CLINICAL STUDY PROTOCOL

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STUDY CODE No.: CCD-050000-01

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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.

Acronym: **LISPAP (L**ess **I**nvasive **S**urfactant administration combined with nC**PAP)**

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VERSION HISTORY

Versi	Date	Change History
1.0	04th May 2016	*Original version*
2.0	30th November 2017	*Non-substantial changes/clarifications requested by the FDA (USA) in the IND Full Clinical Hold letter, dated 07/28/2016*
3.0	7th August 2019	*Change of the sample size from 300 neonates to 100*
4.0	8th September 2020	*Change sample size from 100 neonates to 150; change from multinational study to US only; change start of adverse event reporting from point of signed informed consent to start of procedure; update based on revised protocol template; addition of 40 Weeks PMA visit* *For detailed list of changes see Summary of Changes from Protocol v 3.0 to Protocol v 4.0*

PROTOCOL OUTLINE

Study Title	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
Sponsor	Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43122 Parma, Italy
Name of the Product	Poractant alfa (porcine derived surfactant, Curosurf®) administered through a specific thin catheter, CHF 6440 (LISACATH®), for less invasive surfactant administration (LISA)
Centers	Approximately 25 investigational sites will be involved in US
Indication	Treatment of Respiratory Distress Syndrome (RDS)
Study design	Open-label, multicenter, randomized, controlled study
Study phase	III B
Objectives	The main objective of this study is to evaluate the safety profile of the administration of porcine surfactant (poractant alfa, Curosurf®) through a less invasive method (LISA) using a thin catheter (CHF 6440) during non-invasive ventilation (NIV), compared to conventional surfactant administration during invasive ventilation and rapid extubation, in spontaneously breathing preterm neonates with clinical signs of respiratory distress syndrome (RDS). The short-term and mid-term safety will be assessed: adverse events and adverse drug reactions occurring during overall procedure for surfactant administration, neonatal pain assessment pre- and during surfactant administration, duration of surfactant administration, incidence of bronchopulmonary dysplasia (BPD) at 36 weeks post menstrual age (PMA) , major neonatal morbidities and vital signs. Moreover, short-term and mid-term efficacy profile will also be assessed mainly in terms of: reduced oxygen requirement and ventilatory support, need for invasive mechanical ventilation in the first 72 hours of life and throughout the study period, duration of invasive and non-invasive ventilation and need for additional surfactant doses.

Treatment duration	Spontaneously breathing subjects, stabilized with NIV, will be randomized starting from age 30 minutes up to 24 hours after birth to receive a single dose of poractant alfa 200 mg/kg either via brief insertion of a thin catheter (CHF 6440) into the trachea (LISA group) while NIV is maintained, or conventional intubation with endotracheal tube (ETT) during brief positive pressure ventilation. Randomization will occur as soon as a FiO_2 ≥0.30 is needed to maintain preductal oxygen saturation, determined by pulse oximetry (SpO_2), in the target range of 88–95%. A second surfactant dose (poractant alfa 100 mg/kg) will be administered using the same technique as the first dose administration, in cases of lack of efficacy, or clinical deterioration, as per randomization criteria (FiO_2 ≥0.30 to maintain SpO_2 in the target range of 88–95%) within approximately 12 hours from the previous dose. After the first and the second surfactant administration, neonates could receive a third surfactant dose (poractant alfa 100 mg/kg). If a third dose is administered, it will be provided through a standard technique. Neonates could be intubated (LISA group) or re-intubated (control group) for mechanical ventilation (MV) at neonatologist's discretion, if one or more of the below detailed conditions for MV are satisfied. <u>Criteria for intubation and mechanical ventilation:</u> Intubation for mechanical ventilation and further surfactant doses could happen if one or more of the following criteria are satisfied: • FiO_2 ≥0.45 to maintain preductal SpO_2 in the target range of 88-95% for at least 30 minutes, unless rapid clinical deterioration occurs; • 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); • Respiratory acidosis (pCO_2 >65 mmHg/8.5 kPa and pH <7.20 identified by either arterial or capillary blood gas monitoring). These criteria will be applied during the first 3 days of life (72 hours). <u>Criteria for termination of mechanical ventilation and extubation:</u> The decision to terminate mechanical ventilation will depend on the following criteria: • Clinical signs of respiratory improvement, e.g. presence of a good respiratory drive; • Ability to wean FiO_2, e.g. FiO_2 <0.30 to maintain SpO_2 in the

