# STATISTICAL ANALYSIS PLAN

# STUDY CODE No.: CCD-050000-01

NCT02772081

AN OPEN-LABEL, MULTICENTER, RANDOMIZED, CONTROLLED STUDY IN SPONTANEOUSLY BREATHING PRETERM NEONATES WITH RESPIRATORY DISTRESS SYNDROME TO COMPARE TWO PROCEDURES FOR PORCINE SURFACTANT (PORACTANT ALFA, CUROSURF®) ADMINISTRATION: A LESS INVASIVE METHOD (LISA) DURING NON-INVASIVE VENTILATION (NIV) AND THE CONVENTIONAL ADMINISTRATION DURING BRIEF INVASIVE VENTILATION

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|---|---|
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# Contents

# List of Abbreviations

| | |
|---|---|
| ADaM | Analysis Dataset Model |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| APGAR | Appearance, Pulse, Grimace, Activity, Respiration |
| ATC | Anatomical Therapeutic Chemical |
| BE | Base Excess |
| BPD | Bronchopulmonary Dysplasia |
| CI | Confidence Interval |
| CMH | Cochran-Mantel-Haenszel |
| CSR | Clinical Study Report |
| DBL | Database Lock |
| DBP | Diastolic Blood Pressure |
| DRM | Data Review Meeting |
| DRR | Data Review Report |
| eCRF | Electronic Case Report Form |
| ETT | Endotracheal Tube |
| $FiO_2$ | Fraction of inspired Oxygen |
| GCP | Good Clinical Practice |
| $HCO_3$ | Bicarbonates |
| HR | Heart Rate |
| IMV | Invasive Mechanical Ventilation |
| ITT | Intention-To-Treat |
| LISA | Less Invasive Surfactant Administration |
| MBP | Mean Blood Pressure |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed Model for Repeated Measures |
| MV | Mechanical Ventilation |
| NAESS | INC Neonatal Adverse Event Severity Scale |
| NIV | Non-invasive Ventilation |
| OFC | Occipital-Frontal Circumference |
| OR | Odd Ratio |
| $pCO_2$ | Partial Pressure of Carbon Dioxide |
| PIPP | Premature Infant Pain Profile |
| PMA | Post-menstrual Age |
| PNA | Post-natal age |
| $pO_2$ | Partial Pressure of Oxygen |
| RDS | Respiratory Distress Syndrome |
| RR | Respiratory Rate |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SDTM | Study Data Tabulation Model |
| SOC | System Organ Class |
| $SpO_2$ | Preductal Oxygen Saturation |

| | |
|---|---|
| TEAE | Treatment Emergent Adverse Event |
| WHO-DD | World Health Organization Drug Dictionary |

**VERSION HISTORY**

| Version | Date | Change History |
|---|---|---|
| *1.0* | *18 November 2022* | *First version* |
| | | |

# 1 Introduction

This document presents the Statistical Analysis Plan (SAP) for Chiesi Farmaceutici S.p.A. protocol CCD-050000-01: An open-label, multicenter, randomized, controlled study in spontaneously breathing preterm neonates with respiratory distress syndrome to compare two procedures for porcine surfactant (poractant alfa, Curosurf®) administration: a less invasive method (LISA) during non-invasive ventilation (NIV) and the conventional administration during brief invasive ventilation.

This analysis plan is based on the final protocol (version 4.0, 8 September 2020) and the final electronic case report form (eCRF) (Final 4.0, 23 September 2021).

The SAP provides the description of the final analyses. In case of deviations from the SAP, explanations will be provided in the Clinical Study Report (CSR).

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all outputs described in this document.

**Note**: results from the 24-months (± 3 months) corrected age, will be analyzed and reported separately from the main phase and will not be part of this SAP.

# 2 Study Design

This is a phase III B, open-label, multicenter, randomized, controlled study in 150 randomized preterm neonates with early clinical signs of respiratory distress syndrome (RDS) in approximately 25 US sites.

Neonates will be evaluated according to the selection criteria and then randomized to surfactant treatment via less invasive surfactant administration (LISA) or standard administration procedure.

The enrollment will be staggered: the gestational age will be restricted to $27^{+0}$ weeks up to $28^{+6}$ completed weeks until safety evaluation by an independent safety monitoring board (ISMB) is performed for the first 15 neonates. Provided no safety concerns are raised, the enrolment will then be extended to the whole population (i.e. $25^{+0}$ weeks up to $28^{+6}$ completed weeks).

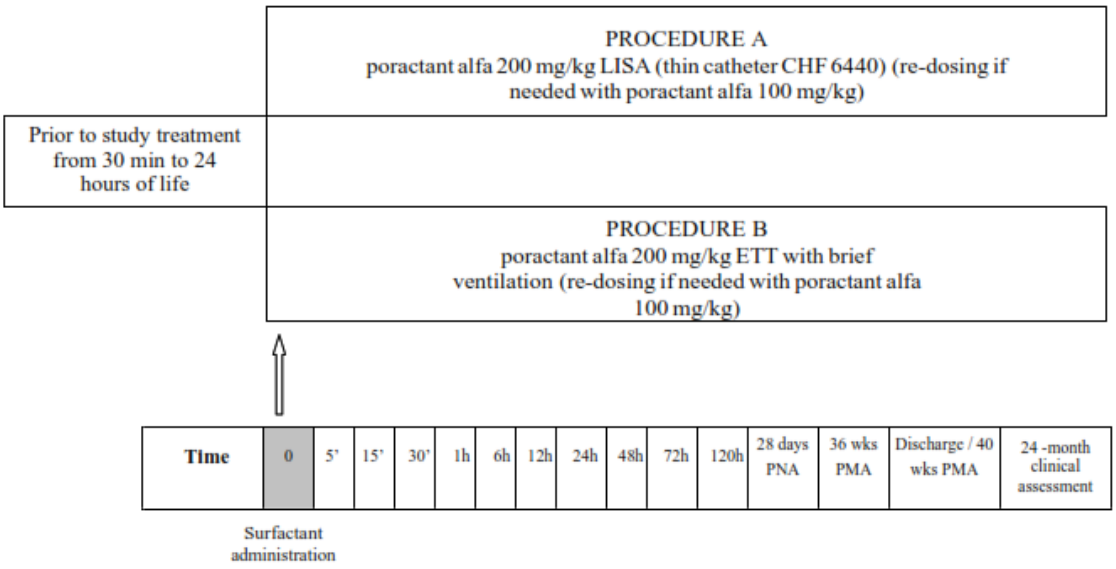
Enrolled neonates will be evaluated:

- until discharge,
- until 40 weeks post-menstrual age (PMA, if still in hospital),
- if discharge occurs before 36 weeks, the last evaluation will be at 36 weeks PMA.

This period represents the main phase of the trial.

Their final assessment of development will be at 24-month corrected age as a separate standalone visit. This 24-month clinical assessment will be analyzed and evaluated separately from the initial part of the study and will be object of an addendum to the initial core clinical study report.

**Table 1: Timetable**




The end of the trial will correspond to the last evaluation of the last neonate from the recruiting site or from the continuing care site in case the treated baby was transferred from the original recruiting site. The last evaluation could be:

-the date of the assessment for bronchopulmonary dysplasia (BPD) diagnosis (i.e. 36 weeks PMA) if the patient is discharged home before 36 weeks PMA,

-discharge home (if discharged between 36 weeks and 40 weeks PMA), or

-40 weeks PMA (if still in hospital)

There are 9 visits planned among three study periods, as below:

- Pre-randomization period: on admission to the study prior to study treatment;
- Treatment period:
    - Day 1: randomization, before start of study procedure, treatment administration up to end of surfactant administration (T0); up to 24 hours after receiving treatment (assessment at 5, 15, 30 min, 1, 6, 12, 24 hours)
    - Day 2: from 24 hours to 48 hours post treatment;
    - Day 3: from 48 hours to 72 hours post-treatment;
    - Day 5: from 96 hours to 120 hours post-treatment
- Follow-up visits:
    - 28 days post-natal age (PNA);
    - 36-weeks PMA;
    - Discharge home or 40 weeks PMA, whichever comes first;
    - 24 months (±3 months) corrected age visit

The study plan and scheduled tests are summarized in the following flow-chart:

**Figure 1: Study Flowchart**

| ASSESSMENT | On admission prior to study treatment from 30 minutes up to 24 hours of life | Before starting procedure[1] | T0 [2] | 5' | 15' | 30' | 1-h | 6-h | 12-h | 24-h | 48-h | 72-h | 120-h | DAY 28 PNA | 36 wk PMA | Disch. Home/40 wk[3]PMA | 24-m Clin. Ass. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Randomization/ Access IRT | | X | | | | | | | | | | | | | | | |
| Study Treatment (Surfactant administration) | | | X | | | | | | | | | | | | | | |
| Informed Consent (Parental/ Maternal) [4] | X | | | | | | | | | | | | | | | | |
| Inclusion/ Exclusion Criteria | X | | | | | | | | | | | | | | | | |
| Pregnancy complications and prenatal corticosteroids use | X | | | | | | | | | | | | | | | | |
| Demographic data (including weight, OFC, length) | X | | | | | | | | | | | | | | X[5] | X | X |
| Apgar Score | X | | | | | | | | | | | | | | | | |
| Medical History (conditions diagnosed before treatment) | X | X | | | | | | | | | | | | | | | |
| Vital signs (HR, RR, BP) | X | X | X [6] | X [6] | X | X | X | X | X | X | X | X | X | X [6] | X [6] | X [6] | X |
| Preductal Oxygen Saturation ($SpO_2$) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Fraction of Inspired Oxygen (FiO2) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Evaluation of respiratory support and oxygen alone use | X | ← | — | — | — | — | — | — | — | — | — | — | — | — | — | → | |
| NIV parameters | | X | | | | X | X | X | X | X | X | X | | | | | |
| Pain Score Assessment | | X | X | | | | | | | | | | | | | | |
| Concomitant Medications | X | ← | — | — | — | — | — | — | — | — | — | — | — | — | — | → | |
| Blood gas analysis | X | X | | | | | X | X | | X | X | X | | | | | |
| Record information for BPD assessment | | | | | | | | | | | | | | | X | | |
| Adverse Events [7] | | | ← | — | — | — | — | — | — | — | — | — | — | — | — | → | |
| Flow rate evaluation | | | | | | | | | | | | | | | X | X | |
| Bayley Scales | | | | | | | | | | | | | | | | | X |
| Health status questionnaire | | | | | | | | | | | | | | | | X | X |

(1) Parameters and Pain score assessment to be collected within 15 minutes before starting procedure (laryngoscope insertion)
(2) End of surfactant administration
(3) Health status visit will be performed at discharge home or 40 weeks PMA, whichever comes first
(4) Signature of Parental/ Maternal Informed Consent can be obtained prior to birth or after birth
(5) Only weight to be assessed
(6) Only heart rate and respiratory rate
(7) AEs to be assessed and recorded starting from the beginning of the procedure

# 3 Study Objectives

## 3.1 Primary Objective

The primary objective of this study is to evaluate the safety profile of the administration of the porcine surfactant (poractant alfa, Curosurf®) through LISA using a thin catheter (CHF6440), compared to an approved conventional surfactant administration during invasive ventilation and rapid extubation, in spontaneously breathing preterm neonates with clinical signs of respiratory distress syndrome (RDS).

## 3.2 Secondary Objectives

The secondary objectives of this study are to assess short-term and mid-term efficacy profiles of the administration of the porcine surfactant (poractant alfa, Curosurf®) through LISA using CHF6440.

# 4 Study Variables

## 4.1 Efficacy Variables

The following variables will be used to describe the efficacy of the two procedures:

- Percentage of neonates needing invasive mechanical ventilation (MV) in the first 72 hours of life, 28 days PNA and within 36 weeks PMA defined as follows:

**Endotracheal Tube (ETT) Group**:

- Neonates not extubated within 1 hour from initial surfactant administration and receiving MV for more than 1 hour;
- Neonates extubated and re-intubated to receive MV of any duration

**LISA Group**:

- Neonates intubated to receive MV of any duration,
    - Duration of invasive ventilation (hours) in the first 72 hours of life, 28 days PNA and within 36 weeks PMA;
    - Percentage of neonates needing any intubation procedure, outside the initial surfactant administration period, in the first 72 hours of life, in the first 28 days PNA and within 36 weeks PMA;
    - $SpO_2$ at time 0 (study treatment administration), 5, 15, 30 minutes, at 1, 6, 12, 24, 48, 72 and 120 hours post treatment; additionally, at 28 days PNA and at 36 weeks PMA for neonates still receiving any form of respiratory support;
    - $FiO_2$ at time 0 (study treatment administration), 5, 15, 30 minutes, at 1, 6, 12, 24, 48, 72 and 120 hours post treatment; additionally, at 28 days PNA and at 36 weeks PMA for neonates still receiving any form of respiratory support;
    - $SpO_2/FiO_2$ at time 0 (study treatment administration), 5, 15, 30 minutes, at 1, 6, 12,24, 48, 72 and 120 hours post treatment; additionally, at 28 days PNA and at 36 weeks PMA for neonates still receiving any form of respiratory support;

- Percentage of neonates needing additional surfactant doses and number of surfactant doses;
- Duration of oxygen alone supplementation (days) and any non-invasive ventilation during the study (days);
- Blood gas analysis, specifically acid-base balance parameters (i.e. pH, partial pressure of carbon dioxide ($pCO_2$), partial pressure of oxygen ($pO_2$), $HCO_3$, BE, lactate) pre-surfactant administration (when applicable), at 1 hour, 6 hours, 24, 48 and 72 hours after study treatment

## 4.2 Safety Variables

Following safety variables are defined for this study in order to describe safety of the two procedures:

**During procedure for surfactant administration**:

- Number and percentage of neonates with adverse events (AEs) starting during overall procedure for surfactant administration;
- Number and percentage of neonates with AEs starting during overall procedure for surfactant administration judged related to the procedure;
- Number of AEs occurring during overall procedure for surfactant administration requiring either oxygen alone or an increase in FiO2 without the need for escalation of invasive or non-invasive ventilator support;
- Number of AEs starting during overall procedure for surfactant administration requiring administration of manual (bag and mask) pressure positive ventilation and related duration of ventilation (non- invasive ventilation);
- Number of AEs starting during overall procedures for surfactant administration requiring endotracheal intubation and related duration of intubation (invasive ventilation);
- Number of AEs starting during overall procedures for surfactant administration requiring circulatory support including administration of crystalloids;
- Number of AEs starting during overall procedures for surfactant administration requiring cardiopulmonary resuscitation including administration of cardiac massage or adrenaline

**After first administration**:

- Number and percentage of neonates with failed 1$^{st}$ attempt to insert the CHF6440/ETT;
- Number of maneuvers discontinued due to neonate's severe destabilization;
- Heart rate (HR) and respiratory rate (RR) (0, 5, 15 and 30 min, 1 hour, 6 and 12 hours after administration);
- Systolic, diastolic, and mean blood pressure (SBP/DBP/ MBP) (15 and 30 min, 1 hour, 6 and 12 hours after administration);
- Premature Infant Pain Profile (PIPP) score (end of surfactant administration)

**After first and second administration**:

- Number of device misallocation for LISA Group (esophageal intubation);
- Number of attempts to the first successful insertion;
- Duration of surfactant administration (min);
- Duration of the whole procedure (starting from the insertion of laryngoscope up to the removal of the catheter or ETT);

**During the study**:

- AEs, including incidence of major neonatal complications of prematurity (listed in APPENDIX I) and adverse drug reactions (ADRs);
- Blood pressure (SBP, DBP, MBP) at 24, 48, 72, 120 hours post-administration;
- HR and RR, at 24, 48, 72, 120 hours post-administration and 28 days PNA, 36 weeks PMA, discharge home or 40 weeks PMA whichever comes first;
- Incidence of BPD at 36 weeks PMA;
- Death/BPD incidence at 36 weeks PMA, defined as the incidence of the neonates who are dead or alive but with a diagnosis of BPD at the time of assessment (i.e. 36 weeks PMA);
- Mortality at Day 28 PNA and 36 weeks PMA;
- Oxygen use (alone and/or during invasive and non-invasive ventilation) at Day 28 PNA and 36 weeks PMA;
- Weight, occipital-frontal circumference (OFC) and length at discharge home or 40 weeks PMA;
- Feeding and hearing status at discharge home or 40 weeks PMA, whichever comes first;
- Incidence of major neonatal morbidities at discharge home or 40 weeks PMA, whichever comes first;
- Neonates needing invasive ventilation or non-invasive respiratory support at discharge home or 40 weeks PMA;
- Neonates needing respiratory medications at discharge home or 40 weeks PMA

**24 months (±3 months) corrected age**:

- Health status questionnaire, including:
    - Bayley Scales of Infant Development (cognitive and language scores);
    - Feeding method: spoon, nasogastric tube or gastrostomy;
    - Cerebral palsy evaluation;
    - Seizure evaluation;
    - Vision, hearing and communication evaluation;

- Clinical assessment of respiratory conditions and morbidity;
- Vital signs (SBP/DBP/MBP, HR, RR);
- Growth assessment (Weight, OFC and length)

This stand-alone assessment will be analyzed and reported separately from the main phase.

### 4.3 Other Variables

No other variables defined.

# 5 Sample Size

No primary efficacy endpoint was defined in this study since the main objective is to describe the overall safety and efficacy profile of administering poractant alfa with two different procedures: LISA technique or conventional administration with endotracheal tubes and brief invasive ventilation. A total of 150 neonates will be randomized in the study with a ratio 2:1 to LISA arm (i.e. 100) and conventional administration arm (i.e. 50).

# 6 Analysis Sets

The definitions of the analysis sets are summarized below. A final agreement on the subjects to be included in or excluded from each analysis set will be reached before the database lock (DBL) during Data Review Meeting (DRM). Inclusions and exclusions from analysis sets will be fully documented in the Data Review Report (DRR).

## 6.1 Safety Set

All randomized subjects who will take at least one dose of study medication.

The Safety population 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).

The AEs will be analyzed based on whether the AE started during the first dose or second dose. An AE will be marked to have started during LISA or ETT by using a flag as follows:

- First administration

AE by Dose flag = LISA; if (‘Did the AE start during 1st procedure or 2nd procedure?’ = ‘Yes’ and ‘If Yes, Clarify which one’ = ‘First’) and [(‘Was procedure for surfactant administration performed according to the randomization group? = Yes’ and ‘Patient group = LISA’) or (“Was procedure for surfactant administration performed according to the randomization group”=No and method used was ‘LISA’)];

AE by Dose flag = ETT, if (‘Did the AE start during 1st procedure or 2nd procedure?’ = ‘Yes’ and ‘If Yes, Clarify which one’ = ‘First) and [(‘Was procedure for surfactant administration performed according to the randomization group?= ‘Yes’ and ‘Patient group = ETT’) or (“Was procedure for surfactant administration performed according to the randomization group”=No and method used was ‘ET tube: Intubation, surfactant administration and rapid extubation (within 1 hour) / ET tube: subject receiving MV > 1 hour)];

- Second administration

AE by Dose flag = LISA; if ('Did the AE start during 1st procedure or 2nd procedure?' = 'Yes' and 'If Yes, Clarify which one' = 'Second') and ('If yes, please specify the method of administration'? ='LISA');

AE by Dose flag = ETT; if ('Did the AE start during 1st procedure or 2nd procedure?' = 'Yes' and 'If Yes, Clarify which one' = 'Second) and ('If yes, please specify the method of administration?"= 'ET Tube: Intubation, surfactant administration and rapid extubation (within 1 hour)' or 'ET Tube: subject receiving MV > 1 hour);

For all other safety assessments, analysis will be performed on Safety population based on the technique used for first treatment dose only, as treated analysis.

