate 'CHF5633 - Curosurf: 3 hrs' treatment 1 -1 treatment*time  0 0 1 0 0 0 0 0 0 -1 0 0 0 0 /CL alpha=0.05;,
Estimate 'CHF5633 - Curosurf: 6 hrs' treatment 1 -1 treatment*time  0 0 0 1 0 0 0 0 0 0 -1 0 0 0 /CL alpha=0.05;
Estimate 'CHF5633 – Curosurf: 12 hrs' treatment 1 -1 treatment*time 0 0 0 0 1 0 0 0 0 0 0 -1 0 0 /CL alpha=0.05;
Estimate 'CHF5633 – Curosurf: 18 hrs' treatment 1 -1 treatment*time 0 0 0 0 0 1 0 0 0 0 0 0 -1 0 /CL alpha=0.05;
Estimate 'CHF5633 – Curosurf: 24 hrs' treatment 1 -1 treatment*time 0 0 0 0 0 0 1 0 0 0 0 0 0 -1 /CL alpha=0.05;
Estimate 'CHF5633 - Curosurf: Overall' treatment 1 -1 / CL alpha=0.05;
ods output estimates=estim lsmeans=ls_means;
QUIT;
/* baseline=pre dose value, agegrp=gestational age group, time in hours */
Time profile plot of mean SpO2/FiO2 in the first 24 hours post treatment will be presented
by treatment group.
```

SpO_2/FiO_2 will be compared between treatments at the remaining post-treatment time points (i.e., Days 2, 3, 5, 7, 28±2 PNA, at discharge home and at 36 weeks PMA) using mixed model including

treatment, investigational site and gestational age group as fixed effects and pre-dose ratio as covariate. These results will be displayed in a separate table.

SpO2/FiO2 summary and analyses will be repeated also in the PP population.

According to the protocol, if the discharge home coincides with 36-wks PMA assessment, data are entered once in the eCRF at 36-wks PMA. In this case, data of 36-wks PMA should be used also for discharge summary and analysis.

The following SAS code will be used:

```
     Proc Mixed data= …;
     Class treatment site agegrp;
     Model var=treatment site agegrp baseline / ddfm=kr;
          Lsmeans treatment / CL alpha=0.05;
          Estimate 'CHF5633 - Curosurf' treatment 1 -1/
          DIFF cl alpha=0.05;
          ods output estimates=estim
                     lsmeans=ls_means;
     BY day;
     QUIT;
/* baseline=pre dose value, agegrp=gestational age group */
```

SpO2/FiO2 will be analyzed by subgroups based on ventilator support used.

6.3.12.1.2 FiO2

FiO_2 will be analyzed at each time point and averaged over the first 24 hours post dose using the same model used for the SpO_2/FiO_2. Pre-dose FiO_2 will be used as covariate.

Time profile plot of mean FiO_2 in the first 24 hours after treatment will be presented by treatment group.

FiO_2 will be compared between treatments at additional post-treatment time points (i.e., Days 2, 3, 5, 7, 28±2 PNA, at discharge home and at 36 weeks PMA) using linear mixed model including, treatment, investigational site and gestational age group as fixed effects and pre-dose FiO_2 as covariate. Same SAS code displayed in the SpO_2/FiO_2 analysis will be used.

FiO2 summary and analyses will be repeated also in the PP population.

According to the protocol, if the discharge home coincides with 36-wks PMA assessment, data are entered once in the eCRF at 36-wks PMA. In this case, data of 36-wks PMA should be used also for discharge summary and analysis.

6.3.12.1.3 RSS

RSS, calculated from ventilator settings as MAP x FiO_2, will be analyzed at each time point and averaged over the first 24 hours post study drug intake using the same model used for the SpO2/FiO2.

Time profile plot of mean RSS in the first 24 hours after treatment will be presented by treatment group.

RSS at Day 2 will be analyzed using linear mixed model including, treatment, investigational site and gestational age group as fixed effects.

Same SAS code displayed in the SpO_2/FiO_2 analysis will be used.

According to the protocol, if the discharge home coincides with 36-wks PMA assessment, data are entered once in the eCRF at 36-wks PMA. In this case, data of 36-wks PMA should be used also for discharge summary and analysis.

6.3.12.1.4 OSI

OSI, will be calculated as MAP x FiO_2 x $100/SpO_2$, will be analyzed at each time point and averaged over the first 24 hours post study drug intake using the same model used for the SpO2/FiO2.