	target range of 88 and 95%; • Ability to wean ventilatory pressures, e.g. MAP ≤7 in conventional ventilation or MAP ≤8 in HFOV; • Normalization of blood gases' values, e.g. pCO_2 <65 mmHg and pH ≥7.20.
Test product dose/route/regimen	Poractant alfa 200 mg/kg or 100 mg/kg (for additional doses, if needed) is a sterile suspension in 3.0 mL glass vials with a total concentration of 80 mg/mL for intratracheal administration. This is a standard natural surfactant prepared from porcine lungs and containing almost exclusively polar lipids, in particular phosphatidylcholine (about 70% of the total phospholipid content), and about 1% of specific low molecular weight hydrophobic proteins SP-B and SP-C. LISA-delivery of poractant alfa to the lung will be done via brief insertion of a thin catheter (CHF 6440) through the mouth into the trachea while the subject is being supported with NIV (CPAP, NIPPV, BiPAP). The thin catheter will be provided by the Sponsor. CHF 6440 is a sterile, single-use catheter. It has a working length of 130.0 mm, presents a 1.7 mm Outer Diameter (corresponding to a 5 French OD), with a 1.1 mm Internal Diameter (corresponding to 3.5 French ID) through which the surfactant is delivered. The hole at the distal edge has a diameter of 0.8 mm. Printed depth markings on the outer surface of the shaft provide visual guide to the depth of device insertion during clinical procedure. The neonate will be placed supine with the head in the neutral position prior to the onset of the LISA procedure. Following direct laryngoscopy, the catheter will be introduced orally and inserted though the vocal cords into the trachea, the laryngoscope will be carefully removed while the position of the catheter is secured by the fingers of the neonatologist/investigator who will finally close the neonate's mouth. Surfactant will be slowly administered over 0.5-3 minutes with careful observation of the neonate's continuous spontaneous breathing. Before removing the LISA catheter, it should be fully cleared of surfactant with some additional air. After completion of surfactant administration, the ventilatory support may require transient adjustments. Airways suction should not be performed for 1 hour after surfactant instillation, unless signs of significant airway obstruction occur.
Reference product dose/route/regimen	As standard control treatment, neonates spontaneously breathing and stabilized on NIV will be intubated with an endotracheal tube to receive poractant alfa 200 mg/kg under invasive ventilation.

	Poractant alfa will be instilled according to the approved endotracheal method of administration, connecting the syringe filled with poractant alfa suspension to either: • a 5-French end-hole catheter inserted into the ETT or • the proximal end of the secondary lumen of a dual lumen ETT. After administration, manual ventilation could be continued, or the neonate could be connected to the ventilator, or the neonate could be immediately extubated and placed again on NIV. If connected to the ventilator, extubation should be performed within one hour after surfactant administration and then the neonate placed again on NIV.
Number of subjects	One hundred (100) randomized neonates to LISA treatment group, fifty (50) randomized neonates to conventional surfactant administration group (150 neonates in total)
Study population	Preterm neonates with early clinical signs of RDS
Inclusion/exclusion criteria	Inclusion Criteria Subjects must meet all the following inclusion criteria to be eligible for enrollment into the study: 1. Written informed consent obtained by parents/legal representative (according to local regulation) prior to or after birth; 2. Preterm neonates of either sex aged ≥30 minutes and <24 hours, spontaneously breathing and stabilized on NIV; 3. Gestational age of 25^{+0} weeks up to 28^{+6} completed weeks; enrollment will be restricted to subjects aged 27^{+0} weeks up to 28^{+6} GA weeks until safety evaluation of first 15 subjects is completed; 4. Clinical course consistent with RDS; 5. FiO_2 ≥0.30 to maintain preductal SpO_2 in the target range of 88–95%.
Inclusion/exclusion criteria	Exclusion Criteria The presence of any of the following will exclude a subject from the study enrollment: 1. Need for immediate endotracheal intubation for cardiopulmonary resuscitation or insufficient respiratory drive; 2. Use of nasal high frequency oscillatory ventilation (nHFOV)