### 6.2 Intention-to-Treat (ITT) Set

All randomized subjects who will receive at least one dose of study medication.

The efficacy analyses will be performed in the ITT population (i.e. an as-randomized analysis will be performed).

### 6.3 Other Sets Defined for Tables and Listings

For the purposes of tables and listings the following sets are defined:

- Enrolled Set: all subjects who have a signed informed consent to participate in the study;
- Randomized Set: all patients randomized to study medication.

# 7 General Considerations for Statistical Analysis

## 7.1 Statistical Significance

All tests of hypotheses will be two-sided and conducted at the 0.05 significance level, and all confidence intervals will be two-sided at the 95% confidence level.

### 7.2 Multiplicity

No multiplicity adjustment will be performed.

### 7.3 Handling of Missing Data

The number of subjects with missing data will be presented under a "Missing" category. Unless otherwise stated, missing values will not be included in the denominator count when calculating percentages.

When quantitative variables are being summarized, only the non-missing values will be evaluated for calculating summary statistics.

### 7.3.1 Missing/Incomplete Dates:

**Medications**:

In case of missing or incomplete dates not directly allowing allocation to any category of medications, a worst-case allocation will be done according to the available parts of the start and the stop dates. The medications will be allocated to the first category allowed by the available data, according to the following order:

- Concomitant medication;
- Maintained medication;
- Prior medication.

**Procedures**:

In case of missing or incomplete dates not directly allowing allocation to any category of procedure, a worst-case allocation will be done according to the available parts of the start and the stop dates. The procedure will be allocated to the first category allowed by the available data, according to the following order:

- Concomitant procedure;
- Maintained procedure;
- Prior procedure.

**Adverse events:**

In case of missing or incomplete date/time not directly allowing allocation to any of the category of AEs, a worst-case allocation will be done according to the available parts of the start and the stop dates/times. The AE will be allocated to the first category allowed by the available data, according to the following order:

- Treatment emergent;
- Pre-treatment.

**Missing severity of adverse events**:

In case of missing severity, the severity will not be imputed and will be reported as “Missing”.

Other critical missing data, if any, will be discussed during the review of the data. Decisions will be fully documented in the DRR.

## 7.4 Covariates

All repeated measures models will include the pre-procedure value of the variable as covariate and treatment, time point, treatment by time point interaction, and gestational age group as fixed effects.

## 7.5 Interim Analyses

No interim analysis will be performed.

## 7.6 Examinations of Subgroups

A subgroup analysis of surfactant related and procedure related AEs and TEAEs will be performed based on the use of neonate sedation and/or analgesia (Yes/No).

Only subjects with sedation and/or analgesia (selected as per Appendix II) taken within ±150 min from treatment (any dose intake) will be considered.

## 7.7 Descriptive Statistics

Descriptive statistics for quantitative variables will include n (the number of observed values), mean, standard deviation (SD), 95% confidence interval (CI), median, minimum and maximum values.

Categorical variables will be summarized by using frequency count and percent distributions. The number of missing values will be displayed as a "Missing" category, where appropriate. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the analysis set and procedure group.

## 7.8 Definitions

### 7.8.1 Baseline and Change from Baseline

Baseline will be pre-procedure assessment. If pre-procedure value is not available, baseline will be defined as the last non-missing value available before procedure.

Change from baseline will be derived as follows:

Assessment value at the time point - Assessment value at baseline

### 7.8.2 Date of First Randomized Treatment

The date of first randomized treatment is the earliest date of randomized treatment considering the eCRF data, corresponding to the date part of the variable RFSTDTC in the SDTM dataset DM.

### 7.8.3 Study Day

The study day relative to the first randomized treatment procedure will be calculated as:

- Date of event – date of first randomized treatment + 1 (if date of event ≥ date of first randomized treatment);

or

- Date of event – date of first randomized treatment intake (if date of event < date of first randomized treatment).

### 7.8.4 Duration

Duration in days of any event/procedure will be calculated as:

- End date of event/procedure – start date of the event/procedure +1

Duration in minutes of a procedure will be calculated as:

- End time of the procedure – start time of the procedure

Duration in hours of any event/procedure will be calculated as:

- (end time of the event/procedure – start time of the event/procedure)/60

## 7.9 Diary Data

Diary data is not collected in this study.

## 7.10 Data Re-allocation

Not applicable.

## 7.11 Exclusion of Data from the Statistical Analyses

All data collected in the database except for the data collected for 24 months evaluation, will be used for all statistical analyses for this SAP.

## 7.12 Listings

All data collected in the eCRF except for the data collected for 24 months evaluation, will be presented in the listings. All the listings will be presented in Randomized Set.

## 7.13 Coding

Medical and surgical history, concomitant diseases, procedures and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 (March 2021 version).

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version WHODrug Global B3 -format March 1, 2021.

# 8 Study Population

## 8.1 Disposition of Subjects and Discontinuations

### 8.1.1 Disposition of Subjects

The number of subjects screened, the number of screen failures and the number of subjects with each reason for screen failure will be presented (overall). All enrolled subjects will be included.

The number of subjects screened, randomized and completed the study will be also presented by country and by site.

### 8.1.2 Discontinuation from the Study

The number and percentage of subjects who completed the study, withdrew from the study, and the reason for withdrawal from the study will be presented by treatment group and overall

for Randomized Set.

An individual subject listing will be provided for the disposition data.

### 8.1.3 Protocol Deviations and Analysis Sets

Important protocol deviations will be classified according but not limited to the following categories:

- Inclusion/Exclusion Criteria
- Informed Consent
- Safety Reporting
- Study Intervention
- Trial Procedures

These categories may be amended or other categories may be added, but any changes will be made prior to DBL and will be discussed during the DRM and documented in the DRR.

Important deviations will be summarized by procedure group and overall on ITT Set.

All significant deviations, including GCP deviations, will be listed.

The number of subjects included in the ITT Set and Safety Set will be summarized for each treatment group and overall using the Enrolled Set.

## 8.2 Demographic and Baseline Characteristics

No formal comparison between treatment groups on demographic and baseline characteristics will be performed.

All demographic and baseline characteristics will use ITT set for reporting.

### 8.2.1 Demographic Characteristics

Demographic characteristics will be summarized by treatment group and overall. These will include age (hours), gestational age (weeks), sex, race, ethnicity, birth weight, and Appearance, Pulse, Grimace, Activity, Respiration (APGAR) total scores at 1 min and 5 min post-birth.

Subject's age (hours) will be calculated as:

- Age (hours) = (Time of randomization – time of birth)/60

Gestational age in weeks will be calculated as:

- Gestations age (weeks) = gestational age (weeks) +gestational age (days)/7

### 8.2.2 Pregnancy History and Maternal Medical History

Mother's age, race and ethnicity will be summarized by treatment group and overall. Number and percentage of mothers who took any antibiotics during the pregnancy, number and percentage of mothers who took any corticosteroids during the pregnancy and total number of doses will be included in the summary table. In addition, number of days since last intake of

corticosteroid before delivery will be calculated and categorically summarized for categories 0-1, 2-7, >7 as follow:

- Number of days since last intake of corticosteroid before delivery = Date/time of neonate's birth – date/time of last dose of corticosteroid before delivery.

Details of maternal COVID-19 infection will be presented in a listing.

Additionally, following pregnancy and medical history will be summarized.

**Table 2: Pregnancy History and Maternal Medical History**

| Pregnancy/medical history of the mother | Categories/subcategories |
|---|---|
| Type of delivery | Spontaneous, C-section with labor, C-section without labor, Emergency C-section |
| If Spontaneous | Operative, Not operative |
| Pregnancy complication, relevant risk factors | Yes/No |
| Complications/relevant risk factors | Gestational diabetes, Chronic Diabetes mellitus, Pregnancy-induced hypertension, Pre-eclampsia, Eclampsia, HELLP syndrome, Chronic hypertension, Chronic epilepsy, Depression, Asthma, Thyroid disease, Anemia, Isoimmunization, Previous fetal or neonatal death, Bleeding in second or third trimester, Maternal infection (subcategories: Toxoplasma, Rubella, Cytomegalovirus, Herpes virus, Hepatitis B/C, HIV, Syphilis, Gonorrhea), Other maternal infections, Polyhydramnios, Oligohydramnios, Premature rupture of membranes >21 days, Multiple gestation, Size-dates discrepancy or Intrauterine Growth Restriction, Drug Therapy (Lithium carbonate, Magnesium, Adrenergic blocking drugs, Selective serotonin reuptake inhibitor antidepressants), Maternal substance abuse, Fetal malformation, Decreased fetal movements, Absent/insufficient prenatal care, Age <16 or >35 years, Overweight/increased BMI, Obesity, Uterine fibroids, Other |
| Any treatment given or in progress for Pregnancy complication(s) | Yes/No |
| Were there any intrapartum complications? | Yes/No |

| | |
|---|---|
| Intrapartum complications | Emergency cesarean section, Forceps or vacuum-assisted delivery, Breech or other abnormal presentation, Premature labor, Precipitous labor, Chorioamnionitis, Prolonged rupture of membranes (>18 hours before delivery), Prolonged labor (>24 hours), Prolonged second stage of labor (>3 hours), Fetal bradycardia, Non-reassuring fetal heart rate patterns, Use of general anesthesia, Uterine tetany, Narcotics given to mother, Meconium-stained amniotic, Prolapsed cord, Abruptio placentae, Placenta previa, Other |
| Treatment given or in progress for intrapartum complication | Yes/No |
| Maternal medical history | Medical diagnosis summarized using MedDRA system organ class (SOC) and preferred term (PT) |
| Medical condition ongoing? | Yes/No |
| Is the subject's mother taking any medications for ongoing diagnosis | Yes/No |
| Medication | Please refer to section 8.4 below. |

**Notes:**

- Number and percentage of women with at least one pregnancy history/maternal medical history will be presented. For the categorical summary, the categories will only be presented if at least one mother reports a particular category i.e. a category with zero count will not be presented.
- A mother can report one or more categories of complication/risk factor/medication and will be counted in all the categories that she reports i.e. the N count may not be equal to sum of n counts.

## 8.3 Neonate Medical History

Neonates' medical history will be summarized for the following variables:

- Whether any complication of prematurity have been identified before treatment administration (Yes/No)
- Whether the baby experienced any other condition before treatment administration (Yes/No)
- Any major organ malformation, genetic disease or chromosomal abnormalities diagnosed (including conditions diagnosed after treatment; Yes/No)

Additionally, neonate medical history will be summarized by MedDRA SOC and PT and treatment group.

## 8.4 Medications

Prior medications and concomitant medications will be summarized by treatment group, using Safety Set through frequency distributions and percentages by Anatomical Main Group [1st level of the Anatomical Therapeutic Chemical (ATC) classification], Therapeutic Subgroup (2nd level of the ATC classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name. Prior medications will also be summarized on Overall.

The medications will be classified according to the following rules:

- Prior medication: start date/time< date/time of first randomized treatment administration and stop date/time ≤ date/time of first study medication administration;
- Medication maintained during the randomized treatment period: start date/time < date/time of first randomized treatment administration and stop date/time > date/time of first randomized treatment administration or ongoing;
- Concomitant medication: date/time of first study medication administration ≤ start date/time < maximum (date of home discharge / date of BPD diagnosis assessment / date of 40 weeks PMA).

Separate summaries will be presented for maternal prior medications during pregnancy or delivery, neonate prior medications, neonate maintained and neonate concomitant medications.

Further, for maternal prior medications, medications used during pregnancy and medications used during delivery will be reported separately.

## 8.5 Procedures

Previous procedures and concomitant procedures will be summarized by treatment group for the Safety Set through frequency distributions and percentages by SOC and PT.

Prior procedures will also be summarized on Overall.

The procedures will be classified according to the following rules:

- Previous procedures: start date/time < date/time of first randomized treatment administration ≤ date/time of first randomized treatment administration;
- Procedure maintained during the randomized treatment period: start date/time < date/time of first randomized treatment administration and stop date/time > date/time of first randomized treatment administration or ongoing;
- Concomitant procedures: date/time of first randomized treatment administration ≤ start date/time < maximum (date of discharge/date of BPD diagnosis assessment/date of 40 weeks PMA);

## 8.6 Compliance

**Treatment Compliance**

Actual volume of poractant alfa administered will be entered on the eCRF. Compliance to treatment will be evaluated based on the actual volume administered in relation to neonate's weight using the following formula:

- Volume administered/Volume scheduled*100 = % of administered volume

where the volume scheduled will be calculated on the basis of neonates' weight as 2.5ml x birth weight (kg) for the first dose and as 1.25 ml x birth weight (kg) for the following doses.

Treatment compliance will be summarized on the ITT Set by treatment group. An additional summary displaying the number and percentage of patients in the following categories will also be presented by treatment group:

- <80%
- [80%-120%]
- >120%

# 9 Efficacy Analyses

All efficacy analyses (see Table 3) will be performed on ITT Set. Following table describes analyses of efficacy variables. Subjects will be flagged in the listings for COVID-19 infection of mothers as well as neonates as follow:

- COVID-19 infection during pregnancy will be identified in the maternal infection form (specification for "Others").
- COVID-19 infection for neonates will be identified in AE form (AEDECOD containing 'COVID-19' or 'COVID').

**Percentage of neonates needing invasive mechanical ventilation (IMV):**

For ETT group, the neonates needing IMV will include those cases:

If the procedure for surfactant administration was performed according to the randomization group:

> If the first administration='ETT' and if the duration of the procedure was less than 1 hour (Date/Time of removal of ETT – Date/Time of the Laryngoscope <1 Hour) and if any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) for any duration.
>
> AND
>
> If the first administration='ETT' and if the duration of the procedure was more than 1 hour (Date/Time of removal of ETT – Date/Time of the Laryngoscope ≥1 Hour) and if any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) and if end date/time of the invasive ventilation – start date/time of the invasive ventilation>1 hour.

If the procedure for surfactant administration was not performed according to the randomization group:

> If the first administration='ENDOTRACHEAL TUBE: Intubation, surfactant administration and rapid extubation (within 1 hour)' and if any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) for any duration.
>
> AND

If the first administration='ENDOTRACHEAL TUBE: subject receiving MV > 1 hour' and if any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) and if end date/time of the invasive ventilation – start date/time of the invasive ventilation>1 hour.

For LISA group: if any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) for any duration.

**Percentage of neonates needing any intubation procedure, outside the initial surfactant administration period during the first 72 Hours of live, in the first 28 days PNA or within 36 weeks PMA**

For both groups (ETT and LISA): if any procedure containing 'Endotracheal intubation' or 'Intubation' is filled in the procedure form and if the start date of the procedure is after the end date of surfactant administration for the first administration the subject will be flagged.

Then if the start date of the procedure is ≤ the 72 hours of live, the neonates will be considered as needing intubation.

Then if the start date of the procedure is ≤ 28 days PNA visit date, the neonates will be considered as needing intubation.

Then if the start date of the procedure is ≤ 36 weeks PMA visit date, the neonates will be considered as needing intubation.

**$SpO_2$ or $FiO_2$ for neonates still receiving respiratory support at 28±2 days PNA or at 36 weeks PMA**

Flags will be created to identify subjects still receiving respiratory support if the start date of respiratory support is <28 days PNA (respectively 36Weeks PMA) using:

- Flag for 28 days PNA = Y if 'Any Respiratory support provided to the patient?' from respiratory support form = yes and end date of ventilatory support is ≥ 28 days PNA visit date.
- Flag for 36 weeks PMA = Y if 'Any Respiratory support provided to the patient?' from respiratory support form = yes and end date of ventilatory support is ≥ 36 weeks PMA visit date.

SpO2 or FiO2 values collected at the 28 Days PNA visit (respectively 36 weeks PMA visit) will be used for the summary statistics.

**Duration of ventilation/oxygen supplementation (alone):**

**Median duration time of IMV in the first 72 hours of life (hours)**

If any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) and if IMV end date is ≤ 72 hours of life for the neonates the duration (hours) will be calculated as:

IMV end date/time – IMV start date/time

if IMV end date is ≥72 hours of life for the neonates or still ongoing the duration (hours) will be calculated as:

72 hours – (start date/time of IMV- birth date/time)

**Median duration time of IMV in the first 28 days PNA**

If any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) and if end date is ≤ 28 days PNA visit date the duration (in days) will be calculated as:

(IMV end date – IMV start date)+1

if IMV end date is >28 days or still ongoing PNA date the duration (days) will be calculated as:

28 days – (start date of IMV- birth date)

**Median duration time of IMV within the 36 weeks PMA**

If any of the invasive ventilation method is ticked (HFOV, SIMV, PTV, SIPPV, IMV, A/C, PSV or other) on the Respiratory Support Form) and if end date is ≤ 36 weeks PMA visit date the duration (in days) will be calculated as:

(IMV end date – IMV start date)+1

if IMV end date is >36 weeks PMA date the duration (days) will be calculated as:

[(date of 36 weeks PMA – date of birth) – (start date of IMV- birth date) +1]

All the duration will be calculated individually and then summarized and compared between procedure groups.

In case of multiple IMV for a same neonate the IMV duration considered for the analyses will be the sum of all IMV durations.

If a subject discontinue the study for any reason before the analysis timepoint (i.e 36Weeks PMA visit date) the discontinuation date will be use instead of the visit date.

**Stand- alone oxygen supplementation (days)**

If any of the oxygen supplementation without positive pressure method is ticked (Low flow nasal cannula, oxygen in incubator or other) on the Respiratory Support Form) the duration (in days) will be calculated as:

(Oxygen supplementation end date – oxygen supplementation start date)+1

In case of multiple oxygen supplementation for a same neonate the duration considered for the analyses will be the sum of all oxygen supplementation durations.

**Non-invasive ventilation (days)**

If any of the non-invasive ventilation method is ticked (CPAP, BiPAP, NIPPV, HFNC, nSIPPV, nSIMV, nIMV, nHFV, nPSV or other) on the Respiratory Support Form) the duration (in days) will be calculated as:

(Non-invasive ventilation end date – non-invasive ventilation start date) +1

In case of multiple non-invasive ventilation for a same neonate the duration considered for the analyses will be the sum of all non-invasive ventilation durations.