Same SAS code displayed in the SpO_2/FiO_2 analysis will be used.

Time profile plot of mean OSI in the first 24 hours after treatment will be presented by treatment group. OSI at Day 2 will be analyzed using linear mixed model including, treatment, investigational site and gestational age group as fixed effects.

Same SAS code displayed in the SpO_2/FiO_2 analysis will be used.

According to the protocol, if the discharge home coincides with 36-wks PMA assessment, data are entered once in the eCRF at 36-wks PMA. In this case, data of 36-wks PMA should be used also for discharge summary and analysis.

6.3.12.1.5 SpO2

SpO_2 values as well as changes from baseline (Day -1) will be summarized by treatment group by means of descriptive statistics at each post-treatment timepoints.

According to the protocol, if the discharge home coincides with 36-wks PMA assessment, data are entered once in the eCRF at 36-wks PMA. In this case, data of 36-wks PMA should be used also for discharge summary and analysis.

6.3.12.1.6 Ventilator Settings

MAP, PIP, PEEP values as well as changes from baseline (Day -1) will be summarized by treatment group by means of descriptive statistics at each post-treatment timepoints.

According to the protocol, if the discharge home coincides with 36-wks PMA assessment, data are entered once in the eCRF at 36-wks PMA. In this case, data of 36-wks PMA should be used also for discharge summary and analysis.

6.3.12.1.7 BPD incidence, Mortality/BPD incidence, mortality and RDS-mortality

Mortality/BPD incidence at 36-week PMA will be compared by treatment by means of Cochran-Mantel-Haenszel (CMH), adjusting for stratification GA group. Relative risk (RR) and related 95% confidence interval will be provided using a SAS code similar to:

```
PROC FREQ DATA = …;
 WEIGHT count;
 TABLE factor*treatment*response/relrisk cmh norow nocol nopercent;
RUN;
/*factor=GA group
```

```
Only GA factor is included since not possible to use the combination
of two factors (i.e. too few neonates by site). Please refer to DR
report */
```

The incidence of BPD at 36-week PMA will be compared by treatment as for Mortality/BPD incidence. Cases not assessed at 36-week PMA visit won't be imputed. Missing cases won't be included in test statistics computation.

The mortality incidence at 36-week PMA and at Day 28 will be compared by treatment as for Mortality/BPD rate.

RDS-associated mortality incidence through 14 days of age will be compared by treatment as for Mortality/BPD rate.

6.3.12.1.8 Rescue surfactant use

The percentage of patients requiring at least one rescue surfactant dose will be compared by treatment group by means of a Fisher's exact test at 5% significance interval. Odds ratio (OR) and related exact 95% CI will be also provided. Patients with pulmonary hemorrhage will be excluded from this summary.

For Fisher's exact test SAS code similar to this will be used:

```
PROC FREQ DATA = …;
 WEIGHT count;
 TABLE treatment*result/measures riskdiff (CL=(WALD MN))alpha=0.05
 exact fisher or / alpha=0.05;
RUN;
```

/* option riskdiff (CL=(WALD MN)) gives the WALD CI and the CI based on inverting a score test, as suggested by Miettinen and Nurminen (1985), but can be adapted if deemed appropriate */

6.3.12.1.9 Duration of ventilation and oxygen use

The median duration time of invasive mechanical ventilation, oxygenation and non-invasive ventilation will be compared between groups by the Mann-Whitney U-test using SAS code similar to:

PROC NPAR1WAY DATA=… hl;
* hl adds Hodges-Lehmann confidence interval for delta;
CLASS treatment;
VAR time;
RUN;

6.3.12.1.10 Normal breathing patients within 24 hours

Percentage of patients with normal breathing within 24 hours will be compared by treatment groups by means of a Fisher's exact test at 5% significance interval. Odds ratio (OR) and related exact 95% CI will be also provided.

The median duration time to reach FiO_2 equal to 0.21 will be compared between treatments by the Mann-Whitney U-test.

6.3.12.1.11 Biomarkers of inflammation

Mean values of biomarkers of inflammation (i.e., CXCL8, IL1β, IL6, TNF-α, MPO) in the tracheal aspirates as well as change from baseline to 24 hours and on Day 2 (48 hours) will be summarized by treatment by means of descriptive statistics. Additionally, total proteins concentration and CXCL8/total protein, IL1β/total protein, IL6/total protein, TNF-α/total protein, MPO /total protein will also been included.