	prior to study entry; 3. Use of surfactant prior to study entry and need for intratracheal administration of any other treatment (e.g. nitric oxide); 4. Known genetic or chromosomal disorders, major congenital anomalies (congenital heart diseases, myelomeningocele, etc); 5. Mothers with prolonged premature rupture of the membranes (>21 days duration) which could cause complications (in particular severe pulmonary hypoplasia due to oligohydramnios); 6. Presence of air leaks if identified and known prior to study entry; 7. Evidence of severe birth asphyxia (e.g. continued need for resuscitation at 10 minutes after birth, altered neurological state or neonatal encephalopathy); 8. Neonatal seizures prior to study entry; 9. Any condition that, in the opinion of the Investigator, would place the neonate at undue risk; 10. Participation in another clinical trial of any medicinal product, placebo, experimental medical device or biological substance conducted under the provisions of a protocol on the same therapeutic target; the participation in studies involving diagnostic devices or studies with treatments for different conditions than lung and respiratory function impairments may be permitted following an agreement with the sponsor. Non-interventional observational studies are allowed.
Most relevant allowed concomitant treatments	Any concomitant medication required for the normal care of preterm neonates will be permitted during the study. The use of sedative/analgesic medication, as well as the use of atropine, before/during surfactant administration, will be at investigator's discretion, according to each neonatal intensive care unit (NICU) standard practice. If premedication is used, the Investigator should define a protocol (with specification of drugs and dosages) before starting enrollment, which allows for a step-by-step management of pain and sedation for the endotracheal administration of surfactant. Each neonate will be managed according to the pre-defined protocol, and decision on which step of the protocol to apply should be based on neonate's needs. The same step-by-step protocol should be applied to both treatment arms. The protocol will be provided to the Sponsor. If caffeine is administered, it should be used in both treatment arms.

Most relevant forbidden concomitant treatments	• Surfactant treatment prior to randomization and study treatment administration • Intratracheal administration of any other treatment (e.g. nitric oxide) prior to randomization and study treatment administration • Other investigational drugs or investigational devices under the provisions of a protocol on the same therapeutic target. See exclusion criteria #10.
Safety variables	***During procedures 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 and judged related to the procedure • Number of AEs starting 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 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 1st attempt to insert the CHF 6440/ETT • Number of attempts to the first successful insertion • Number of device misallocation (i.e., esophageal insertion) • Number of maneuvers discontinued due to neonate's severe destabilization

	• Duration of surfactant administration (min) • Duration of the overall surfactant administration procedure (from the insertion of laryngoscope up to the removal of the catheter or ETT)
Safety variables	• Heart rate and respiratory rate (0, 5, 15, 30 min, 1 hour, 6 hours, and 12 hours after administration) • Systolic, diastolic and mean blood pressure (15 min, 30 min, 1 hour, 6 hours, and 12 hours after administration) • Premature Infant Pain Profile (PIPP) score (end of surfactant administration) ***During the study*** • AEs, including incidence of major neonatal complications of prematurity (listed in APPENDIX III), and adverse drug reactions (ADRs) • Blood pressure (SBP, DBP, MBP), at 24, 48, 72, 120 hours post-administration • Heart Rate (HR) and Respiratory Rate (RR) at 24, 48, 72, 120 hours post-administration, 28 Post-Natal Age (PNA), 36 weeks Post-Menstrual Age (PMA) and at discharge or 40 weeks PMA whichever comes first • Incidence of major neonatal morbidities at discharge home or 40 weeks PMA, whichever comes first • Incidence of BPD at 36 weeks PMA • Death/BPD incidence at 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 • Feeding and hearing status at discharge home or 40 weeks PMA, whichever comes first • Weight, occipital-frontal circumference (OFC) and length at discharge home or 40 weeks PMA • Neonates needing invasive 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*** *(This stand-alone assessment will be analyzed and reported separately from the main phase)*

	• 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, DPB, MBP, HR, RR)
	  • Growth assessment (Weight, OFC and length).

Efficacy variables	• Percentage of neonates needing invasive mechanical ventilation in the first 72 hours of life, at 28 days PNA and within 36 weeks PMA • 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 of the initial surfactant administration period, in the first 72 hours of life, 28 days PNA and 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 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 36 weeks PMA for neonates still receiving any form of respiratory support • Percentage of neonates needing additional surfactant (Curosurf®) doses and number of surfactant doses • Duration of oxygen supplementation (days), any non-invasive ventilation during the study (days) • Blood gas analysis, specifically acid-base balance parameters (i.e. pH, pCO_2, pO_2, HCO_3, BE, lactate) pre-surfactant administration (when applicable), at 1 hour, 6 hours, 24, 48, 72 hours after study treatment