**Table 3: Analyses of Efficacy Variables**

| Efficacy Variable | Endpoint | Analysis Method |
|---|---|---|
| **Need for mechanical ventilation/intubation** | Percentage of neonates needing invasive mechanical ventilation (IMV) in the first 72 hours of life | Cochran-Mantel-Haenszel (CMH) test adjusted for gestational age group will be used to compare the percentage of neonates between treatment groups. The CMH adjusted difference with its 95% CI will be presented.<br>Additional analysis will be performed to explore the impact of use of sedation and/or analgesia. The CMH test will be repeated stratified for the use of sedation/analgesia (Yes/No), adjusted difference and corresponding 95% CI will be presented. |
| | Percentage of neonates needing IMV in the first 28 days PNA | |
| | Percentage of neonates needing IMV within 36 weeks PMA | |
| | Percentage of neonates needing any intubation procedure, outside the initial surfactant administration period in the first 72 hours of life | The similar comparisons will be made as need of IMV. |
| | Percentage of neonates needing any intubation procedure, outside the initial surfactant administration period in the first 28 days PNA | |

| | | |
|---|---|---|
| | Percentage of neonates needing any intubation procedure, outside the initial surfactant administration period within 36 weeks PMA | |
| **$SpO_2$** | $SpO_2$ | • A linear mixed model for repeated measures (MMRM) including treatment, time point, treatment by time point interaction, and gestational age group as fixed effects and pre-procedure $SpO_2$ as covariate will be used to analyze $SpO_2$ values. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at each time point and averaged over the first 120 hours post-treatment will be estimated by the model.<br>• Time profile plot of mean $SpO_2$ in the first 120 hours post-administration will be presented by treatment group.<br>• A forest plot will also be presented. |
| | $SpO_2$ for neonates still receiving respiratory support at 28±2 days PNA | $SpO_2$ values will be summarized descriptively by treatment group. |
| | $SpO_2$ for neonates still receiving respiratory support at 36 weeks PMA | $SpO_2$ values will be summarized descriptively by treatment group. |

| | | |
|---|---|---|
| **$FiO_2$** | $FiO_2$ | • A linear mixed model for repeated measures (MMRM) including treatment, time point, treatment by time point interaction, and gestational age group as fixed effects and pre-procedure $FiO_2$ as covariate will be used to analyze $FiO_2$ values. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at each time point and averaged over the first 120 hours post-treatment will be estimated by the model.<br>• Time profile plot of mean $FiO_2$ in the first 120 hours post-administration will be presented by treatment group.<br>• A forest plot will also be presented. |
| | $FiO_2$ for neonates still receiving respiratory support at 28±2 days PNA | $FiO_2$ values will be summarized descriptively by treatment group. |
| | $FiO_2$ for neonates still receiving respiratory support at 36 weeks PMA | $FiO_2$ values will be summarized descriptively by treatment group. |
| **$SpO_2/FiO_2$ ratio** | $SpO_2/FiO_2$ ratio | • $SpO_2/FiO_2$ ratio will be analyzed using a linear MMRM including treatment, time point, treatment by time point interaction, and gestational age group as fixed effects and pre-procedure $SpO_2/FiO_2$ ratio as covariate. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at each time point and averaged over the first 120 hours post-treatment will be estimated by the model. |

| | | |
|---|---|---|
| | | • Time profile plot of mean $SpO_2/FiO_2$ ratio in the first 120 hours post-treatment will be presented by treatment group.<br>• $SpO_2/FiO_2$ ratio will be summarized between treatments at 28±2 Days PNA and at 36 weeks PMA by means of descriptive statistics.<br>• A forest plot will also be presented. |
| **Blood gas analysis** | pH, $pCO_2$, $pO_2$, $HCO_3$, BE, lactate | Descriptive statistics by treatment group for absolute values and change from pre-procedure values will be reported. |
| **Use of additional surfactant doses** | % of subjects requiring at least one additional surfactant dose | The percentage of subjects requiring at least one additional surfactant dose will be compared by treatment group by means of a Fisher's exact test. Odds ratio (OR) and related exact 95% CI will be also provided.<br>Subjects with pulmonary hemorrhage (from AE form, occurred during the first procedure) will not be included in this analysis. |
| | Number of additional surfactant doses | Descriptive statistics will be reported by treatment group. |
| **Duration of ventilation/oxygen supplementation (alone)** | Median duration time of IMV in the first 72 hours of life (hours) | Duration of IMV will be presented in hours for the first 72 hours of neonate's life. For the rest of the study, the duration will be presented in days.<br>Comparison between treatment groups will be performed using Mann-Whitney U-test. Estimates of median difference and corresponding 95% CI will be presented. |
| | Median duration time of IMV in the first 28 days PNA | |
| | Median duration time of IMV within the 36 weeks PMA | |
| | Stand- alone oxygen supplementation (days) | |
| | Non-invasive ventilation (days) | |

# 10 Safety Analyses

The safety variables will be analyzed on the Safety Set.

## 10.1 Extent of Exposure

The number of poractant alfa drug administrations (1, 2 or 3) will be presented using frequencies for the treatment groups. Actual volume administered (ml) will be summarized using summary statistics.

### 10.1.1 First Administration

Following analyses will be presented for parameters related to first administration of poractant alfa:

- Number of 1st failed attempt to insert the catheter/ETT will be summarized by treatment group. Percentage of neonates with 1st failed attempt will be compared between groups using the CMH adjusted for gestational age group. The CMH adjusted difference with its 95% CI will be presented.
- Number of maneuvers discontinued due to neonate's severe destabilization will be summarized by treatment group by means of descriptive statistics.

### 10.1.1 First and Second Administration

Following analyses will be presented for parameters related to first and second administration of poractant alfa, **based on actual treatment received for first administration.**

If the second amistration actually received is not compliant with the first administration, the data will not be analysed.

- Number of device misallocation (i.e., esophageal intubation) will be summarized, only for LISA group, by means of descriptive statistics.
- Number of attempts to the first successful insertion will be summarized by treatment group by means of descriptive statistics
- Duration of surfactant administration (min) and overall procedure (hours and min) for surfactant administration will be compared between treatment groups by using the Mann-Whitney U-test. Procedure start is defined as date/time of laryngoscope insertion and end date/time is defined as the date/time of removal of the catheter/ETT.

## 10.2 Adverse Events

An adverse event (AE) will be classified as pre-treatment AE if it starts before the first randomized study medication administration (AE onset date/time < date/time of first randomized treatment administration).

An AE will be classified as a TEAE if it starts on or after the date of first randomized treatment administration up to date of discharge (date/time of first randomized treatment administration ≤ AE onset date/time ≤ maximum (date of discharge/date of BPD diagnosis assessment/date of 40 weeks PMA)).

An Adverse Drug Reaction (ADR) is an AE judged as related to the study medication.

A serious ADR is a serious AE (SAE) judged as related to the study medication.

A severe AE is an AE with severe intensity. AEs will be graded using INC Neonatal Adverse Event Severity Scale (NAESS) v1.0. This is a 5-grade table hence the grades will be converted as below for reporting:

- AEs grade 1: Mild
- AEs grade 2: Moderate
- AEs grade 3, 4 and 5: Severe

Refer to section 7.3 for missing severity.

An AE leading to death is an AE with outcome equal to "Fatal".

Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only.

Following AEs will be summarized by treatment group and overall:

- Number and percentage of neonates with AEs starting during overall procedure for surfactant administration by dose ($1^{st}$ or $2^{nd}$; please refer to section 6.1);
- Number and percentage of neonates with AEs starting during overall procedure for surfactant administration judged related to the procedure by dose ($1^{st}$ or $2^{nd}$; please refer to section 6.1);
- Number of AEs occurring during overall procedure for surfactant administration requiring either oxygen alone or an increase in $FiO_2$ without the need for escalation of invasive or non-invasive ventilator support;
- Number of AEs starting during overall procedure for surfactant administration requiring administration of manual (bag and mask) pressure positive ventilation and related duration of ventilation (non-invasive ventilation);
- Number of AEs starting during overall procedure for surfactant administration requiring endotracheal intubation and related duration of intubation (invasive ventilation);
- Number of AEs starting during overall procedure for surfactant administration requiring circulatory support including administration of crystalloids;
- Number of AEs starting during overall procedure for surfactant administration requiring cardiopulmonary resuscitation including administration of cardiac massage or adrenaline

Incidence of related AEs (ADRs), serious AEs (SAEs) and AEs leading to death will be summarized by treatment group both in term of frequency of neonates with at least one AE and in term of frequency of AEs (number of events). All the aforementioned categories of AEs will be summarized by SOC and PT.

Incidence of AEs indicating neonatal complications of prematurity (see APPENDIX I for complete list) will be summarized using frequency and percentage of neonates experiencing an

AE for each complication along with the grades. A neonate can experience more than one complication of prematurity and will be counted in all the categories experienced.

If a complication is reported more than once (with the same AEDECOD) for the same neonate, the complication will be counted only one time and the maximum grade will be considered.

To identify the complications of prematurity from other AEs, AE terms from appendix I will be flagged from AE form.

Complication of prematurity flag = Y if events (AETERM) in ("*terms identified in appendix I"*).

Only for AE starting during the procedure, the related duration of invasive ventilation and positive pressure ventilation will be summarized as well.

The duration in minutes is calculated as

- End time of invasive ventilation/ positive pressure ventilation – start time of invasive ventilation / positive pressure ventilation

The duration in hours will be calculated as

- Duration in minutes / 60

The duration of invasive ventilation/PPV will be only calculated for AE starting during the procedure and for invasive ventilation/PPV used as 'Other action taken' = 'Manual positive pressure ventilation' or 'Other action taken' = 'Endotracheal intubation and invasive ventilation' as recorded on the eCRF page of 'Adverse event with timing' and the start and end time of the procedure will be used from the eCRF page of 'Respiratory support' where 'Indication' = 'Adverse event'.

A subgroup analysis of AEs during procedure for surfactant administration and TEAEs will be performed based on the use of sedation and/or analgesia (Yes/No). The above summaries will be repeated by use of sedation/analgesia if enough subjects.

Additionally, incidence of COVID-19 will be summarized separately. Related listing will also be presented.

The relative day of AE onset will be calculated as follows:

- for pre-treatment AEs:
    - AE onset date - date of first randomized treatment administration (if AE onset date is completely known);
    - Missing (if AE onset date is incomplete or unknown).
- For TEAEs:
    - AE onset date - date of first randomized treatment administration +1 (if AE onset date is completely known);
    - Missing (if AE onset date is incomplete or unknown).

The duration of an AE (days) will be calculated as follows:

- AE end date – AE onset date + 1 (when both dates are completely known);

- Date of completion/discontinuation – AE onset date + 1 (when the AE onset date is fully known but the AE is not resolved at the end of the trial): in this case the duration will be presented as ">x days" in the listing rather than "x days";
- Missing (when the AE onset date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date, or when the AE onset date is > date of completion/discontinuation and the AE is not resolved).

## 10.3 Vital Signs

Vital signs parameters (SBP, DBP, MBP, HR and RR) will be summarized as absolute and the change from pre-procedure by treatment group using descriptive statistics at each scheduled visit. Changes from pre-procedure will not be calculated at 28 Days PNA, 36 Weeks PMA and Week 40 (Discharge).

## 10.4 Pain Assessment

Pain will be assessed using PIPP score. PIPP consists of 7 parameters to assess pain: gestational age, behavioral state, maximum HR, minimum $O_2$ saturation, brow bulge, eye squeeze, nasolabial furrow and which are graded from 0 to 3. Total score will be calculated for each subject by summing up the individual scores. The interpretation can vary from a minimum score of 0 to a maximum score of 21. The higher the score the greater the pain.

PIPP total score on Day 1, calculated as sum of pre-procedure total PIPP score and total PIPP score recorded at T0; will be summarized using descriptive statistics by treatment group.

## 10.5 Mortality and BPD

- Number of deaths/BPD incidence at 36 weeks PMA will be compared by CMH test . Relative risk and related 95% CI will be presented. Frequency and percentages under each gestational group (25 to $26^{+6}$ weeks and 27 to $28^{+6}$ weeks) will also be displayed.
- The incidence of BPD at 36 weeks PMA will be compared by treatment as for the Death/BPD incidence. Severity of BPD will also be summarized, defined as:
    - Mild BPD (breathing room air), if ('Is there a requirement for supplemental oxygen?' = 'No') AND if ('Is the patient receiving respiratory support via nasal cannula?' = 'No' OR ('Is the patient receiving respiratory support via nasal cannula?' = 'Yes' and Flow rate is <=2 l/min in BPD form))
    - Moderate BPD (need for <30% oxygen), if oxygen level value ($FiO_2$) collected in BPD form <30%;
    - Severe BPD (need for ≥30% oxygen and/or positive pressure (PPV or NCPAP)) if:
        - $FiO_2$ ≥30% and/or
            - 'Is the subject receiving positive pressure for respiratory support' = 'Yes' or
            - 'Is the patient receiving respiratory support via nasal cannula?' = 'Yes' and Flow rate is > 2 l/min in BPD form.

In case of missing BPD assessment the neonate will not be included in the analysis.

- The mortality at 36 weeks PMA and at Day 28 will be compared by treatment as for Death/BPD incidence.
- Oxygen use at Day 28 and at Week 36 (alone and/or during any kind of MV) will be compared by treatment as for Death/BPD incidence. In case of missing BPD assessment the neonate will not be included in the analysis.

If a subject discontinue the study for any reason before the analysis timepoint (i.e 36Weeks PMA visit date) the discontinuation date will be use instead of the visit date.

### 10.6 Other Safety Variables

- Feeding and hearing status at discharge or 40 weeks PMA (whichever comes first) will be summarized by treatment group by frequency distributions.
- Frequency of neonates with major neonatal morbidities at discharge or 40 weeks PMA (whichever comes first) will be summarized by treatment group.
- For hearing status, percentage of subjects with at least one "failed-referred" or abnormal result and percentage of monolateral (if either right or left ear is indicated) or bilateral (if both right and left ear are indicated) status will be summarized.
- Weight (kg), OFC (cm) and length (cm) at discharge home or 40 weeks PMA will be summarized by treatment group by descriptive statistics.
- Neonates needing invasive or non-invasive respiratory support at discharge home or 40 weeks PMA will be summarized by treatment group by frequency distribution.

Neonates needing invasive respiratory support are defined as subject with 'Is the patient receiving mechanical ventilation via endotracheal tube' = 'Yes' in respiratory evaluation form.

Neonates needing non-invasive respiratory support are defined as subjects with 'Is the patient receiving non-invasive ventilation?' = 'Yes' or 'Is the patient receiving respiratory support via nasal cannula?'= 'Yes' or 'Is the patient receiving any supplementary oxygen? = 'Yes' in respiratory evaluation form.

- Neonates needing respiratory medications at discharge home or 40 weeks PMA will be summarized by treatment group by frequency distribution

# 11 Other Analyses

No other analyses planned.

# 12 Changes in the Planned Analyses from Study Protocol

The following Safety variables:

- Number of device misallocation for LISA Group (esophageal intubation);
- Number of attempts to the first successful insertion;
- Duration of surfactant administration (min);
- Duration of the whole procedure (starting from the insertion of laryngoscope up to the removal of the catheter or ETT);

will be analysed for first AND second administration.

Adjusted Differences and 95%CI using CMH test adjusted for gestational age groups has been deleted for Death/BPD and BPD analyses due to low number of subjects.

Percentage of neonates needing Invasive Mechanical Ventilation (IMV) by use of sedation/analgesia (Intention-To-Treat Set) will not include treatment comparison due to low number of subjects.

# 13 Output

## 13.1 Software

SAS version 9.4 will be used to perform all the statistical analyses.

## 13.2 Reporting Conventions

### 13.2.1 Treatment, Visit and Subgroup Descriptors

In the tables, listings and figures, the treatments and the visits will be identified as described below.

| Treatment group | Descriptor for treatment |
|---|---|
| Poractant alfa Administered through LISA | LISA Administration |
| Poractant alfa Administered through Conventional Intubation with ETT | Conventional Administration |

For listing purpose, the treatment descriptor will be shortened to “LISA” and “Conventional” according to actual treatment.

| Output | Descriptor for timepoints/visits |
|---|---|
| Tables | Pre-procedure, T0, 5 Min Post-procedure, …, 24 Hours Post-procedure, …, Day 28 PNA, 36 Weeks PMA, Discharge or 40 Weeks PMA |
| Listings | Same as above. |
| Figures | Same as ‘Tables’ above. |

### 13.2.2 Decimal places

Quantitative variables will be listed with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses rounding will not be performed):

- Duration time of IMV (hours for the first 72 hours and then in days), duration of ventilation (hours/days), duration of an AE (days), duration of endotracheal intubation/PPV (hours), duration of surfactant administration (min), neonate age (hours), maternal age (years), medication duration (days) and duration of whole procedure (min): integer numbers;
- Gestational age (weeks), compliance (%): 1 decimal
- Duration of whole procedure (Hours): 2 decimals
- SpO2/FiO2 ratio: 2 decimals
- Birth weigth (Kg): 2 decimals
- Change from baseline/pre-dose: same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- Min, max: same as actual data;
- Mean and its confidence limits (unadjusted and adjusted), adjusted difference between means and its confidence limits, SD, median, first and third quartiles: actual data + 1

decimal place (with the exception of health economic data: actual data + 2 decimal places);

- Percentage: 1 decimal place;
- Odds ratio and its confidence limits: 3 decimal places;
- p-values will be presented to 3 decimal places. If the p-value is less than 0.001, it will be presented as <0.001

### 13.2.3 Other reporting conventions

Treatments will be presented with the following order in the tables: poractant alfa through LISA, poractant alfa through ETT.

Unless otherwise stated, listings will be sorted by Subject ID.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes.

## 13.3 Format

The following information should always be presented:

- 'Clinical Study Code No.: <Study Code No.>' followed by Chiesi denomination in the top portion of each page. Chiesi denomination is 'Chiesi Farmaceutici S.p.A'.
- The table/listing/figure number followed by the title, the analysis set used and the output page number in the format of 'Page x of Y' in the top portion of each page of any table/listing/figure.
- The SAS program name followed by the date time of the output production and the analysis type (e.g. Dry Run; Draft Version; Final Version) in the bottom portion of each page of any table/listing/figure. The source listing/table/dataset will appear bottom left for every table/figure/listing.
- Tables and listings will be produced in rich text format (i.e., they will be tabular in format). Individual outputs must be provided in both portable format document (.pdf) and rich text format (.rtf).
- Combined PDF and RTF documents must also be provided, including a table of contents with hyperlinks. The combined documents should be divided by document type (tables, figures, listings).
- SAS outputs will be provided to the Sponsor in a similar manner (PDF and RTF; combined and with hyperlinked table of contents). The SAS outputs will be a separate deliverable to the Sponsor and are not intended for inclusion within the CSR.
- The combined documents page number in the format of 'Page n of N' will be presented bottom right corner.

The following should be followed for the tables:

- A landscape layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Horizontal lines will appear before and after the column heading of the output.
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The left and right margins will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The top and bottom margins will be a minimum 2.92 cm. Header and footer will be both 1.27 cm.

The following should be followed for the listings:

- A landscape layout and Letter size will be used.
- An 8-point font size will be used using Courier New font.
- Horizontal lines will appear before and after the column heading of the output.
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The left and right margins will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The top and bottom margins will be a minimum 2.92 cm. Header and footer will be both 1.27 cm.