Biomarker values below/above the limit of quantification (BLQ/ALQ) will be imputed as follows:

1) BLOQ (Dil), Bad Replicate (BR) and Insufficient Volume (IV) will be considered as missing
2) BLOQ will be imputed by the value of low detection limit divided by 2 (Example: if the database contains a value like 0.917, 0.459 value will be imputed).
3) ALQ by the value of detection limit plus one unit. Since diluted values have been used the following will apply

   IL6 ALQ value will be imputed with 27001 (i.e. 270*100+1)
   IL8 ALQ value will be imputed with 20201 (i.e. 202*100+1)
   MPO ALQ value will be imputed with 12400001 (i.e. 24800*500+1)

6.3.12.1.12 Alveolar–Arterial Gradient

The alveolar–arterial gradient (A-aO_2) values as well as change from baseline in the first 48 hours after the first surfactant intake (i.e., at 3, 6, 12, 18, 24 hours and on Day 2) will be summarized by treatment by means of descriptive statistics.

6.3.12.1.13 Oxygenation Index

The Oxygenation Index (OI) values as well as change from baseline in the first 48 hours after the first surfactant intake (i.e., at 3, 6, 12, 18, 24 hours and on Day 2) will be summarized by treatment by means of descriptive statistics.

7. REFERENCES

1. SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in controlled clinical trials. Biometrics. 1975 Mar;31(1):103-15.
3. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213-226.
4. Jobe A, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001; 163:
5. 1723-9.

8. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

All the Tables, Figures and Listings with asterisk will be included in the Key First Results package.

DISPOSITION AND DEMOGRAPHIC DATA

Table 14.1.1.1 Patient Disposition (All Screened)

*Table 14.1.1.2 Patient Disposition:(All Randomized)

Table 14.1.1.5 Major Protocol Deviations (ITT population)

Table 14.1.1.6 Minor Protocol Deviations (ITT population)

*Table 14.1.1.7 Summary of Analysis Sets (All Randomized)

*Table 14.1.2.1 Demographic Characteristics (ITT Population)

*Table 14.1.2.2 Demographic Characteristics (Safety Population)

Table 14.1.4.1 Chest x-Ray (Safety Population)

Table 14.1.4.2 Complications of Prematurity at Baseline (Safety Population)

Table 14.1.5.1 Mother Medical and Surgical History (Safety Population)

Table 14.1.5.2 Pregnancy History (Safety Population)

Table 14.1.6.1 Mother Previous and Concomitant Medication (Safety Population)

Table 14.1.6.2 Neonatal Concomitant Medication (Safety Population)

Table 14.1.7.1 Cranial Sonography at Screening (Safety Population)

*Table 14.1.8.1 Treatment Exposure (Safety Population)

EFFICACY DATA

*Table 14.2.1.1.1 Summary of Ratio of Arterial Oxygen Saturation (SpO2/FiO2) versus Time Point by Treatment (ITT Population)

Table 14.2.1.1.2 Summary of Ratio of Arterial Oxygen Saturation (SpO2/FiO2) versus Time Point by Treatment (PP Population)

*Table 14.2.1.2.1 Statistical Analysis of the Arterial Oxygen Saturation (SpO2/FiO2) ratio in the First 24 hrs (ITT Population)

Table 14.2.1.2.2 Statistical Analysis of the Arterial Oxygen Saturation (SpO2/FiO2) ratio in the First 24 hrs (PP Population)

Table 14.2.1.3.1 Statistical Analysis of the Arterial Oxygen Saturation (SpO2/FiO2) Ratio – Additional Timepoints (ITT Population)

Table 14.2.1.3.2 Statistical Analysis of the Arterial Oxygen Saturation (SpO2/FiO2) Ratio – Additional Timepoints (PP Population)

*Table 14.2.2.1.1 Summary of Fraction of inspired oxygen (FiO2, %) versus Time Point by Treatment (ITT Population)

Table 14.2.2.1.2 Summary of Fraction of inspired oxygen (FiO2, %) versus Time Point by Treatment (PP Population)

*Table 14.2.2.2.1 Statistical Analysis of FiO2 (%) in the First 24 hrs (ITT Population)

Table 14.2.2.2.2 Statistical Analysis of FiO2 (%) in the First 24 hrs (PP Population)