Safety Monitoring	An Independent Safety Monitoring Board (ISMB) will provide ongoing trial review for the monitoring of subjects' safety. An ISMB meeting will be scheduled after the first 15 neonates have been enrolled. If no safety concerns are raised, enrollment will continue and will be extended to newborns with GA at birth between 25^{+0} weeks up to 28^{+6}. Before obtaining a favorable opinion from the ISMB, only newborns with GA from 27^{+0} to 28^{+6} weeks will be enrolled. Further ISMB meetings will be scheduled after the first 60, 105 and 150 subjects, respectively. *Ad-hoc* ISMB meetings can be scheduled, if needed, in case of unexpected safety issues.
Sample size calculation	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 tube and brief invasive ventilation. A total number of one hundred-fifty (150) neonates is deemed appropriate for the study aim. Neonates will be randomized with a ratio 2:1 to the LISA technique arm (i.e. 100 neonates) and to the conventional technique (i.e. 50 neonates).
Statistical methods	**Safety variables** • Number and percent of neonates reporting AEs started during procedure for surfactant administration as well as AEs started during the procedure and judged related to the procedure will be summarized by treatment group. For LISA group, any AE assessed as related to CHF 6440 medical device will be considered procedure-related. These events will be also summarized by treatment group based on action required, if any (i.e. supplementary oxygen or transient increase in FiO_2, manual positive pressure ventilation, endotracheal intubation, administration of crystalloids, cardiac massage or administration of adrenaline). The duration of endotracheal intubation (invasive ventilation) and manual positive pressure ventilation will be summarized as well. A subgroup analysis of surfactant- and procedure- related AEs will be performed based on the use of sedation and/or analgesia (Yes/No). • Incidence of all the AEs (including neonatal complications of prematurity), related AEs (ADRs), serious AEs (SAEs) and AEs leading to death will be summarized by treatment group both in terms of frequency of neonates with at least one AE and in terms of frequency of AEs (number of events). All the aforementioned

	categories of AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). • Vital signs parameters (SBP, DBP, MBP, RR and HR) will be summarized by treatment group using descriptive statistics. Change from baseline (pre-procedure) will be also presented. • PIPP score will be summarized by treatment group by means of descriptive statistics. • Number of 1st failed attempt to insert CHF 6440/ETT will be summarized by treatment group. Percentage of neonates with 1st failed attempt will be compared between group using the Cochran-Mantel-Haenszel test (CMH) test adjusted for gestational age group. The CMH adjusted difference with its 95% CI will be presented.
Statistical methods	• Number of attempts to the first successful insertion will be summarized by treatment group by means of descriptive statistics. • Number of device misallocation (i.e., esophageal intubation) will be summarized by treatment group by means of descriptive statistics. • Number of maneuvers discontinued due to neonate's severe destabilization will be summarized by treatment group by means of descriptive statistics. • Duration of surfactant administration (min) and overall procedure for surfactant administration will be compared between treatment groups by using the Mann-Whitney U-test. • Death/BPD incidence at 36 weeks PMA will be compared by treatment by means of CMH test adjusted for GA group and related 95% CI will be provided. • The incidence of BPD at 36 weeks PMA will be compared by treatment as for Death/BPD incidence. • The incidence of oxygen use (alone and / or during any kind of MV) at Day 28 PNA will be compared by treatment as for Death/BPD incidence. • The mortality at 36 weeks PMA and at Day 28 PNA will be compared by treatment as for Death/BPD incidence. • Frequency of neonates with major neonatal morbidities at discharge/40 weeks PMA (whichever comes first) will be summarized by treatment group. • Feeding and hearing status at discharge or 40 weeks PMA (whichever comes first) will be summarized by treatment group by frequency distributions.

	• Weight, OFC and length at discharge home or 40 weeks PMA will be summarized by treatment group by descriptive statistics. • Percentage of 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 respiratory medications at discharge home or 40 weeks PMA will be summarized by treatment group by frequency distribution • Bayley Scales of Infant Development (BSID) (cognitive and language scores) will be summarized using descriptive statistics by treatment group and BSID version (III or IV). • Vital signs and all other variables collected through the questionnaire (i.e., anthropometric measures, cerebral palsy, seizures, feeding method, functional disability and respiratory morbidity) will be summarized by treatment group by frequency distribution or descriptive statistics as appropriate.
Statistical methods	**Efficacy variables** • Percentage of neonates needing invasive mechanical ventilation in the first 72 hours of life, in the first 28 days PNA and within 36 weeks PMA will be compared between groups using the Cochran-Mantel-Haenszel (CMH) test adjusted for gestational age group. The CMH adjusted difference with its 95% confidence interval (CI) will be presented. Additional analysis will be performed to explore the impact of use of sedation and/or analgesia. • Duration of invasive mechanical ventilation in the first 72 hours of life, in the first 28 days PNA and within 36 weeks PMA will be compared between treatment groups by using the Mann-Whitney U-test. • Percentage of neonates needing any intubation procedure, outside the initial surfactant administration period, in the first 72 hours, in the first 28 days PNA and within 36 weeks PMA will be compared between treatment as need for invasive mechanical ventilation. • SpO_2 will be analysed using 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. 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 in the first 120