The following should be followed for the figures:

- A portrait layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Figures will be produced in RTF and PDF formats (as described above), including relevant titles and footnotes as separate elements on the page (not within the body of the figure).
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The size of the figures will be: width=16.3 cm, height=12.2 cm. The resolution will be set using the option IMAGE_DPI=400. Figures will have a footer specifying the source table or listing. Figures should clearly identify each treatment arm and require care of colors/symbols.
- The left margin will be a minimum of 2.5 cm, the right margin will be a minimum of 2 cm. The top and bottom margins will be a minimum 0.8 cm.

### 13.4 Quality Control

The Quality Control steps are defined in the Datasets, Tables, Listings, Figures QC Plan.

# 14 SAS Code

## 14.1 Mixed model for repeated measures for $SpO_2$, $FiO_2$, and $SpO_2/FiO_2$ ratio:

```
PROC MIXED DATA = dataset;
    CLASS tmt timepoint gest_age subject;
    MODEL aval = tmt timepoint tmt*timepoint gest_age pre_proc_val/ DDFM=KR;
    REPEATED timepoint / SUBJECT=subject TYPE=UN;
    LSMEANS tmt tmt*timepoint / OM AT MEANS CL;
    LSMESTIMATE tmt*timepoint
        'LISA vs. ETT: Day 1 T0'      1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0,
        'LISA vs. ETT: Day 1 5M'      0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0,
        'LISA vs. ETT: Day 1 15M'     0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0 0,
        'LISA vs. ETT: Day 1 30M'     0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 0,
        'LISA vs. ETT: Day 1 1H'      0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 0 ,
        'LISA vs. ETT: Day 1 6H'      0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0,
        'LISA vs. ETT: Day 1 12H'     0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0,
        'LISA vs. ETT: Day 1 24H'     0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0 0,
        'LISA vs. ETT: Day 2'         0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 0,
        'LISA vs. ETT: Day 3'         0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0,
        'LISA vs. ETT: Day 5'         0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1/ CL;
    LSMESTIMATE tmt
        'LISA vs. ETT: Overall (120 first hours)'      1 -1 / CL;
RUN;
```

**Notes**:

- "Aval": value at each time point of the variable;
- "Tmt": treatment group (treatment order: 1 = LISA Administration, 2 = Conventional Administration);
- "Timepoint": scheduled time point during main phase of the study;
- "Gest_age: gestational age group of neonate
- "Pre_proc_val": pre-procedure value of the variable;
- "Subject": subject number;

- **Calculation of adjusted means (least squares means):**

  The approach described above will ensure that the least squares means calculated by SAS will be based on:
  - coefficients for classification effects (i.e., the effects of categorical covariates) proportional to the margins observed in the group of patients analyzed;
  - effects of quantitative covariates set equal to their mean values in the group of patients analyzed.

  The analysis is based on the following steps:
  1. generate a dataset by selecting:

  - For repeated post-randomization measurements (e.g., parameters at each visit, analyzed using a linear MMRM): all the post-randomization records for patients with at least one available and valid post-randomization measurement and no missing covariates;
2. in case of repeated post-randomization measurements, add to the dataset generated in step 1 the records for missing post-randomization visits of the patients included in the dataset. In the added records the value of the response variable will be missing, but the full information on covariates has to be included;
3. use the dataset obtained as the input dataset for the MIXED or the GENMOD procedure, specifying the following options in the LSMEANS statement:
   - in case of repeated post-randomization measurements: OM AT MEANS;

Example: analysis of value at all-time point based on a mixed model for repeated measures including the effects of treatment, time point (categorical variable), treatment by time point interaction, pre-procedure (V2) and another covariate. Visit 1 represents the screening visit.

Original dataset (X = available value, '.' = missing or invalid value):

| Patient | Treatment | Covariate | Baseline | Visit | Value |
|---|---|---|---|---|---|
| 1 | A | X | X | 1 | X |
| 1 | A | X | X | 2 | X |
| 1 | A | X | X | 3 | X |
| 1 | A | X | X | 4 | X |
| 1 | A | X | X | 5 | X |
| 2 | B | X | X | 1 | X |
| 2 | B | X | X | 2 | X |
| 2 | B | X | X | 3 | X |
| 3 | A | X | X | 1 | X |
| 3 | A | X | X | 2 | X |
| 3 | A | X | X | 3 | X |
| 3 | A | X | X | 4 | . |
| 3 | A | X | X | 5 | . |
| 4 | B | X | X | 1 | X |
| 4 | B | X | X | 2 | X |
| 5 | A | . | X | 1 | X |
| 5 | A | . | X | 2 | X |
| 5 | A | . | X | 3 | X |

Step 1 (visits 1 and 2 not selected since pre-randomization, patient 4 not selected due to missing post-randomization measurements, patient 5 not selected due to missing covariate):

| Patient | Treatment | Covariate | Baseline | Visit | Value |
|---|---|---|---|---|---|
| 1 | A | X | X | 3 | X |
| 1 | A | X | X | 4 | X |
| 1 | A | X | X | 5 | X |
| 2 | B | X | X | 3 | X |
| 3 | A | X | X | 3 | X |
| 3 | A | X | X | 4 | . |
| 3 | A | X | X | 5 | . |

Step 2 (added records in *italic*):

| Patient | Treatment | Covariate | Baseline | Visit | Value |
|---|---|---|---|---|---|
| 1 | A | X | X | 3 | X |
| 1 | A | X | X | 4 | X |
| 1 | A | X | X | 5 | X |
| 2 | B | X | X | 3 | X |
| *2* | *B* | *X* | *X* | *4* | . |
| *2* | *B* | *X* | *X* | *5* | . |
| 3 | A | X | X | 3 | X |
| 3 | A | X | X | 4 | . |
| 3 | A | X | X | 5 | X |

## 14.2 Comparison of two groups using Fisher's exact test

```
PROC FREQ DATA = dataset;
    TABLES Tmt * Variable / FISHER OR (CL=Exact);
    EXACT OR;
    ODS output OddsRatioCLs =OR1 fishersexact=pval;
    run;
```

**Notes**:

- "TMT": the treatment group, (treatment order: 1=LISA Administration, and 2=Conventional Administration);
- "Variable": the categorical variable value.

## 14.3 Comparison of Two Groups using Mann-Whitney U-Test

```
PROC NPAR1WAY DATA = dataset WILCOXON;
    CLASS Tmt;
    VAR Variable;
RUN;
```

**Notes**:

- "TMT": the treatment group, (treatment order: 1=LISA Administration, and 2=Conventional Administration)
- "Variable": the variable that need to be analyzed.
- The normal approximation results will be displayed.

## 14.4 Estimates of median difference and corresponding 95% CI

```
PROC QUANTREG DATA= dataset;
        CLASS Tmt;
  MODEL Variable = Tmt / quantile=0.5;
  ESTIMATE 'Difference in Medians' Tmt 1 -1 / CL;
  ODS output ParameterEstimates=Param Estimates=Est;
run;
```

**Notes**:

- "TMT": the treatment group, (treatment order: 1=LISA Administration, and 2=Conventional Administration)
- "Variable": the variable that need to be analyzed.

## 14.5 Tables that need 95% CIs within group for continuous variables:

```
DATA outdata;
SET outname;
    LCL=mean-(TINV(0.975,n-1)*(std/SQRT(n)));
    UCL=mean+(TINV(0.975,n-1)*(std/SQRT(n)));
RUN;
```

## 14.6 Comparison of Two Groups using Cochran-Mantel-Haenszel Test

```
PROC FREQ DATA=dataset;
        TABLES GEST_AGE*TMT* Variable /cmh;
RUN;
```

*Note for Death/BPD and BPD gestational age group will be omitted.*

**Notes**:

- "TMT": the treatment group, (treatment order: 1=LISA Administration, and 2=Conventional Administration)
- "Variable": the variable that need to be analyzed.
- "Gest_age": gestational age of neonate

For adjusted mean difference and corresponding 95% for stratified please refer to the macro used in "Adjusted proportion difference and confidence interval in stratified randomized trials" published in PharmaSUG 2013 – Paper SP04 [2].

Use WALD CI Options

# 15 References

1. Stevens B Johnston C et al. Premature Infant Pain Profile: Development and initial validation. Clinical Journal of Pain. 1996; 12: 13-22.
2. Yeonhee K et al. Adjusted proportion difference and confidence interval in stratified randomized trials. PharmaSUG 2013 - Paper SP04.

# 16 List of Tables, Listings and Figures

## 16.1 Tables

The SAS output for the analyses included in the flagged (***) tables below will be provided for internal use only and not for inclusion into the CSR.