Table 14.2.2.3.1 Statistical Analysis of FiO2 (%) – Additional Timepoints (ITT Population)

Table 14.2.2.3.2 Statistical Analysis of FiO2 (%) – Additional Timepoints (PP Population)

Table 14.2.2.4 Normal Breathing (i.e. at room air) Patients within 24 hours (ITT Population)

Table 14.2.3.1 Summary of Respiratory Severity Score (RSS) versus Time Point by Treatment (ITT Population)

Table 14.2.3.2 Statistical Analysis of the RSS in the First 24 hrs (ITT Population)

Table 14.2.3.3 Statistical Analysis of the RSS – Additional Timepoints (ITT Population)

Table 14.2.4.1 Summary of Oxygen Saturation Index (OSI) versus Time Point by Treatment (ITT Population)

Table 14.2.4.2 Statistical Analysis of the OSI in the First 24 hrs (ITT Population)

Table 14.2.4.3 Statistical Analysis of the OSI – Additional Timepoints (ITT Population)

*Table 14.2.5 Summary of SpO2 (%) versus Time Point by Treatment (ITT Population)

Table 14.2.6 Summary of Ventilator Settings (MAP, PIP, PEEP) versus Time Point by Treatment (ITT Population)

*Table 14.2.7 Mortality and BPD (ITT Population)

*Table 14.2.8 Rescue Medication (ITT Population)

Table 14.2.9 Duration of Ventilation (ITT Population)

Table 14.2.10 Summary of Duration of Oxygen Use (ITT Population)

Table 14.2.11 Biomarkers (ITT Population)

Table 14.2.12 Summary of Alveolar-Arterial Gradient (A-aO2) (ITT Population)

Table 14.2.13 Summary of Oxygenation Index (OI) (ITT Population)

SAFETY DATA

ADVERSE EVENTS

*Table 14.3.1.3.1 Summary of Treatment-Emergent Adverse Events (Safety Population)

*Table 14.3.1.3.2 Treatment-emergent Adverse Events by Treatment, System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.3.3 Adverse Drug Reactions by Treatment, System Organ Class and Preferred Term (Safety Population)

*Table 14.3.1.3.4 Serious AEs by Treatment, System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.3.5 Neonatal Morbidities (Safety Population)

VITAL SIGNS

Table 14.3.4.1 Vital Signs: Actual Values and Changes from Baseline (Safety Population)

FIGURES

*Figure 14.2.1Mean (+/-95% CI) for SpO2/FiO2 ratio by Time and Treatment

*Figure 14.2.2Mean (+/-95% CI) for Fraction of Inspired Oxygen by Time and Treatment

Figure 14.2.3 Mean (+/-95% CI) for Respiratory Severity Score by Time and Treatment

Figure 14.2.4 Mean (+/-95% CI) for Oxygen Saturation Index by Time and Treatment

Figure 14.2.5 Mean (+/-95% CI) for Arterial Oxygen Saturation (SpO2) by Time and Treatment

Figure 14.2.6 Mean (+/-95% CI) for MAP by Time and Treatment

9. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

RANDOMIZATION SCHEDULE

Listing 16.1.7 Randomization Schedule (All Randomized)

SUBJECT DISPOSITION

Listing 16.2.1.1 Screening Failures (All Enrolled)

Listing 16.2.1.3. Study Discontinuation (All Randomized)

Listing 16.2.1.4 Study Visit dates (All Randomized)

Listing 16.2.1.5 Study Kits Details (All Randomized)

PROTOCOL DEVIATIONS

Listing 16.2.2.1: Major Protocol Deviations (All Randomized)

Listing 16.2.2.2: Minor Protocol Deviations (All Randomized)

Listing 16.2.2.3 Violation of Inclusion/Exclusion Criteria (All Randomized)

ANALYSIS POPULATIONS

Listing 16.2.3.1 Population Disposition (All Randomized)

DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Listing 16.2.4.1 Demographic Characteristics (All Randomized)

Listing 16.2.4.2 Complications of Prematurity (All Randomized)

Listing 16.2.4.3 Chest X-Ray (All Randomized)

Listing 16.2.4.4 Cranial Sonography (All Randomized)

Listing 16.2.4.5.1 Mother Medical and Surgical History (All Randomized)

Listing 16.2.4.5.2 Pregnancy History (All Randomized)

Listing 16.2.4.6.1 Mother Previous and Concomitant Medication (All Randomized)

Listing 16.2.4.6.2 Neonatal Concomitant Medications (All Randomized)

COMPLIANCE AND/OR DRUG CONCENTRATION DATA