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.1.1.1 | Screen Failures (Enrolled Set) | DST001 | - Only Overall column should be displayed | Source: Listing 16.2.1.1 |
| Table 14.1.1.2 | Disposition by Treatment (Randomized Set) | DST002 | - Treatment groups and Overall columns should be displayed. | Source: Listing 16.2.1.2 |
| Table 14.1.1.3 | Disposition by Country and Site (Enrolled Set) | DST004 | - Treatment groups and Overall columns should be displayed.<br>- Replace Country with Country or Site<br>- Present first Country (overall) then Site within each Country in the first column (Country sorted by Alphabetic order, Site sorted by ascending value).<br>- Number of subjects Enrolled, Randomized Completed and Discontinued should be displayed. | Source: Listing 16.2.1.2 |
| Table 14.1.1.4 | Important Protocol Deviations Leading to the Exclusion of the Whole Subject from Analysis (Intention-To-Treat Set) | DVT001 | - Overall column should be displayed.<br>- Only Important deviation to be display. | Source: Listing 16.2.2.1 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.1.1.5 | Important Protocol Deviations not Leading to the Exclusion of the Whole Subject from Analysis (Intention-To-Treat Set) | DVT001 | Same as Table 14.1.1.4 | Source: Listing 16.2.2.1 |
| Table 14.1.1.6 | Analysis Sets (Intention-To-Treat Set) | DST005 | - Overall column should be displayed.<br>- Safety Set and ITT set to be displayed. | Source: Listing 16.2.3.1 |
| Table 14.1.2 | Demographic Characteristics (Intention-To-Treat Set) | DMT001 | - Overall column should be displayed.<br>- Variables to be summarized: Gestational Age Categories ($25^{+0}$ weeks to $26^{+6}$ weeks / $27^{+0}$ weeks to $28^{+6}$ weeks), Gestational Age (Weeks), Gender, Race (categories as per CRF to be displayed), Ethnicity (categories as per the CRF to be displayed), Birth Weight (kg), APGAR Total Score at 1 minute post-birth and APGAR Total Score at 5 minutes post-birth.<br>- All categories should be displayed even if empty. | Source: Listing 16.2.4.1<br><br>Add footnote:<br>[1] APGAR: Appearance, Pulse, Grimace, Activity, Respiration) |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.1.3.1 *(Table split in 2 parts)* | Pregnancy History and Maternal Medical History (Intention-To-Treat Set) | BLT001 | - Overall column should be displayed.<br>- Variables to display:<br>- Mother's Age (Years)<br>- Mother's Race<br>- Mother's Ethnicity<br>- Any Antibiotics during the Pregnancy<br>- Any Corticosteroids during the Pregnancy<br>- Total Number of Corticosteroids Doses<br>- Number of Days from Last Corticosteroid Dose up to Birth (Categories to be presented are 1, 2-7 and >7)<br>- Type of Delivery<br>C-section with Labor<br>C-section without Labor<br>Emergency C-section<br>Spontaneous<br>Operative<br>Not Operative<br>-<br>Pregnancy/Complication/Relevant Risk Factor<br>- Pregnancy Complication/Relevant Risk Factor (Categories to be presented as recorded in the CRF)<br>- Any Treatment Given or in Progress for Pregnancy Complication (Yes/No) [1/2] | Add footnotes:<br>[1] A mother can report one or more categories of complication/risk factor/medication/intrapartum complication and will be counted in all the categories that she reports.<br>[2] Number of days since last intake of corticosteroid before delivery = Date/time of neonate's birth – date/time of last dose of corticosteroid before delivery<br>[3] Operative/Not Operative Frequencies are based on Spontaneous type number<br><br>Source: Listings 16.2.4.2.1, 16.2.4.2.2, 16.2.4.2.3. |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| | | | | |
| Table 14.1.3.1 *(Table split in 2 parts)* | Pregnancy History and Maternal Medical History (Intention-To-Treat Set) | BLT001 | [2/2]<br>- Any Intrapartum Complications? (Yes/No)<br>- Intrapartum Complications (Categories to be presented as recorded in the CRF)<br>- Treatment Given or in Progress for Intrapartum Complication (Yes/No)<br>- Maternal Medical Condition Ongoing (Yes/No)<br>- Any Medication for Ongoing Diagnosis (Yes/No)<br><br>Note: Categories will be presented only if at least one mother reports a particular category. | Add footnotes:<br>[1] A mother can report one or more categories of complication/risk factor/medication/intrapartum complication and will be counted in all the categories that she reports.<br>[2] Number of days since last intake of corticosteroid before delivery = Date/time of neonate's birth – date/time of last dose of corticosteroid before delivery<br>[3] Operative/Not Operative Frequencies are based on Spontaneous type number<br><br>Source: Listings 16.2.4.2.1, 16.2.4.2.2, 16.2.4.2.3. |
| Table 14.1.3.2 | Maternal Medical History (Intention-To-Treat Set) | MHT001 | - Replace <Condition/Procedure> by Maternal Medical History. | Add footnotes:<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br><br>Source: Listing 16.2.4.2.5 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.1.3.3 | Neonate Medical History (Intention-To-Treat Set) | MHT001 | - Replace <Condition/Procedure> by Neonate Medical History. | Add the footnote<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br><br>Source: Listing 16.2.4.2.4 |
| Table 14.1.3.4 | Prior Neonate Procedures (Safety Set) | MHT001 | - Replace <Condition/Procedure> by Prior Neonate Procedure. | Add the footnote<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br><br>Source: Listing 16.2.4.5 |
| Table 14.1.3.5 | Maintained Neonate Procedures (Safety Set) | MHT002 | - Please display as first row 'Number of Subjects with at Least One Maintained Neonate Procedure' | Same as Table 14.1.3.4 |
| Table 14.1.3.6 | Concomitant Neonate Procedures (Safety Set) | MHT002 | - Please display as first row 'Number of Subjects with at Least One Concomitant NeonateProcedure' | Same as Table 14.1.3.4 |
| Table 14.1.4.1 | Prior Neonate Medications (Safety Set) | CMT001 | - Overall column should be displayed<br>- Please display as first row 'Number of Subjects with at Least One Prior Neonate Medication' | Add the footnote<br>[1] ATCs and Preferred Name are coded using WHO-DD <month year>.<br>Source: Listing 16.2.4.9 |
| Table 14.1.4.2-a | Prior Maternal Medications used During Pregnancy (Safety Set) | CMT002 | - Please display as first row 'Number of Subjects with at Least One Prior Maternal Medication used During Pregnancy' | Source: Listing 16.2.4.8 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.1.4.2-b | Prior Maternal Medications used During Delivery (Safety Set) | CMT002 | - Please display as first row 'Number of Subjects with at Least One Prior Maternal Medication used During Delivery' | Source: Listing 16.2.4.8 |
| Table 14.1.4.3 | Maintained Neonate Medications (Safety Set) | CMT002 | - Please display as first row 'Number of Subjects with at Least One Maintained Neonate Medication' | Source: Listing 16.2.4.9 |
| Table 14.1.4.4 | Concomitant Neonate Medications (Safety Set) | CMT002 | - Please display as first row 'Number of Subjects with at Least One Concomitant Neonate Medication' | Source: Listing 16.2.4.9 |
| Table 14.1.5 | Compliance to Study Treatment (Intention-To-Treat Set) | EXT002 | - For categorical summary present categories as: <80%, 80%-120%, > 120%.<br>- Do not display overall column | Add footnotes:<br>[1] Compliance to Treatment (%) = Volume administered/Volume scheduled x 100.<br>[2] Volume Scheduled (ml) = 2.5 x birth weight (kg) for the first dose and 1.25 x birth weight (kg) for following doses.<br><br>Source: Listing 16.2.5.5 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.1.1 | Statistical Analysis of Percentage of Neonates Needing Mechanical Ventilation/Intubation (Intention-To-Treat Set) | TPT005 | - Change Visit by Parameter, Visit X by the list of parameters below:<br>Percentage of Neonates Needing IMV in First 72 Hours of Life<br>Neonates Needing IMV in the First 28 Days PNA<br>Neonates Needing IMV within 36 Weeks PMA<br>Percentage of Neonates Needing any Intubation Procedure outside the Initial Surfactant Administration Period in first 72 Hours of Life<br>Neonates Needing any Intubation Procedure outside Initial Surfactant Administration Period in First 28 Days PNA<br>Neonates Needing any Intubation Procedure outside Initial Surfactant Administration Period within 36 Weeks PMA.<br><br>Add a column Treatment Comparison and display below it 3 columns Adjusted Difference, 95% CI and p-value. | Add footnotes:<br>[1] IMV = Invasive Mechanical Ventilation; PMA = Post-menstrual Age; PNA = Post-natal Age.<br>[2] Adjusted difference, its 95% CI and p-value are estimated using Cochran-Mantel-Haenszel test<br><br>Source: Listing 16.2.6.1 |
| Table 14.2.1.1_so | SAS Output: Statistical Analysis of Neonates Needing Invasive Mechanical Ventilation (IMV) (Intention-To-Treat Set) | | Raw SAS output | |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.1.2 | Subgroup Analysis: Summary of Percentage of Neonates Needing Invasive Mechanical Ventilation (IMV) by Use of Sedation/Analgesia (Intention-To-Treat Set) | TPT005 | - Repeat Table 14.2.1.1 without Treatment comparison columns (only summary statistics)<br>- Add header row above the table for Use of Sedation/Analgesia: <Yes/No> | |
| Table 14.2.2.1-a | Summary of $SpO_2$ – Absolute Values and Change from Pre-procedure Values (Intention-To-Treat Set) | TPT001 | - Include timepoints Pre-procedure, T0, 5 Min, 15 Min, 30 Min, 1 Hour, 6 Hours, 12 Hours, 24 Hours, 48 Hours (Day 2), 72 Hours (Day 3), 120 Hours (Day 5).<br>- Replace Baseline with Pre-procedure.<br>- Replace Visit by Timepoint<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnote:<br><br>[1] $SpO_2$ = Preductal Oxygen Saturation<br><br>Source: Listing 16.2.6.2 |
| Table 14.2.2.1-b | Summary of $SpO_2$ Values for Neonates still Receiving Respiratory Support at 28±2 days PNA and 36 Weeks PMA (Intention-To-Treat Set) | TPT002 | - Only present statistics for 28±2 days PNA and 36 Weeks PMA<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnote:<br>[1] PMA = Post-menstrual Age; PNA = Post-natal Age; $SpO_2$ = Preductal Oxygen Saturation<br><br>Source: Listing 16.2.6.2 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.2.2 | Statistical Analysis of $SpO_2$ Values in the first 120 hours (Intention-To-Treat Set) | ANT001 | | Add footnotes:<br>[1] n corresponds to the number of subjects included in the analysis.<br>[2] $SpO_2$ = Preductal Oxygen Saturation.<br>[3] The analysis is based on a mixed model for repeated measure (MMRM) model with treatment, timepoint, treatment by timepoint interaction, gestational age group as fixed effects and pre-procedure $SpO_2$ as covariate.<br><br>Source: Listing 16.2.6.2 |
| Table 14.2.3.1-a | Summary of $FiO_2$ – Absolute Values and Change from Pre-procedure Values (Intention-To-Treat Set) | TPT001 | - Include timepoints Pre-procedure, T0, 5 Min, 15 Min, 30 Min, 1 Hour, 6 Hours, 12 Hours, 24 Hours, 48 Hours (Day 2), 72 Hours (Day 3), 120 Hours (Day 5).<br>- Replace Baseline with Pre-procedure.<br>- Replace Visit by Timepoints<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnote:<br><br>[1] $FiO_2$ = Fraction of inspired Oxygen<br><br>Source: Listing 16.2.6.2 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.3.1-b | Summary of $FiO_2$ Values for Neonates still Receiving Respiratory Support at 28±2 days PNA and 36 Weeks PMA (Intention-To-Treat Set) | TPT002 | - Only present statistics for 28±2 days PNA and 36 Weeks PMA<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnote:<br>[1] PMA = Post-menstrual Age; PNA = Post-natal Age; $FiO_2$ = Fraction of inspired Oxygen<br><br>Source: Listing 16.2.6.2 |
| Table 14.2.3.2 | Statistical Analysis of $FiO_2$ Values in the first 120 hours (Intention-To-Treat Set) | ANT001 | | Add footnotes:<br>[1] n corresponds to the number of subjects included in the analysis.<br>[2] $FiO_2$ = Fraction of inspired Oxygen<br>[3] The analysis is based on a mixed model for repeated measures (MMRM) model with treatment, timepoint, treatment by timepoint interaction, gestational age group as fixed effects and pre-procedure $FiO_2$ as covariate.<br><br>Source: Listing 16.2.6.2 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.4.1-a | Summary of $SpO_2/FiO_2$ Ratio – Absolute Values and Change from Pre-procedure Values (Intention-To-Treat Set) | TPT001 | - Include timepoints Pre-procedure, T0, 5 Min, 15 Min, 30 Min, 1 Hour, 6 Hours, 12 Hours, 24 Hours, 48 Hours (Day 2), 72 Hours (Day 3), 120 Hours (Day 5),<br>- Replace Baseline with Pre-procedure.<br>- Replace Visit by Timepoints.<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnote:<br>[1] $FiO_2$ = Fraction of inspired Oxygen; $SpO_2$ = Preductal Oxygen Saturation<br><br>Source: Listing 16.2.6.2 |
| Table 14.2.4.1-b | Summary of $SpO_2/FiO_2$ Ratio for Neonates still Receiving Respiratory Support at 28±2 days PNA and 36 Weeks PMA (Intention-To-Treat Set) | TPT002 | - Only present statistics for 28±2 days PNA and 36 Weeks PMA<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnote:<br>[1] $FiO_2$ = Fraction of inspired Oxygen; PMA = Post-menstrual Age; PNA = Post-natal Age; $SpO_2$ = Preductal Oxygen Saturation<br><br>Source: Listing 16.2.6.2 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.4.2 | Statistical Analysis of $SpO_2/FiO_2$ Ratio in the first 120 hours (Intention-To-Treat Set) | ANT001 | | Add footnotes:<br>[1] n corresponds to the number of subjects included in the analysis.<br>[2] $FiO_2$ = Fraction of inspired Oxygen; $SpO_2$ = Preductal Oxygen Saturation<br>[3] The analysis is based on a mixed model for repeated measured. MMRM model with treatment, timepoint, treatment by timepoint interaction, gestational age group as fixed effects and pre-procedure $SpO_2/FiO_2$ as covariate.<br><br>Source: Listing 16.2.6.2 |
| Table 14.2.5 | Summary of Blood Gas Analysis Parameters – Absolute Values and Change from Pre-Procedure (Intention-To-Treat Set) | LBT001 | - Include timepoints Pre-procedure, 1 Hour, 6 Hours, 24 Hours, 48 Hours (Day 2), and 72 Hours (Day 3).<br>- Replace Baseline with Pre-procedure.<br>- Label first column as Timepoint instead of Visit – Timepoint.<br>- Include parameters pH, $pCO_2$, $pO_2$, $HCO_3$, BE, lactate<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnotes:<br>[1] HCO3 = Bicarbonates; $pCO_2$ = Partial Pressure of Carbon Dioxide; $pO_2$ = Partial Pressure of Oxygen.<br><br>Source: Listing 16.2.6.3 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.6.1 | Summary of Percentage of Subjects Requiring at least one Additional Dose of Surfactant (Intention-To-Treat Set) | TPT005 | - There is no Visit column to be presented.<br>- Display number and percentage of subjects requiring at least one additional dose of surfactant At Least one Additional Dose of Surfactant (Yes/No).<br>- Display number and percentage of subjects receiving additional surfactant dose under Number of Doses Received (2 and 3).<br>- Display number and percentage of subjects under Method of Administration for the second dose.<br>- Display number and percentage of subjects under Method of Administration for the third dose. | Add footnote:<br>[1] Subjects with pulmonary hemorrhage occurred during the first procedure are not included in the analysis.<br><br>Source: Listings 16.2.5.2-a, 16.2.5.2-b and 16.2.5.3 |
| Table 14.2.6.2 | Statistical Analysis of Percentage of Subjects Requiring at least one Additional Surfactant Dose (Intention-To-Treat Set) | ANT004 | - There is no Timepoint to be presented.<br>- Display on the table body only: <ARM A> (N=XXX), <ARM B> (N=XXX) lines and ARM A vs. ARM B line.<br>- Display text in the first column 'Subjects Requiring at least one Additional Surfactant Dose'.<br>- Display all the column as per template ('n', 'ODDs RATIO (95% CI)', ' P-VALUE'). | Add footnotes:<br>[1] Odds ratio, its 95% CI and p-value are obtained using Fisher's exact test.<br>[2] Subjects with pulmonary hemorrhage occurred during the first procedure are not included in the analysis.<br><br>Source: Listings 16.2.5.2-a, 16.2.5.2-b and 16.2.5.3 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.2.7 | Statistical Analysis of Duration of Ventilation and Oxygen Supplementation Alone (Intention-To-Treat Set) | TPT002 | - Change Visit by Parameter, Visit X by the list of parameters below:<br>Duration Time of IMV in the First 72 Hours of Life<br>Duration time of IMV in the First 28 Days PNA<br>Duration time of IMV within 36 Weeks PMA<br>Stand-alone Oxygen Supplementation (Days)<br>Non-invasive Ventilation (Days)<br><br>- Add 2 additional columns: First with median difference and CI95% and second one presenting the Mann-Whitney U-test p-value. | Add footnotes:<br>[1] IMV = Invasive Mechanical Ventilation; PMA = Post-menstrual Age; PNA = Post-natal Age<br>[2] Median difference, its 95% CI and p-value are obtained using Mann-Whitney U-test.<br><br>Source: Listing 16.2.6.1 |
| Table 14.3.1.1 | Extent of Exposure (Safety Set) | EXT001 | - Display number and percentage of subjects for Number of Poractant Alfa Doses with categories 1, 2 and 3.<br>- Display summary statistics for Actual Volume (mL); present n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Source: Listing 16.2.5.5 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.2.1 | Statistical Analysis of Number and Percentage of Neonates with Failed First Attempt to Insert Catheter/Endotracheal Tube (Safety Set) | TPT005 | - Change Visit by Parameter and baseline, Visit X by the list of parameters below:<br>Number and Percentage of Neonates with Failed First Attempt to Insert Catheter/Endotracheal Tube in the Parameter column.<br>*Display the results for the First and the Second Administration in 2 distincts blocks.*<br>- Add a column Treatment Comparison and display below 3 columns with Adjusted Difference,95% CI and p-value | Add footnote:<br>[1] Adjusted difference, its 95% and p-value CI are estimated using Cochran-Mantel-Haenszel test<br>[2] Treatment groups are based on the first actual treatment received. In case of a second administration that did not match the first dose, data were discarded.<br><br>Source: Listings 16.2.5.1-a, 16.2.5.1-b, 16.2.5.2-a and 16.2.5.2-b |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.2.2 | Number of Attempts Description and Statistical Analysis of Duration of Surfactant Administration and Overall Procedure (Safety Set) | TPT002 | - There is no visit to display.<br>- Number of Attempts to First Successful Insertion<br>*Then display the variable below for the First and Second administration with the following subtitles: 'First Admistration' and then 'Second Administration'*<br>- Number of Device Misallocations<br>- Number of Maneuvers Discontinued due to Neonate's Severe Destabilization<br>- Duration of Surfactant Administration (Minutes)<br>- Duration of Overall Procedure (Hours)<br>- Duration of Overall Procedure (Minutes)<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum<br><br>- Add a p-value column presenting the Mann-Whitney U test p-value for the last two parameters (Duration of Surfactant Administration and of Overall procedure) | Add fottnote:<br>[1] P-value is obtained using Mann-Whitney U-test.<br>[2] Treatment groups are based on the first actual treatment received. In case of a second administration that did not match the first dose, data were discarded.<br><br>Source: Listings 16.2.5.1-a, 16.2.5.1-b, 16.2.5.2-a and 16.2.5.2-b |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.3.1-a | Summary of Treatment Emergent Adverse Events (Safety Set) | AET001 | - Display Number of Subject with at least One:<br>-TEAEs<br>- Serious TEAEs<br>- ADRs<br>- TEAEs Leading to Death | Source: Listing 16.2.7.2 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.3.1-b<br>*(Table splited – first part)* | Summary of Adverse Events Starting during Overall Procedure (Safety Set) | AET001 | Data to display:<br>- Number of Subjects with AEs Starting during Overall Procedure for Surfactant Administration<br>- Number of Subjects with AEs Starting During Overall Procedure for Surfactant Administration Judged Related to the Procedure<br>- Number of Subjects with AEs Occurring During Overall Procedure for Surfactant Administration Requiring Either Oxygen Alone or an Increase in $FiO_2$ without the Need for Escalation of Invasive or Non-invasive Ventilator Support<br>- Number of Subjects with AEs Starting During Overall Procedure of Surfactant Administration Requiring Administration of Manual (Bag and Mask) Pressure Positive Ventilation<br>- Number of Subjects with AEs Starting During Overall Procedure for Surfactant Administration Requiring Endotracheal Intubation<br>[1/2] | Add the footnote:<br>[1] Adverse events starting between the procedure start and medication and adverse events occurred during the medication administration are also considered here.<br><br>Source: Listings 16.2.7.1 16.2.7.2 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.3.1-b<br>*Table splited – last part)* | Summary of Adverse Events Starting during Overall Procedure (Safety Set) | AET001 | [2/2]<br>-Number of Subjects with AEs Starting During Overall Procedures for Surfactant Administration Requiring Circulatory Support including Administration of Crystalloids<br>- Number of Subjects with AEs Starting During Overall Procedures for Surfactant Administration Requiring Cardiopulmonary Resuscitation including Administration of Cardiac Massage or Adrenaline<br>- Number of Subjects with at Least One SAE<br><br>*Present AE during the first 2 administrations following the dose flags described in section 6.1 of SAP.* | Add the footnote:<br>[1] Adverse events starting between the procedure start and medication and adverse events occurred during the medication administration are also considered here.<br><br>Source: Listings 16.2.7.1 16.2.7.2 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.3.2.a | Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set) | AET003 | *For actual treatment column, please refer to section 6.1.* | Add the footnotes<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] Adverse events starting before the first randomized study medication administration are defined as pre-treatment AEs including adverse events starting between the procedure start and medication start and are not considered.<br><br>Source: Listing 16.2.7.2 |
| Table 14.3.1.3.2.b | Subgroup Analysis: Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Use of Sedation/Analgesia (Safety Set) | AET003 | Repeat Table 14.3.1.3.2 and present by Use of Sedation/Analgesia = Yes and Use of Sedation/Analgesia = No | |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.3.3 | Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set) | AET003 | *For actual treatment column, please refer to section 6.1.* | Add the footnotes<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] Adverse events starting before the first randomized study medication administration are defined as pre-treatment AEs including adverse events starting between the procedure start and medication start and are not considered.<br><br>Source: Listing 16.2.7.4 |
| Table 14.3.1.3.4 | Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set) | AET003 | *For actual treatment column, please refer to section 6.1.* | Add the footnotes:<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] Adverse events starting before the first randomized study medication administration are defined as pre-treatment AEs including adverse events starting between the procedure start and medication start and are not considered.<br><br>Source: Listing 16.2.7.3 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.3.5 | Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Set) | AET003 | *For actual treatment column, please refer to section 6.1.* | Add the footnotes:<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] Adverse events starting before the first randomized study medication administration are defined as pre-treatment AEs including adverse events starting between the procedure start and medication start and are not considered.<br><br>Source: Listing 16.2.7.5 |
| Table 14.3.1.3.6 | Incidence of Adverse Events Indicating Neonatal Complications of Prematurity (Safety Set) | TPT006 | - Display number and percentage of subjects with At least one Complication and below the number and percentage of each Complication (by decreasing overall frequency) as listed in Appendix I along with the grades for each complication.<br>- If a neonate experiences more than 1 complications, he/she will be counted under all categories. | Add footnote:<br>[1] A neonate can experience more than one complication of prematurity and will be counted in all the categories experienced.<br><br>Source: Listing 16.2.7.6 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.1.3.7 | Summary of Duration of Endotracheal Intubation and Positive Pressure Ventilation (Safety Set) | TPT002 | - Change Visit by Parameter and baseline, Visit X by the list of parameters below:<br>Duration of Endotracheal Intubation (Min) and Duration of Positive Pressure Ventilation (Min).<br>- Present n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum.<br><br>Display results **only** for AE occurring during the overall procedure (see section 10.2 of SAP) | Add footnotes:<br>[1] Duration of Endotracheal Intubation = End Time of Intubation – Start Time of Intubation.<br>[2] Duration of Positive Pressure Ventilation = End Time of Positive Pressure Ventilation – Start Time of Positive Pressure Ventilation<br>[3] Duration of endotracheal intubation and PPV is calculated only for the procedure required for an AE starting during the treatment procedure.<br><br>Source: Listing 16.2.4.7 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.4.1 | Vital Signs: Actual Values and Change from Pre-procedure (Safety Set) | VST001 | - Include Timepoints Pre-procedure, T0, 5 Min, 15 Min, 30 Min, 1 Hours, 6 Hours, 12 Hours, 24 Hours, 48 Hours (Day 2), 72 Hours (Day 3), 120 Hours (Day 5), 28 Days PNA, 36 Weeks PMA and Week 40 (Discharge)<br>- Include parameters Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Mean Blood Pressure (mmHg), Heart Rate (beats/min), Respiratory Rate (breaths/minute)<br>- Replace Baseline with Pre-procedure<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum.<br><br>*Changes from pre-procedure will not be displayed at 28 Days PNA, 36 Weeks PMA and Week 40 (Discharge).* | Add footnote:<br>[1] PMA = Post-menstrual Age; PNA = Post-natal Age.<br><br>Source: Listing 16.2.8.1 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.4.2 | Premature Infant Pain Profile (PIPP) Score: Actual Values (Safety Set) | VST002 | - Include Timepoint T0 *(For T0, score is calculated as sum of pre-procedure total PIPP score and total PIPP score recorded at T0).*<br>- Present summary statistics for PIPP total score.<br>- Replace Baseline with Pre-procedure.<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Add footnote:<br>[1] T0 score is calculated as sum of pre-procedure total PIPP score and total PIPP score recorded at T0.<br><br>Source: Listing 16.2.8.2 |
| Table 14.3.5.1 | Bronchopulmonary Dysplasia and Oxygen Use at 36 Weeks PMA (Safety Set) | TPT006 | Do not display At Any Timepoint lines.<br>Present variables as follow:<br>-Subject Treated with Oxygen >21% for at least 28 Days <Yes/No><br>- Requirement for Supplemental Oxygen <Yes/No><br>- Positive Pressure for Respiratory Support <Yes/No>.<br>- Respiratory Support via Nasal Cannula <Yes/No><br>Non-Invasive Ventilation <Yes/No><br>- Mechanical Ventilation via an Endotracheal Tube <Yes/No><br>- BPD Severity <Mild/Moderate/Severe> | Source: Listing 16.2.7.7 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.5.2 | Statistical Analysis of Deaths/ Bronchopulmonary Dysplasia Incidence at 36 Weeks PMA (Safety Set) | TPT005 | - Replace Visit by Parameter in the header<br>Present in the Parameter column:<br>- Number of Deaths/BPD at 36 Weeks PMA<br>- BPD at 36 Weeks PMA [3]<br>Mild<br>Moderate<br>Severe<br>- Mortality at Day 28 PNA<br>- Mortality at 36 Weeks PMA<br>- Oxygen Use at Day 28 PNA [3]<br>- Oxygen Use at 36 Weeks PMA [3]<br><br>- For Oxygen use, please use ""Is there a requirement for supplemental oxygen?" in BPD form.<br>- Treatment Arm (<ARM A> will be replaced by 'Treatment/Gestational Age Category'. Display in this column first Treatment (N=XX)' then the 'Gestational Age Category (N=XX)' within treatment group.<br>- Replace <ARM B> by Number of subject for each category.<br>-Add 3 columns at the end: 'Relative Risk (95%CI)' and 'p-value'. | Add footnotes:<br>[1] PMA = Post-menstrual Age.<br><br>[2] Relative Risk, its 95% CI and p-value are estimated using Cochran-Mantel-Haenszel test.<br><br>[3] Neonates with BPD assessment done.<br><br>Source: Listing 16.2.7.7 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.6.1 | Incidence of Neonatal Morbidities at Week 40 or Discharge (Safety Set) | TPT006 | - Present number and percentage of Subjects with at least one Morbidity and then display number and percentage of subjects in each morbidity: Gastroesophageal Reflux, Retinopathy of Prematurity <Impacted Eye>, Laser/Cryotherapy/Anti-VEGF, Vitrectomy, Apnea of Prematurity, Pulmonary Hypertension <Medication for Pulmonary Hypertension , Ductus Arteriosus, Medication to Treat Seizure, Ventricular Stunt, Ileostomy/Ostomy.<br><br>Display all morbidities even if 0 subject concerned. Display the morbidities by decreasing total frequency. | Add footnote:<br>[1] A neonate can experience more than one morbidity and will be counted in all the categories experienced.<br><br>Source: Listing 16.2.7.8 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.6.2 | Summary of Feeding Status at Discharge/40 Weeks (Safety Set) | TPT006 | - There is no visit and Timepoint to display.<br>- Present frequency and percentage for:<br>Receiving Feedings via a Nasogastric Tube<br>Receiving Feedings via a Nasojejunal Tube<br>Gastrostomy<br>Receiving Overnight Enteral Feeding, Require an Enteral Feeding Pump at Discharge<br>- Present categories as recorded in the eCRF. | Source: Listing 16.2.8.3 |
| Table 14.3.6.3 | Summary of Hearing Status at Discharge/40 Weeks (Safety Set) | TPT006 | - There is no visit and Timepoint to display.<br>- Present frequency and percentage for:<br>Otoacoustic Emission Test<br>Failure (%)<br>Bilateral (%)<br>Monolateral (%)<br><br>Auditory Brainstem Response Test<br>Abnormal (%)<br>Bilateral (%)<br>Monolateral (%) | Source: Listing 16.2.8.3 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.6.4 | Summary of Neonates Needing Respiratory Support at Discharge/40 Weeks (Safety Set) | TPT005 | - There is no Visit column to be presented.<br>- Display following variables collected at discharge or 40 weeks PMA:<br>Treated with Oxygen > 21% for at Least 28 Days<br>- Supplementary Oxygen<br>- FiO2 (Fraction)<br>- Supplementary Oxygen Delivered in the Last 24 Hours<br>- Respiratory Support via Nasal Cannula<br>- Non-Invasive Ventilation<br>- Receiving Mechanical Ventilation via ETT<br>- Tracheostomy<br>- Additional Aid at Discharge<br><br>- Present categories as recorded on the eCRF. | Source: Listing 16.2.8.5 |

| Table Number | Table Title | Template Code | Notes | Footnotes/Source Listing Number |
|---|---|---|---|---|
| Table 14.3.6.5 | Summary of Neonates Needing Respiratory Medications at Discharge /40 Weeks (Safety Set) | TPT005 | - There is no visit and Timepoint to display.<br>- Present frequency and percentage for:<br>Diuretics for BPD<br>Inhaled Steroids for BPD<br>Systemic Steroids for BPD<br>Inhaled Bronchodilators<br><br>- Present categories as recorded on the eCRF. | Source: Listing 16.2.5.4 |
| Table 14.3.6.6 | Summary of Growth Assessment: Actual Values and Change form Baseline. (Safety Set) | VST002 | -Visit to be displayed: Baseline, 36 weeks (PMA) only for weight and Discharge Home/40 Weeks PMA.<br>- Present summary for parameters Weight (kg), Occipital-Frontal Circumference (cm), Length (cm).<br>- Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum. | Source: Listing 16.2.8.4 |

## 16.2 Listings

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.1.7 | Randomization Schedule (Randomized Set) | DSL001 | Note: Date of randomization to include both Date and Time<br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.1.1 | Screening Failures (Enrolled Set) | DSL002 | - Do not present 'Date of Visit' columns<br>- Replace Age (Unit) by Gestational Age (Weeks)<br>- Add last column for 'Death Date'.<br>- Add annotations '*' or '**' to subject ID as applicable<br>- Date of Informed consent for both parents/ Legal representative to be reported; | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.1.2 | Subjects Disposition (Randomized Set) | DSL004 | - Add annotations '*' or '**' to subject ID as applicable<br>- Date of Informed consent for both parents/ Legal representative to be reported;<br>- Do not present columns Period of Last Intake of Study Treatment, Last Treatment Received and DAY [3]<br>- Add last column for Death Date. | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.1.3 | Study Visits (Randomized Set) | SVL001 | - Remove the words Retest and Unscheduled in header.<br>- Study Day in Period not to be presented.<br>- Add annotations '*' or '**' to subject ID as applicable<br>- Remove column Reason for Early Termination Visit<br>- Add column for On-Site Visit to be reported for visit 36 Weeks PMA<br>- Add column for Contacted People to be reported for visit 36 Weeks PMA in case On-Site Visit is 'No'<br>- Add a flag to specify when visit 'Discharge Home or 40 Weeks PMA' was performed: add # for 'Discharge Home' or § for'40 Weeks PMA' | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study.[3] # Discharge home<br>[4] § 40 Weeks PMA |
| Listing 16.2.2.1 | Protocol Deviation (Randomized Set) | DVL002 | - Include all deviations from DV.<br>- Add the following columns if any data to be displayed<br>- Visit<br>- Start Date/Time of Deviation<br>- End Date/Time of Deviation<br>- Timepoint<br><br>- Remove Randomized sequence, Period, and Reference analysis set columns.<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.2.2 | Violation of Inclusion/Exclusion Criteria (Randomized Set) | DVL001 | - Only deviations from DV in relation to inclusion/exclusion criteria.<br>- There is no Visit to display<br>- Remove Reference analysis set column.<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.3.1 | Analysis Sets Disposition (Randomized Set) | DSL006 | - Remove Period and Randomized sequence<br>- Include Safety Set and ITT Set<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.3.2 | Exclusion from Safety and Intention-To-Treat Sets (Randomized set) | DSL007 | - Remove Period and Randomized sequence<br>- Include reason for exclusion from safety set and from ITT sets<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.4.1 | Neonate's Demographic Characteristics (Randomized Set) | DML001 | - In Column Date of birth include Date and Time<br>- Age to be reported in hours<br>Include parameters: Gestational Age (Weeks) concatenated with Gestational Age (Days), Gestational Age Categories, Sex - Race [Race 'Other' specification in the same column, concatenated with 'Others'], Ethnicity, Birth Weight (kg), APGAR Total Score at 1 min Post-birth and APGAR Total Score at 5 min Post-birth, Clinical Diagnosis of RDS<br>- Do not present Age Category, Height, BMI and Childbearing Potential columns.<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study.[3] APGAR :Appearance, Pulse, Grimace, Activity, Respiration) |
| Listing 16.2.4.2.1 | Maternal Demographic Characteristics (Randomized Set) | SCL001 | Variables to display:<br>- Mother's Age (Years),<br>- Mother's Race [Race 'Other' specification in the same column, concatenated with 'Others']<br>- Mother's Ethnicity<br>- Mothers Taking any Antibiotics during the Pregnancy | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| | | | - Mothers taking any Corticosteroids during the Pregnancy<br>- Total Number of Corticosteroids Doses<br>- Date of last Corticosteroids Administration prior to Birth/Number of Days since Last Corticosteroid Administration up to Birth<br>- Type of Delivery (add detail for Spontaneous: Operative / Not Operative in the same column)<br>- Add annotations '*' or '**' to subject ID as applicable | |
| Listing 16.2.4.2.2 | Pregnancy Complications (Randomized Set) | SCL001 | Variables to display:<br>- If a Mother had any Pregnancy - Complication/Relevant Risk Factor (Yes/No)<br>- Pregnancy Complication/Relevant Risk Factor (Categories to be presented as recorded in the CRF including 'Other, specify')<br>- Any Treatment Given or in Progress for Pregnancy Complication (Yes/No)<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.4.2.3 | Intrapartum Complications (Randomized Set) | SCL001 | Variables to display:<br>- Were there any Intrapartum Complications? (Yes/No)<br>- Intrapartum Complications (Categories to be presented as recorded in the CRF including 'Other, specify')<br>- Treatment Given or in Progress for Intrapartum Complication (Yes/No)<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.4.2.4 | Neonate Medical History (Randomized Set) | MHL001 | Add a column after Randomized Treatment 'Medical History Category' with following categories populated in 3 sub-columns:<br>- Complication of Prematurity<br>- Other Condition<br>- Major Organ Malformation/Genetic Disease /Chromosomal Abnormalities<br>Then display the columns as per template for the description of the disease.<br>- Add annotations '*' or '**' to subject ID as applicable | Add the footnotes<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.4.2.5 | Maternal Medical History (Randomized Set) | MHL001 | Variables to display:<br>- Additional Maternal Medical Condition<br>- If Yes, then add columns for Medical History, Start /End Date or Ongoing for the Medical Condition<br>- Mother taking any Medication for Ongoing Diagnosis<br>If Yes, then add columns for the Medication from Maternal Previous and Concomitant Medications form.<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] **Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.4.3 | Maternal Medical History by System Organ Class and Preferred Term (Randomized Set) | MHL001 | - Add annotations '*' or '**' to subject ID as applicable | Add the footnotes<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.4.4 | Neonate's Concomitant Diseases (Randomized Set) | MHL002 | Add annotations '*' or '**' to subject ID as applicable | Add the footnotes<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] **Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.4.5 | Procedures (Randomized Set) | PRL001 | - Remove Analysis Period in the header<br>- [CAT]: Prior, Maintained and Concomitant.<br>- If indication = 'Other', then present Other: specify (where specify is the specified text)<br>- If indication = Adverse event, then present Adverse Event: XXX (where XXX is the AE term), if more than one AE are specified, to be listed separated by ','<br>If indication = Medical History, then present Medical History: YYY (where YYY is the MH term); if more than one MH are specified, to be listed separated by ','<br><br>Add annotations '*' or '**' to subject ID as applicable | Add the footnotes<br>[1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] **Neonate COVID-19 Infection during the Study. |
| Listing 16.2.4.6 | Non-Invasive Ventilation Parameters (Randomized Set) | | Include columns:<br>- Subject ID<br>- Randomized Treatment<br>- Scheduled Time<br>- NIV Support in Use at the Assessment (CPAP, BiPAP, NIPPV, Not Applicable)<br>- If CPAP, CPAP Pressure (cmH2O)<br>- If BiPAP,<br>  - Upper Pressure Level (cmH2O)<br>  - Lower Pressure Level (cmH2O)<br>  - Mean Airway Pressure (cmH2O)<br>- If NIVPP,<br>  - Peak Respiratory Pressure (cmH2O)<br>  - Positive End Expiratory Pressure (cmH2O)<br>  - Mean Airway Pressure (cmH2O)<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] BiPAP = Bi-level Positive Airway Pressure; CPAP = Continuous Positive Airway Pressure; NIPPV = Nasal Intermittent Positive Pressure Ventilation<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] **Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
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| Listing 16.2.4.7 | Respiratory Support (Randomized Set) | | Include columns:<br>- Subject ID<br>- Randomized Treatment<br>- Any Respiratory Support Provided<br>- Oxygen Supplementation without Positive Pressure (add details for Other specifications in the same column as Other: <Specifications>)<br>- Non-Invasive Ventilation Method (add details for Other specifications in the same column as Other <Specifications>)<br>- Invasive Ventilation Method (add details for Other specifications in the same column as Other: <Specifications>)<br>- Reason for Invasive Ventilation (FiO2>=45%, Significant Apnea, Respiratory Acidosis, Other, add details for Other specifications in the same column as Other: <Specifications>)<br>- $FiO_2$ ***<br>- $SpO_2$ ***<br>- Ventilation as title for two columns Start Date/Time [Day] and End Date/Time [Day]<br>- Indication (add details for Other specifications in the same column as Other: <Specifications>)<br>- If indication = Adverse event, then present Adverse Event: XXX (where XXX is the AE term), if more than one AE are specified, to be listed separated by ‘,’<br><br>Add annotations ‘*’ or ‘**’ to subject ID as applicable | Add the footnote:<br>[1]Day = date of ventilation – date of first randomized treatment + 1<br>[2] $FiO_2$>=45%’ = $FiO_2$ >=0.45 to maintain preductal SpO2 of 88-95% for at least 30 minutes, unless rapid clinical deterioration occurs,<br>[3] Significant Apnea = Significant Apnea (more than four episodes of Apnea /hour or more than two episodes of Apnea /hour if ventilation with bag and mask was required);<br>[4] Respiratory Acidosis = Respiratory acidosis (pCO2 >65 mmHg/8.5 kPa and pH <7.20 identified by either arterial or capillary blood gas monitoring)<br>[5] *Maternal COVID-19 Infection during Pregnancy.<br>[6] ** Neonate COVID-19 Infection during the Study<br>[7] *** at the start of invasive ventilation. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
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| Listing 16.2.4.8 | Maternal Medications (Randomized Set) | CML001 | - Remove “Analysis Period” In the header<br>- Remove “Dosage” In the header<br>- [CAT]: Prior, Maintained and Concomitant.<br><br>For Indication, concatenate the Indication (MH, Pregnancy complication, Intrapartum complication) with the specified text as follow:<br>- if indication = ‘Medical History’, then present Medical History: YYY (where YYY is the MH term);<br>- if Indication = Pregnancy complication, then present Pregnancy complication: XXX (where XXX is the text reported in the field ‘If pregnancy complication, please specify’)<br>- if Indication = Intrapartum complication, then present Intrapartum complication: ZZZ (where ZZZ is the text reported in the field ‘If Intrapartum complication, please specify’)<br>- Add annotations ‘*’ or ‘**’ to subject ID as applicable | Add the footnotes:<br>[1] ATCs and Preferred Name are coded using WHO-DD <month year>.<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] ** Neonate COVID-19 Infection during the Study. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.4.9 | Neonate Medications (Randomized Set) | CML001 | - Remove Analysis Period In the header<br>- [CAT]: Prior, Maintained and Concomitant.<br>- Start date to include both date and time<br>- End date to include both date and time<br>In case of other route, Concatenate the specification as Other: <Specification><br><br>For Indication, concatenate the Indication (MH, AE, Procedure, Other) with the specified text as follow:<br><br>- If Indication = 'Medical History', then present Medical History: YYY (where YYY is the MH term);<br>- If Indication = Adverse Event, then present Adverse Event: XXX (where XXX is the AE term)<br>- If Indication = Procedure, then present Procedure: ZZZ where (ZZZ is the PR text)<br>- If indication = 'Other', then present Other: <Specification><br><br>Dosage is the concatenation of dose per administration, Unit and frequency. In case of Other specifications (for Dose Unit or Frequency), the details will be used for the concatenation<br>- Add annotations '*' or '**' to subject ID as applicable<br>-Add flag for sedation | Add the footnotes:<br>[1] ATCs and Preferred Name are coded using WHO-DD <month year>.<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] ** Neonate COVID-19 Infection during the Study.<br>[4] ° Use of sedative and /or analgesic<br>[5] CAT[1]: C = Concomitant; M = Maintained; P = Prior; PS = Post-Study. |
| Listing 16.2.5.1-a | Study Drug Administration (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Randomization Date/Time<br>- Randomization Number | Add footnotes:<br>[1] Day = date of application/administration – date of first randomized treatment + 1 |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| | | | - Kit Number/Catheter Batch Number as title and then below 2 columns 'IRT' and 'Used'<br>- Reason for change from IRT assignment (Kits and Catheters)<br>- Volume to be Administered (ml) as title and then below 2 columns 'Planned' and 'Actual'<br>- Start Date/Time of Laryngoscopy Application [Day]<br>- Administration as title and then below 2 columns 'Start Date/Time [Day]' and 'End Date/Time [Day]<br>- Duration of Surfactant Administration (Minutes)<br>- Duration of Overall Procedure (Hours)<br>- Attempts to Successfully Insert Catheter/ETT as title and then below 2 columns 'Number' and 'Reason for failure'<br><br>Note: in case more than one kit/batch have been assigned/used all of them need to be listed, separated by ','<br><br>Add annotations '*' or '**' to subject ID as applicable | [2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] ** Neonate COVID-19 Infection during the Study |
| Listing 16.2.5.1-b | Study Drug Administration (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Randomization Date/Time<br>- Number of Device Misallocations (for LISA Group only)<br>- Number of Maneuvers Discontinued due to Neonate's Severe Destabilization<br>- Date/Time of Removal of the Catheter/ETT | Add footnotes:<br><br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| | | | - Administration Interrupted Without Completing the Planned Administration <Reason for Interruption><br>- Surfactant Administration According to the Randomization Group <Specification> (note for programmers: in Specification if surfactant administration according to randomization group is ='No', concatenate the actual method used and reason separate by "/"<br><br>Add annotations '*' or '**' to subject ID as applicable | |
| Listing 16.2.5.2-a | Second Surfactant Dose (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Second Dose of Curosurf Administered<br>- Reason for Second Dose (Lack of efficacy, Clinical deterioration, Intubation criterion: Fio2>=0.45, Intubation criterion: significant Apnea', Intubation criterion: respiratory acidosis, Other <Specification>)<br>- Method of Administration<br>- Kit Number/Catheter Batch Number as title and then below 2 columns 'IRT' and 'Used'<br>- Reason for change from IRT assignment (Kits and Catheters)<br>- Volume to be Administered (ml) as title and then below 2 columns 'Planned' and 'Actual'<br>- Start Date/Time of Laryngoscopy Application [Day]<br>- Administration as title and then below 2 columns 'Start Date/Time [Day]' and 'End Date/Time [Day] | Add footnotes:<br>[1] Day = date of application/administration – date of first randomized treatment + 1<br>[2] Lack or efficacy = Lack of efficacy of the first dose ($FiO_2$ >= 0.30 to maintain SpO2 in the range 88-95%);<br>Clinical deterioration = Clinical deterioration ($FiO_2$ >= 0.30 to maintain $SpO_2$ in the range 88-95%);<br>Intubation criterion: Fio2>=0.45 = Meeting criteria for intubation and MV: FiO2 >= 0.45 to maintain SpO2 between 88-95% for at least 30 |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| | | | - Attempts to Successfully Insert Catheter/ETT as title and then below 2 columns 'Number' and 'Reason for failure'<br>Note: in case more than one kit/batch have been assigned/used all of them need to be listed, separated by ',' | min (or rapid clinical deterioration);<br>Intubation criterion: significant Apnea = Meeting criteria for intubation and MV: significant Apnea;<br>Intubation criterion: respiratory acidosis = Meeting criteria for intubation and MV: respiratory acidosis<br><br>[3] *Maternal COVID-19 Infection during Pregnancy.<br>[4] ** Neonate COVID-19 Infection during the Study |
| Listing 16.2.5.2-b | Second Surfactant Dose (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Randomization Date/Time<br>- Number of Device Misallocations (for LISA Group only)<br>- Number of Maneuvers Discontinued due to Neonate's Severe Destabilization<br>- Date/Time of Removal of the Catheter/ETT<br>- Administration Interrupted Without Completing the Planned Administration <Reason for Interruption><br>- Surfactant Administration According to the Randomization Group <Specification> (note for programmers: in Specification if surfactant administration according to randomization group | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| | | | is ='No', concatenate the actual method used and reason separate by "/"<br><br>Add annotations '*' or '**' to subject ID as applicable | |
| Listing 16.2.5.3 | Third Surfactant Dose (Randomized Set) | | The following columns will be presented<br>- Subject ID<br>- Randomized Treatment<br>- Third Dose of Curosurf Administered?<br>- Reason for Third Dose (Lack of efficacy, Clinical deterioration, Intubation criterion: Fio2>=0.45, Intubation criterion: significant Apnea', Intubation criterion: respiratory acidosis, Other: <Specification>)<br>- Method of Administration<br>- Kit Number/Catheter Batch Number as title and then below 2 columns 'IRT' and 'Used'<br>- Reason for Change from IRT assignment<br>- Volume to be Administered (ml) as title and then below 2 columns 'Planned' and 'Actual'<br>- Administration as title and then below 2 columns 'Start Date/Time [Day]' and 'End Date/Time [Day]<br>- Administration Interrupted Without Completing the Planned Administration <Reason for Interruption><br><br>Note: in case two kits have been assigned/used both need to be listed, separated by ','<br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] Day = date of application/administration – date of first randomized treatment + 1<br>[2] Lack or efficacy = Lack of efficacy of the first dose ($FiO_2$ ≥0.30 to maintain $SpO_2$ in the range 88-95%);<br>Clinical deterioration = Clinical deterioration ($FiO_2$ ≥0.30 to maintain $SpO_2$ in the range 88-95%);<br>Intubation criterion: Fio2 ≥0.45 = Meeting criteria for intubation and MV: $FiO_2$ >= 0.45 to maintain $SpO_2$ between 88-95% for at least 30 min (or rapid clinical deterioration);<br>Intubation criterion: significant Apnea = Meeting criteria for intubation and MV: significant Apnea;<br>Intubation criterion: respiratory acidosis = |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| | | | | Meeting criteria for intubation and MV: respiratory acidosis<br><br>[3] *Maternal COVID-19 Infection during Pregnancy.<br>[4] ** Neonate COVID-19 Infection during the Study |
| Listing 16.2.5.4 | Respiratory Medications at Discharge Home or 40 Weeks PMA (Randomized Set) | | The following columns will be presented<br>- Subject ID<br>- Actual Treatment<br>- Visit<br>- “Treatment for BPD” as header for the following 4 columns “Diuretics”, “Inhaled Steroids”, “Systemic Steroids”, “Inhaled Bronchodilators”.<br><br>Add annotations ‘*’ or ‘**’ to subject ID as applicable | Add footnotes:<br>[1] BPD = Bronchopulmonary Dysplasia<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.5.5 | Listing of Exposure and Compliance (Randomized Set) | | The following columns will be presented<br>- Subject ID<br>-Randomized Treatment<br>- Actual Treatment<br>- Number of Poractant Alfa Doses Administered<br>- Total Volume Administered (ml)<br>- Treatment Compliance (%)<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] Treatment Compliance = Volume administered/Volume scheduled*100% = % of administered volume; where volume scheduled = 2.5ml x neonate's birth weight (kg) for first dose and 1.5 (ml) x neonate's birth weight for second and third doses.<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.6.1 | Mechanical Ventilation/Intubation, Non-Invasive Ventilation and Oxygen Supplementation (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Neonate Needing IMV in first 72 Hours of Life. If yes, concatenate with the Duration (Hours)<br>- Neonate Needing IMV in first 28 Days PNA. If yes, concatenate with the duration (Days)<br>- Neonate Needing IMV within 36 Weeks PMA. If yes, concatenate with the duration (Days)<br>- Neonate Needing Intubation Procedure in First 72 Hours of Life<br>- Neonate Needing Intubation Procedure in First 28 Days PNA<br>- Neonate Needing Intubation Procedure within 36 Weeks PMA<br>- Duration of Oxygen Supplementation (Days)<br>- Duration of Non-Invasive Ventilation (Days)<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] IMV = Invasive Mechanical Ventilation; PMA = Post-menstrual Age; PNA = Post-natal Age<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.6.2 | $SpO_2$, $FiO_2$ and $SpO_2/FiO_2$ Values (Randomized Set) | VSL001 | - Remove 'Analysis Period'<br>- Change the column Subect ID/Sex/Age to "Subect ID/Sex/Age (Hours)"<br>- Present Randomized Treatment in place of Actual Treatment<br>- Display "Assessment Date/Time [Study Day]" instead of "Assessment Date/time [study day / study day in period]"<br>- Skip the last column (Change from pre-dose)<br>- Display values for:<br>- $SpO_2$ (%)<br>- $FiO_2$ (Fraction)<br>- $SpO_2/FiO_2$<br>- Present CHG and change annotation to [2] instead of [3], do not present CFB<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] Pre-procedure =B flags pre-procedure value<br>[2] Use=Y: included in the analysis<br>CHG is change from pre-procedure<br>[3] $FiO_2$ = Fraction of Inspired Oxygen; $SpO_2$ = Preductal Oxygen Saturation<br>[4] *Maternal COVID-19 Infection during Pregnancy.<br>[5] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.6.3 | Blood Gas Analysis (Randomized Set) | LBL001 | - Remove 'Analysis Period'<br>- Display "Assessment date/Time [Study Day]" instead of "Assessment date/time [study day / study day in period]"<br>- Remove 'Fasted'<br>- Do not display [H] flag.<br>- Do not display Normal Range column<br>- Replace Change from Baseline with Change from Pre-procedure<br>- In Test <Unit> column, display:<br>- pH<br>- $pCO_2$ (mmHg)<br>- $pO_2$ (mmHg)<br>- $HCO_3$ (mEq/L)<br>- Lactate (mmol/L)<br>- Base Excess (mEq/L)<br>- Sort test alphabetically<br>-Add a column displaying 'Sample Type' (LBSPEC) betweenAssessment Date/Time and Result column<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] Pre-procedure =Y flags pre-procedure value<br>[2] Use=Y: included in the analysis<br>[3] CSA=Abnormal, Clinically Significant<br>[4] $pCO_2$ = Partial Pressure of Carbon Dioxide; $pO_2$ = Partial Pressure of Oxygen; $HCO_3$ = Bicarbonates<br><br>[5] *Maternal COVID-19 Infection during Pregnancy.<br>[6] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.7.1 | Pre-treatment Adverse Events (Randomized Set) | AEL001 | - Remove Age, Race, Ethnicity, and Pattern.<br>- Remove Action Taken with study drug<br>- Remove Causality<br>- Add Gestational Age (Weeks)<br>- Add all the possible options for 'Other action taken', including specifications where available<br>- Outcome in a separate column<br>- Add annotations '*' or '**' to subject ID as applicable | Add the footnotes:<br>[1] Adverse events starting before the first randomized study medication administration are defined as pre-treatment AEs as well as Adverse events starting between the procedure start and medication start.<br>[2] DI = Results in persistent or significant disability or incapacity; DTH = Results in death; HSP = Requires hospitalization or prolongation of existing hospitalization; LTH = Is life-threatening; SIG = Is a medically significant adverse event.<br>[3] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.<br>[4] *Maternal COVID-19 Infection during Pregnancy.<br>[5] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.7.2 | Treatment Emergent Adverse Events (Randomized Set) | AEL002 | - Remove Ethnicity, Period/Randomized Treatment, Starting dose/dose at onset/weight and Pattern.<br>- Remove Period/, only present Actual Treatment<br>- Remove [D2] from 'Onset Date', annotate End Date with [D2] instead of [D3]<br>- Remove 'Action Taken with study drug'<br>- Add column reporting if the event started during First or Second procedure<br>- Add a separate column for Causality; it should reflect the answers for relationship to study drug, study procedure and study device;<br>- Add a column to show if the relationship is to the first or second administration;<br>- Add all the possible options for 'Other Action Taken' including specifications where available<br>- Outcome in a separate column<br><br>Add annotations '*' or '**' to subject ID as applicable<br>Add a flag for Complication of prematurity '#' for each Concerned AE (Refer to section 10.2 for further details.) | Add the footnotes:<br>[1] DI = Results in persistent or significant disability or incapacity; DTH = Results in death; HSP = Requires hospitalization or prolongation of existing hospitalization; LTH = Is life-threatening; SIG = Is a medically significant adverse event.<br>[2] D1 = is the study Day at Onset Date calculated with reference to the date of first randomized treatment administration<br>[3] D2 = is the Study Day at End Date calculated with reference to the date of first randomized treatment administration<br>[4] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.'<br>[5] *Maternal COVID-19 Infection during Pregnancy.<br>[6] ** Neonate COVID-19 Infection during the Study<br>[7] # Complication of Prematurity |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
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| Listing 16.2.7.3 | Serious Treatment Emergent Adverse Events (Randomized Set) | AEL002 | Repeat Listing 16.2.7.2 for SAEs | |
| Listing 16.2.7.4 | Treatment Emergent Adverse Drug Reactions (Randomized Set) | AEL002 | Repeat Listing 16.2.7.2 for ADRs | |
| Listing 16.2.7.5 | Treatment Emergent Adverse Events Leading to Death (Randomized Set) | AEL002 | Repeat Listing 16.2.7.2 for TEAEs leading to death | |
| Listing 16.2.7.6 | Neonatal Complications of Prematurity (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Actual Treatment<br>- Start Date/Time [Day]<br>- End Date/Time [Day]<br>- Event<br>- Air Leaks specifications<br>- Germinal Matrix Hemorrhage/ Intraventricular Hemorrhage Severity Grades.<br>- Necrotizing Enterocolitis Severity Stages<br>- Retinopathy of prematurity Severity Stages<br>- Plus Disease < Impacted Eye><br><br>Add annotations '*' or '**' to subject ID as applicable<br>Add a flag to identify TEAE | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study.<br>[3] $ = Treatment Emergent Adverse Event. |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.7.7 | Bronchopulmonary Dysplasia Evaluation (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Actual Treatment<br>- Assessment Date/Time<br>- BPD [3] / BPD Grade<br>- Requirement for Supplemental Oxygen and if Yes: < $FiO_2$ (Fraction)><br>- Positive Pressure for Respiratory Support<br>- Respiratory Support via Nasal Cannula in title and display below 2 columns with Flow Rate (L/min) and Oxygen Concentration in the Gas Mixture (%)<br>(%)<br>- Non-Invasive Ventilation<br>- Mechanical Ventilation via ETT<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study<br>[3] Neonates treated with Oxygen >21% for at least 28 Days |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.7.8 | Neonatal Co-Morbidities at Discharge or 40 Weeks PMA (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Actual Treatment<br><br>Create a column "Neonatal Co-Morbidities" and list for each subject only the morbidities when Yes is ticked including those variables below:<br>- Gastroesophageal Reflux Requiring Treatment<br>- Retinopathy of Prematurity<br>-Treatment for Retinopathy of Prematurity if yes add Impacted Eye <Unilateral: Left Eye/Right Eye, Bilateral> and Stage<br>- Treated with Laser, Cryotherapy and/or Anti-VEGF therapy<br>- Vitrectomy<br>- Apnea of Prematurity Requiring Treatment<br>- Pulmonary Hypertension<br>- Medication<br>- Patent Ductus Arteriosus<br>- Medication to Treat Seizures Required<br>- Ventricular Shunt in place<br>- Ileostomy / Ostomy<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.7.9 | Device Deficiency (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Actual Treatment<br>- Device Deficiency encountered<br>- Device Deficiency Number<br>- Device Deficiency Observed<br>- Batch number<br>- Expiration date<br>- Date of Device Deficiency Observation<br>- Immediate Action <Specification><br>- Reason for the Device Deficiency <Specification><br>- Device Deficiency Leading to an AE Concatenated with the AE #<br>- Description of the Device Deficiency | |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
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| Listing 16.2.8.1 | Vital Signs (Randomized Set) | VSL002 | - Remove 'Analysis Period'<br>- Display Assessment Date/Time [Study Day] instead of Assessment date/time [study day / study day in period]<br>- Do not display [H] flag in Change from baseline column<br>- Skip the last column (Change from pre-dose) and replace Change from Baseline with Change from Pre-procedure<br><br>- In Test <Unit> column, display:<br>- Systolic Blood Pressure (mmHg)<br>- Diastolic Blood Pressure (mmHg)<br>- Mean Blood Pressure (mmHg)<br>- Heart Rate (beats/min)<br>- Respiratory Rate (breaths/min)<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] Baseline =Y flags pre-procedure value<br>[2] Use=Y: included in the analysis<br>[3] *Maternal COVID-19 Infection during Pregnancy.<br>*[4] * Neonate COVID-19 Infection during the Study |
| Listing 16.2.8.2 | Pain Assessment (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Actual Treatment<br>- Timepoint<br>- Date /time of Assessment [Day]<br>- PIPP Total Score at T0 (*derivation made directly in the eCRF collected data)*<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] PIPP = Premature Infant Pain Profile<br>[2] Day = Date of PIPP Assessment – first randomized treatment date + 1<br>[3] Total PIPP score is the sum of individual scores.<br>[4] *Maternal COVID-19 Infection during Pregnancy.<br>[5] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.8.3 | Feeding and Hearing Status at Discharge Home or 40 Weeks PMA (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Actual Treatment<br>- Visit<br>- Feeding Status<br>- Receiving Feedings via a Nasogastric Tube<br>- Receiving Feeding via a Nasojejunal Tube<br>- Subject have a Gastrostomy<br>- Receiving Overnight Enteral Feeding<br>- Require an Enteral Feeding Pump at Discharge<br>- Hearing Status<br>- Otoacoustic Audio Test Performed<br>If Yes concatenate the specification <Right Ear / Left Ear><br>- Auditory Brainestem Response test Performed<br>If Yes concatenate the specification <Right Ear / Left Ear><br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study |
| Listing 16.2.8.4 | Growth Assessment (Randomized Set) | VSL001 | - Remove "Analysis Period" column.<br>- Remove "Study day in Period".<br>- Present Actual Treatment<br>- Change body weight to Weight (kg), SBP to OFC (cm) and DBP to Length (cm)<br>- Do not present Use, CFB and CHG<br>- Only present the test result but this label should be removed<br>- Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] OFC = Occipital-Frontal Circumference<br>[2] *Maternal COVID-19 Infection during Pregnancy.<br>[3] ** Neonate COVID-19 Infection during the Study |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.8.5 | Respiratory Support Evaluation at Discharge Home or 40 weeks PMA (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Actual Treatment<br>- Treated with Oxygen > 21% for at Least 28 Days<br>- Receiving any Supplementary Oxygen, if Yes: < $FiO_2$ (Fraction)><br>- Oxygen Saturation Target in title and display below 2 columns with Lower Target (%) and Higher Target (%)<br>- Supplementary Oxygen Delivered in the Last 24 Hours<br>- Respiratory Support via Nasal Cannula in title and display below 2 columns with Flow Rate (L/min) and Oxygen Concentration in the Gas Mixture (%)<br>- Non-Invasive Ventilation<br>- Mechanical Ventilation via ETT<br>- Tracheostomy<br>- Additional Aid at Discharge, if Yes: <Specification><br>Note: if 'Other' is selected, to be showed 'Other: XXX' where XXX is the text reported in If Other, please specify<br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study |
| Listing 16.2.8.6 | Hospital Transfer (Randomized Set) | | The following columns will be presented:<br>- Subject ID<br>- Randomized Treatment<br>- Actual Treatment<br>- Date/ Time of Hospital Transfer<br>- Discharge summary from the receiving hospital, if No: <Specification> | |