Listing 16.2.5.1 Study Medication Administration (All Randomized)

Listing 16.2.5.2 Hospital Transfer (All Randomized)

Listing 16.2.5.3 Breaking the Blind (All Randomized)

EFFICACY/PHARMACODYNAMIC DATA

Listing 16.2.6.1 Arterial Oxygen Saturation (SpO2), Fraction of Inspired Oxygen (FiO2), SPO2/FiO2 (All Randomized)

Listing 16.2.6.2 Ventilator Settings and Respiratory Parameters (PIP, MAP, PEEP, RSS, OSI)

Listing 16.2.6.3 A-a Oxygen Gradient and Oxygenation Index (OI)

Listing 16.2.6.4 Blood Gas Analysis (BGA) (All Randomized)

Listing 16.2.6.5 Biomarkers of Inflammation in Tracheal Aspirates (All Randomized)

Listing 16.2.6.6 Respiratory Support/Duration of Ventilation (All Randomized)

Listing 16.2.6.7 Duration of Oxygen use Alone (All Randomized)

Listing 16.2.6.8 Assessment of Mortality and BPD (All Randomized)

ADVERSE EVENTS

Listing 16.2.7.1 Pre Treatment Adverse Events (All Randomized)

Listing 16.2.7.2 Treatment-emergent Adverse Events (All Randomized)

Listing 16.2.7.3 Adverse Drug Reactions (All Randomized)

Listing 16.2.7.4 Serious Adverse Events (All Randomized)

Listing 16.2.7.5 Adverse Events Leading to Death (All Randomized)

Listing 16.2.7.6 Neonatal Complication of Prematurity (All Randomized)

LABORATORY AND OTHER SAFETY ASSESSMENTS

Listing 16.2.8.1 Biochemistry (All Randomized)

Listing 16.2.8.2 Hematology

Listing 16.2.8.3 Abnormal Biochemistry Values (All Randomized)

Listing 16.2.8.4 Abnormal Hematology Values

Listing 16.2.8.5 Vital Signs (All Randomized)

Listing 16.2.8.6 Immunogenicity Assessment in Serum (All Randomized)

Listing 16.2.8.7 Surgical/Medical Procedure (All Randomized)

Listing 16.2.8.8 Comments (All Randomized)

10. DOCUMENTATION OF STATISTICAL METHODS

Appendix 16.1.9.1: SAP and related documents

Appendix 16.1.9.2: SAS Raw output of statistical analyses

11. APPENDIX

11.1 Study Schedule (according to protocol Amendment 1)

ASSESSMENT	ON ADMISSION PRIOR TO STUDY TREATMENT WITHIN FIRST 24 HOURS OF LIFE (Day -1)	MINUTES/HOURS/DAYS								DAYS/WEEKS							
		0	30' (±5')	1-h (±10')	3-h (±30')	6-h (±30')	12-h (±30')	18-h (±30')	24-h (±30')	Day 2	Day 3	Day 5	Day 7	Day 28±2 PNA	Discharge home	36-WEEK PMA	24-month clinical assess.
Randomization/Study treatment administration		X															
Parental Informed Consent (1)	X																
Inclusion/Exclusion Criteria	X																
Complications during pregnancy	X																
Demographic data	X																X
Apgar Score	X																
Neonatal complications	X																
Vital signs	X	X(+)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray	X(*)								X(*)								
Cranial sonography	X(*)												**X (**)**	(X)*			
Hematology and Biochemistry									X								
Arterial Oxygen Saturation (SpO_2)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ventilator settings (FiO_2, PIP, MAP, PEEP) (2)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
A-a Oxygen gradient and OI (3)	X				X	X	X	X	X	X							
Duration of oxygen alone									X	X	X	X	X	X	X	X	
Neonatal Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Immunogenicity assessment in serum	X													(X)***			
Tracheal aspirates [3]	X								X	X							
Assessment of BPD																X	
Adverse Events/Adverse Drug Reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Bayley Scales																	X
Health status questionnaire																	X

1. Signature of Parental Informed Consent can be obtained prior to birth or after birth;
2. PIP, MAP, PEEP to be monitored and collected until Day 7;
3. In a subgroup of babies when feasible; $(X)^{+}$ Only heart rate at time 0; (X)* When applicable, at discretion of the Investigator ; (X)** At least one cranial ultrasound within the first **7 days of life**; (X)*** The blood sampling has to be taken with a window of 3 to 6 weeks from administration