| Listing Number | Listing Title | Template Code | Notes | Footnotes |
|---|---|---|---|---|
| Listing 16.2.8.7 | Comments (Randomized Set) | COL001 | Variables to be listed:<br>- Subject ID<br>- Randomized Treatment<br>- Assessment<br>- Timepoint<br>- Comment<br><br>Add annotations '*' or '**' to subject ID as applicable | Add footnotes:<br>[1] *Maternal COVID-19 Infection during Pregnancy.<br>[2] ** Neonate COVID-19 Infection during the Study |

## 16.3 Figures

| Figure Number | Figure Title | Template code | Notes | Footnote / source Table number |
|---|---|---|---|---|
| Figure 14.1.1 | Disposition Flow Chart (Enrolled Set) | DSF001 | | Source: Tables 14.1.1.1 and 14.1.1.2 |
| Figure 14.1.2 | Flow Chart of Analysis Sets (Randomized Set) | DSF003 | Present Safety Set and Intention-To-Treat Set. | Source: Table 14.1.1.6 |
| Figure 14.2.1 | $SpO_2$: Mean Values over Time (Intention-To-Treat Set) | TPF002 | - Present absolute $SpO_2$ values on Y-axis.<br>- Timepoints to be presented are Day 1 (T0), Day 1 (5 min post-procedure), […], Day 1 (24h post-procedure), Day 2, Day 3, Day 5, on X-Axis.<br>Please show number of subjects only at baseline and at each day (24 Hours, 48Hours, 72Hours and 120 Hours). | Source: Table 14.2.2.1-a |
| Figure 14.2.2 | $SpO_2$: Forest Plot (Intention-To-Treat Set) | TPF003 | Present adjusted mean difference between treatments (95%CI) on X-Axis.<br>- Timepoints to be presented are Day 1 (T0), Day 1 (5 min post-procedure), …, Day 1 (24h post-procedure), Day 2, Day 3, Day 5 and averaged over the 120 hours post-treatment on Y-axis | Source: Table 14.2.2.2 |
| Figure 14.2.3 | $FiO_2$: Mean Values over Time (Intention-To-Treat Set) | TPF002 | Repeat Figure 14.2.1 for $FiO_2$ | Source: Table 14.2.3.1-a |
| Figure 14.2.4 | $FiO_2$: Forest Plot (Intention-To-Treat Set) | TPF003 | Repeat Figure 14.2.2 for $FiO_2$ | Source: Table 14.2.3.2 |
| Figure 14.2.5 | $SpO_2/FiO_2$ Ratio: Mean Values over Time (Intention-To-Treat Set) | TPF002 | Repeat Figure 14.2.1 for $SpO_2/FiO_2$ Ratio | Source: Table 14.2.4.1-a |
| Figure 14.2.6 | $SpO_2/FiO_2$ Ratio: Forest Plot (Intention-To-Treat Set) | TPF003 | Repeat Figure 14.2.2 for $SpO_2/FiO_2$ Ratio | Source: Table 14.2.4.2 |

# APPENDIX I

## COMPLICATIONS OF PREMATURITY

- Air leaks
- Apnea of prematurity
- Focal intestinal perforation (Neonatal spontaneous intestinal perforation)
- Germinal matrix hemorrhage/Intraventricular hemorrhage: to be classified according to the following:
    - Grade I - Germinal matrix hemorrhage only or germinal matrix hemorrhage plus intraventricular hemorrhage less than 10% of ventricular area.
    - Grade II – Germinal matrix hemorrhage and intraventricular hemorrhage; 10 to 50% of ventricular area.
    - Grade III - Germinal matrix hemorrhage and intraventricular hemorrhage involving more than 50% of ventricular area; lateral ventricles are usually distended.
    - Grade IV: Hemorrhagic infarction in periventricular white matter ipsilateral to intraventricular hemorrhage (also called periventricular hemorrhagic infarction).
- Necrotizing enterocolitis, to be classified according to modified Bell staging criteria
- Patent ductus arteriosus
- Periventricular leukomalacia
- Pulmonary hemorrhage
- Pulmonary interstitial emphysema
- Retinopathy of prematurity – classification related to stage, localization and extent according to “The International Classification of Retinopathy of Prematurity Revisited”

# APPENDIX II

**List of sedative and analgesic**

| Drug Name | ATC codes |
|---|---|
| FENTANYL | N01AH, N02AB |
| FENTANYL CITRATE | N01AH, N02AB |
| FENTANYL HYDROCHLORIDE | N01AH, N02AB |
| ALFENTANIL | N01AH |
| ALFENTANIL HYDROCHLORIDE | N01AH |
| SUFENTANIL | N01AH, N02AB |
| SUFENTANIL CITRATE | N01AH, N02AB |
| REMIFENTANIL | N01AH |
| REMIFENTANIL HYDROCHLORIDE | N01AH |
| CLONIDINE;FENTANYL | N01AH |
| CLONIDINE HYDROCHLORIDE;FENTANYL CITRATE | N01AH |
| THIOPENTAL | N01AF, N05CA |
| KETAMINE | N01AX |
| KETAMINE HYDROCHLORIDE | N01AX |
| FENTANYL | N01AH, N02AB |
| PROPOFOL | N01AX |
| CLONIDINE;FENTANYL | N01AH |
| SODIUM CARBONATE ANHYDROUS;THIOPENTAL | N01AF |
| KETAMINE;PROPOFOL | N01AX |
| 1-(P-AETHOXYPHENYL)-1-DIAETHYLAMINO-3-M;CODEINE PHOSPHATE;PROPYPHENAZONE | N02AG |
| 1-(P-AETHOXYPHENYL)-1-DIAETHYLAMINO-3-M;CODEINE;PROPYPHENAZONE | N02AG |
| ATROPINE SULFATE;CODEINE PHOSPHATE;METAMIZOLE SODIUM;PROMETHAZINE HYDROCHLORIDE | N02AG |
| ALVERINE CITRATE;OXYCODONE | N02AG |
| ALVERINE;OXYCODONE | N02AG |
| AMINOPHENAZONE;CODEINE PHOSPHATE;PAPAVERINE HYDROCHLORIDE;PHENAZONE | N02AG |
| AMINOPHENAZONE;CODEINE;PAPAVERINE;PHENAZONE | N02AG |
| CAFFEINE;CODEINE PHOSPHATE;HYOSCYAMINE SULFATE;METAMIZOLE;PARACETAMOL | N02AG |
| ATROPA BELLADONNA EXTRACT;CAFFEINE;CODEINE PHOSPHATE HEMIHYDRATE;PARACETAMOL | N02AG |
| ATROPA BELLADONNA EXTRACT;CAFFEINE;CODEINE;PARACETAMOL | N02AG |

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|---|---|
| ATROPA BELLADONNA EXTRACT;CAFFEINE;PAPAVER SOMNIFERUM TINCTURE;PARACETAMOL | N02AG |
| ATROPA BELLADONNA;CAFFEINE;CODEINE;PARACETAMOL | N02AG |
| ATROPA BELLADONNA;CAFFEINE;PAPAVER SOMNIFERUM;PARACETAMOL | N02AG |
| ATROPINE SULFATE;BENZYL ALCOHOL;PETHIDINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE MONOHYDRATE;HYDROCOTARNINE HYDROCHLORIDE MONOHYDRATE;OXYCODONE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;BENZYL ALCOHOL;PETHIDINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;CODEINE HYDROCHLORIDE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;CODEINE PHOSPHATE;METAMIZOLE SODIUM;PROMETHAZINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;DIHYDROMORPHINE | N02AG |
| ATROPINE SULFATE;HYDROMORPHONE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE SULFATE | N02AG |
| ATROPINE SULFATE;MORPHINE;PAPAVERETUM;PAPAVERINE HYDROCHLORIDE;PROPYPHENAZONE | N02AG |
| ATROPINE SULFATE;OPIUM ALKALOIDS TOTAL | N02AG |
| ATROPINE SULFATE;OPIUM ALKALOIDS TOTAL;PAPAVERINE HYDROCHLORIDE | N02AG |
| ATROPINE;BENZYL ALCOHOL;PETHIDINE | N02AG |
| ATROPINE;CODEINE;METAMIZOLE;PROMETHAZINE | N02AG |
| ATROPINE;CODEINE;MORPHINE;NOSCAPINE;PAPAVERINE | N02AG |
| ATROPINE;HYDROCOTARNINE;OXYCODONE | N02AG |
| ATROPINE;HYDROMORPHONE | N02AG |
| ATROPINE;MORPHINE | N02AG |
| ATROPINE;MORPHINE SULFATE | N02AG |
| ATROPINE;MORPHINE;PAPAVERETUM;PAPAVERINE;PROPYPHENAZONE | N02AG |
| ATROPINE;OPIUM ALKALOIDS TOTAL | N02AG |
| ATROPINE;OPIUM ALKALOIDS TOTAL;PAPAVERINE | N02AG |
| ATROPINE;OXYCODONE | N02AG |
| ATROPINE;PETHIDINE HYDROCHLORIDE;PROMETHAZINE HYDROCHLORIDE | N02AG |
| ATROPINE;PETHIDINE;PROMETHAZINE | N02AG |
| CODEINE;HOMATROPINE;SPARTEINE SULFATE | N02AG |
| EPHEDRINE HYDROCHLORIDE;HYOSCYAMINE HYDROBROMIDE;OXYCODONE HYDROCHLORIDE | N02AG |
| CAFFEINE;CODEINE PHOSPHATE;HYOSCYAMINE SULFATE;METAMIZOLE;PARACETAMOL | N02AG |
| CAFFEINE;CODEINE;HYOSCINE HYDROBROMIDE;PARACETAMOL | N02AG |
| CAFFEINE;CODEINE;HYOSCINE;PARACETAMOL | N02AG |
| CAFFEINE;CODEINE;HYOSCYAMINE;METAMIZOLE;PARACETAMOL | N02AG |
| CALCIUM CARBONATE;KAOLIN, LIGHT;MORPHINE | N02AG |

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|---|---|
| CALCIUM CARBONATE;KAOLIN, LIGHT;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| CHLORDIAZEPOXIDE;DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CHLORDIAZEPOXIDE;DEXTROPROPOXYPHENE;DICYCLOVERINE;PARACETAMOL | N02AG |
| CHLORMEZANONE;CODEINE PHOSPHATE;PARACETAMOL;PIPOXOLAN HYDROCHLORIDE | N02AG |
| CHLORMEZANONE;CODEINE;PARACETAMOL;PIPOXOLAN | N02AG |
| CODEINE HYDROCHLORIDE;HYOSCINE METHONITRATE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE | N02AG |
| CODEINE HYDROCHLORIDE;HYOSCINE METHONITRATE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE;PHENOBARBITAL | N02AG |
| CODEINE PHOSPHATE HEMIHYDRATE;DROTAVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CODEINE PHOSPHATE HEMIHYDRATE;ETHENZAMIDE;TROSPIUM CHLORIDE | N02AG |
| CODEINE PHOSPHATE HEMIHYDRATE;FENPIVERINIUM BROMIDE;PARACETAMOL;PITOFENONE HYDROCHLORIDE | N02AG |
| CODEINE PHOSPHATE;DICYCLOVERINE HYDROCHLORIDE;POTASSIUM CHLORIDE;SODIUM CHLORIDE;SODIUM CITRATE | N02AG |
| CODEINE PHOSPHATE;DROFENINE HYDROCHLORIDE;PROPYPHENAZONE | N02AG |
| CODEINE PHOSPHATE;DROTAVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CODEINE PHOSPHATE;FENPIVERINIUM BROMIDE;PARACETAMOL;PITOFENONE HYDROCHLORIDE | N02AG |
| CODEINE PHOSPHATE;HYOSCINE BUTYLBROMIDE;METAMIZOLE SODIUM | N02AG |
| CODEINE PHOSPHATE;HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE | N02AG |
| CODEINE PHOSPHATE;METAMIZOLE SODIUM;SECBUTABARBITAL;VALETHAMATE BROMIDE | N02AG |
| CODEINE PHOSPHATE;METAMIZOLE SODIUM;TIEMONIUM METHYLSULPHATE | N02AG |
| CODEINE;DICYCLOVERINE;POTASSIUM;SODIUM CHLORIDE;SODIUM CITRATE | N02AG |
| CODEINE;DROFENINE;PROPYPHENAZONE | N02AG |
| CODEINE;DROTAVERINE;PARACETAMOL | N02AG |
| CODEINE;ETHENZAMIDE;METAMIZOLE SODIUM;MILVERINE HYDROCHLORIDE;PITOFENONE | N02AG |
| CODEINE;ETHENZAMIDE;METAMIZOLE;MILVERINE;PITOFENONE | N02AG |
| CODEINE;ETHENZAMIDE;TROSPIUM | N02AG |
| CODEINE;FENPIVERINIUM;PARACETAMOL;PITOFENONE | N02AG |
| CODEINE;HOMATROPINE;SPARTEINE | N02AG |

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|---|---|
| CODEINE;HOMATROPINE;SPARTEINE SULFATE | N02AG |
| CODEINE;HYOSCINE;METAMIZOLE | N02AG |
| CODEINE;HYOSCINE;MORPHINE;NOSCAPINE;PAPAVERINE | N02AG |
| CODEINE;HYOSCINE;MORPHINE;NOSCAPINE;PAPAVERINE;PHENOBARBITAL | N02AG |
| CODEINE;METAMIZOLE;SECBUTABARBITAL;VALETHAMATE | N02AG |
| CODEINE;METAMIZOLE;TIEMONIUM | N02AG |
| CODEINE;MORPHINE HYDROCHLORIDE;NOSCAPINE;PAPAVERINE HYDROCHLORIDE;THEBAINE | N02AG |
| CODEINE;MORPHINE;NOSCAPINE;PAPAVERINE;THEBAINE | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CALCIUM CARBONATE;KAOLIN, LIGHT;MORPHINE HYDROCHLORIDE | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| DEXTROPROPOXYPHENE NAPSILATE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| DEXTROPROPOXYPHENE;DICYCLOVERINE;PARACETAMOL | N02AG |
| CODEINE PHOSPHATE;DICYCLOVERINE HYDROCHLORIDE;POTASSIUM CHLORIDE;SODIUM CHLORIDE;SODIUM CITRATE | N02AG |
| DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL;TRAMADOL HYDROCHLORIDE | N02AG |
| DICYCLOVERINE;PARACETAMOL;TRAMADOL | N02AG |
| DICYCLOVERINE;PARACETAMOL;TRAMADOL HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;HYDROMORPHONE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;HYDROMORPHONE HYDROCHLORIDE | N02AG |
| DIMETHYL-3,3-DIPHENYL-1-METHYLALLYLAMINE HCL;KETOBEMIDONE | N02AG |
| DIMETHYL-3,3-DIPHENYL-1-METHYLALLYLAMINE HCL;KETOBEMIDONE HYDROCHLORIDE | N02AG |
| CODEINE;ETHENZAMIDE;METAMIZOLE SODIUM;MILVERINE HYDROCHLORIDE;PITOFENONE | N02AG |
| CODEINE PHOSPHATE;HYOSCINE BUTYLBROMIDE;METAMIZOLE SODIUM | N02AG |
| EPHEDRINE HYDROCHLORIDE;HYOSCYAMINE HYDROBROMIDE;OXYCODONE HYDROCHLORIDE | N02AG |
| EPHEDRINE;HYOSCYAMINE;OXYCODONE | N02AG |
| CODEINE PHOSPHATE;METAMIZOLE SODIUM;SECBUTABARBITAL;VALETHAMATE BROMIDE | N02AG |
| EPINEPHRINE;HYOSCINE HYDROBROMIDE;PAPAVER SOMNIFERUM LATEX;PROCAINE HYDROCHLORIDE | N02AG |
| EPINEPHRINE;HYOSCINE;PAPAVER SOMNIFERUM;PROCAINE | N02AG |
| CODEINE PHOSPHATE;DROFENINE HYDROCHLORIDE;PROPYPHENAZONE | N02AG |
| CAFFEINE;CODEINE;HYOSCINE HYDROBROMIDE;PARACETAMOL | N02AG |
| FENPIPRAMIDE HYDROCHLORIDE;METHADONE | N02AG |

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|---|---|
| FENPIPRAMIDE;METHADONE | N02AG |
| ATROPA BELLADONNA EXTRACT;CAFFEINE;CODEINE;PARACETAMOL | N02AG |
| ATROPINE SULFATE;MORPHINE SULFATE | N02AG |
| ATROPINE SULFATE;DIHYDROMORPHINE | N02AG |
| ATROPINE SULFATE;HYDROMORPHONE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE;SPARTEINE SULFATE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE SULFATE | N02AG |
| HYOSCINE HYDROBROMIDE;OPIUM ALKALOIDS TOTAL | N02AG |
| HYOSCINE HYDROBROMIDE;OXYCODONE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;OXYCODONE HYDROCHLORIDE;RACEPHEDRINE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;PAPAVERETUM | N02AG |
| HYOSCINE HYDROBROMIDE;PETHIDINE HYDROCHLORIDE;PROMETHAZINE HYDROCHLORIDE | N02AG |
| HYOSCINE;MORPHINE | N02AG |
| HYOSCINE;MORPHINE | N02AG |
| HYOSCINE;MORPHINE;SPARTEINE | N02AG |
| HYOSCINE;OPIUM ALKALOIDS TOTAL | N02AG |
| HYOSCINE;OXYCODONE | N02AG |
| HYOSCINE;OXYCODONE;RACEPHEDRINE | N02AG |
| HYOSCINE;PAPAVERETUM | N02AG |
| HYOSCINE;PETHIDINE;PROMETHAZINE | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| DIMETHYL-3,3-DIPHENYL-1-METHYLALLYLAMINE HCL;KETOBEMIDONE HYDROCHLORIDE | N02AG |
| DIMETHYL-3,3-DIPHENYL-1-METHYLALLYLAMINE HCL;KETOBEMIDONE HYDROCHLORIDE | N02AG |
| ATROPA BELLADONNA EXTRACT;CAFFEINE;PAPAVER SOMNIFERUM TINCTURE;PARACETAMOL | N02AG |
| FENPIPRAMIDE HYDROCHLORIDE;METHADONE | N02AG |
| ALVERINE CITRATE;OXYCODONE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE;MORPHINE SULFATE | N02AG |
| ATROPINE;MORPHINE SULFATE | N02AG |
| ATROPINE SULFATE;MORPHINE SULFATE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE SULFATE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE SULFATE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |

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|---|---|
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE HYDROCHLORIDE | N02AG |
| CODEINE PHOSPHATE HEMIHYDRATE;DROTAVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CODEINE PHOSPHATE;HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;HYDROMORPHONE HYDROCHLORIDE | N02AG |
| CODEINE;MORPHINE HYDROCHLORIDE;NOSCAPINE;PAPAVERINE HYDROCHLORIDE;THEBAINE | N02AG |
| CODEINE;MORPHINE HYDROCHLORIDE;NOSCAPINE;PAPAVERINE HYDROCHLORIDE;THEBAINE | N02AG |
| HYOSCINE;OPIUM ALKALOIDS TOTAL | N02AG |
| ATROPINE SULFATE;OPIUM ALKALOIDS TOTAL | N02AG |
| HYOSCINE;OPIUM ALKALOIDS TOTAL | N02AG |
| OPIOIDS IN COMBINATION WITH ANTISPASMODICS | N02AG |
| HYOSCINE HYDROBROMIDE;OPIUM ALKALOIDS TOTAL | N02AG |
| CODEINE PHOSPHATE HEMIHYDRATE;ETHENZAMIDE;TROSPIUM CHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;OXYCODONE HYDROCHLORIDE | N02AG |
| HYOSCINE;OXYCODONE | N02AG |
| ATROPINE;PETHIDINE HYDROCHLORIDE;PROMETHAZINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;HYDROMORPHONE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;PETHIDINE HYDROCHLORIDE;PROMETHAZINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;OPIUM ALKALOIDS TOTAL;PAPAVERINE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;PAPAVERETUM | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| ATROPINE SULFATE MONOHYDRATE;HYDROCOTARNINE HYDROCHLORIDE MONOHYDRATE;OXYCODONE HYDROCHLORIDE | N02AG |
| CHLORDIAZEPOXIDE;DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL;TRAMADOL HYDROCHLORIDE | N02AG |
| CHLORMEZANONE;CODEINE PHOSPHATE;PARACETAMOL;PIPOXOLAN HYDROCHLORIDE | N02AG |
| CHLORMEZANONE;CODEINE PHOSPHATE;PARACETAMOL;PIPOXOLAN HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;OXYCODONE HYDROCHLORIDE;RACEPHEDRINE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE | N02AG |
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE;SPARTEINE SULFATE | N02AG |

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|---|---|
| HYOSCINE HYDROBROMIDE;MORPHINE HYDROCHLORIDE | N02AG |
| 1-(P-AETHOXYPHENYL)-1-DIAETHYLAMINO-3-M;CODEINE PHOSPHATE;PROPYPHENAZONE | N02AG |
| ATROPINE SULFATE;OPIUM ALKALOIDS TOTAL;PAPAVERINE HYDROCHLORIDE | N02AG |
| CODEINE PHOSPHATE;DROFENINE HYDROCHLORIDE;PROPYPHENAZONE | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CODEINE PHOSPHATE;DROFENINE HYDROCHLORIDE;PROPYPHENAZONE | N02AG |
| CODEINE PHOSPHATE;DROFENINE HYDROCHLORIDE;PROPYPHENAZONE | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CODEINE HYDROCHLORIDE;HYOSCINE METHONITRATE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE | N02AG |
| CODEINE HYDROCHLORIDE;HYOSCINE METHONITRATE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE;PHENOBARBITAL | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CODEINE PHOSPHATE HEMIHYDRATE;FENPIVERINIUM BROMIDE;PARACETAMOL;PITOFENONE HYDROCHLORIDE | N02AG |
| CODEINE PHOSPHATE;FENPIVERINIUM BROMIDE;PARACETAMOL;PITOFENONE HYDROCHLORIDE | N02AG |
| DEXTROPROPOXYPHENE NAPSILATE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| ATROPINE SULFATE;CODEINE HYDROCHLORIDE;MORPHINE HYDROCHLORIDE;NOSCAPINE HYDROCHLORIDE;PAPAVERINE HYDROCHLORIDE | N02AG |
| ATROPINE SULFATE;MORPHINE;PAPAVERETUM;PAPAVERINE HYDROCHLORIDE;PROPYPHENAZONE | N02AG |
| DEXTROPROPOXYPHENE HYDROCHLORIDE;DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| ATROPA BELLADONNA EXTRACT;CAFFEINE;CODEINE PHOSPHATE HEMIHYDRATE;PARACETAMOL | N02AG |
| EPINEPHRINE;HYOSCINE HYDROBROMIDE;PAPAVER SOMNIFERUM LATEX;PROCAINE HYDROCHLORIDE | N02AG |
| AMINOPHENAZONE;CODEINE PHOSPHATE;PAPAVERINE HYDROCHLORIDE;PHENAZONE | N02AG |
| DICYCLOVERINE;PARACETAMOL;TRAMADOL HYDROCHLORIDE | N02AG |
| DICYCLOVERINE HYDROCHLORIDE;PARACETAMOL;TRAMADOL HYDROCHLORIDE | N02AG |
| CODEINE PHOSPHATE;DROTAVERINE HYDROCHLORIDE;PARACETAMOL | N02AG |
| CODEINE PHOSPHATE;METAMIZOLE SODIUM;TIEMONIUM METHYLSULPHATE | N02AG |

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| MORPHINE | N02AA |
| ETOMIDATE | N01AX |
| LORMETAZEPAM | N05CD |
| MIDAZOLAM | N03AE, N05CD |
| MIDAZOLAM HYDROCHLORIDE | N03AE, N05CD |
| MIDAZOLAM MALEATE | N05CD |