	hours post-administration will be presented by treatment group. • SpO_2 will be summarized by treatments on neonates still receiving respiratory support at 28±2 PNA, and at 36 weeks PMA using descriptive statistics. • FiO_2 will be analyzed as SpO_2. • SpO_2/FiO_2 will be analyzed as SpO_2. • Percentage of subjects requiring at least one additional surfactant dose will be compared by treatment group by means of a Fisher's exact test at 5% significance interval. Odds ratio (OR) and related exact 95% CI will be also provided. Subjects with pulmonary hemorrhage will be excluded from this summary.
Statistical methods	• Number of additional surfactant doses will be summarized by treatment group by means of descriptive statistics. • Duration of stand-alone oxygen supplementation (days) and non-invasive ventilation (days) will be compared between treatment groups by using the Mann- Whitney U-test. • Acid-base balance parameters (i.e. pH, pCO_2, pO_2, HCO_3, BE, lactate) will be summarized by treatments group as absolute and change from pre-treatment values by means of descriptive statistics.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
ATC	Anatomical Therapeutic Chemical classification
BiPAP	Bi-level Positive Airway Pressure
BPD	Bronchopulmonary Dysplasia
BSID	Bayley Scales of Infant Development
BE	Base Excess
BW	Birth Weight
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical
CMH	Cochran-Mantel-Haenszel test
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CTS	Clinical Trial Supply
DBP	Diastolic Blood Pressure
DPPC	Dipalmitoylphosphatidylcholine
eCRF	electronic Case Report Form
EC	Ethics Committee
ETT	Endotracheal Tube
FiO2	Fraction of inspired Oxygen
FIP	Focal Intestinal Perforation
GA	Gestational Age
GCP	Good Clinical Practice
HCO_{3-}	Bicarbonates
HFOV	High Frequency Oscillatory Ventilation
HR	Heart Rate
ICH	International Conference on Harmonization
IFU	Instructions For Use
IIT	Investigator Initiated Trial
IRB	Institutional Review Board
IND	Investigational New Drug Application
IRT	Interactive Response Technology
ISMB	Independent Safety Monitoring Board
ITT	Intention to Treat
IVH	Intraventricular Hemorrhage
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LISA	Less Invasive Surfactant Administration
LSMs	Least Square Means
MAP	Mean Airway Pressure
MBP	Mean Blood Pressure
MDI	Mental Development Index

MDR	Medical Device Report
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MV	Mechanical Ventilation
nCPAP	Nasal Continuous Positive Airway Pressure
NDA	New Drug Application
nHFOV	Nasal High Frequency Oscillatory Ventilation
NICHD	National Institute of Child Health and Human
NICU	Neonatal Intensive Care Unit
NIPPV	Nasal Intermittent Positive Pressure Ventilation
NIV	Non-Invasive Ventilation
OFC	Occipital-Frontal Circumference
OR	Odds ratio
pO_2	Partial Pressure of Oxygen
pCO_2	Partial Pressure of Carbon Dioxide
PDA	Patent Ductus Arteriosus
PEEP	Positive End-Expiratory Pressure
PIE	Pulmonary Interstitial Emphysema
PIP	Peak Inspiratory Pressure
PIPP	Premature Infant Pain Profile
PMA	Post-Menstrual Age
PNA	Post-Natal Age
PPV	Positive Pressure Ventilation
PVL	Periventricular Leukomalacia
RCT	Randomized Clinical Trial
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
RR	Respiratory rate
RSS	Respiratory Severity Score
SAE	Serious Adverse Event
SaO_2	Oxygen Saturation
SAP	Statistical Analysis Plan
SP-B	Surfactant Protein B
SP-C	Surfactant Protein C
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
SpO_2	Preductal Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization

CONTENT

APPENDICES

1. INTRODUCTION

1.1 Background Information and Study Rationale

Respiratory distress syndrome (RDS) is the most common respiratory disease of premature neonates and its incidence is directly proportional to the degree of prematurity. The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network showed a 93% incidence of RDS in a cohort of 9575 extreme premature neonates with gestational age (GA) of 28 weeks or below, born between 2003 and 2007 [1]. In fact, despite a constant improvement of neonatal care, RDS still represents one of the major causes of mortality in preterm neonates, as confirmed in a recent US review (64 deaths per 1000 live births) [2].

The clinical features of RDS start appearing soon after birth. RDS is characterized by tachypnea (rapid breathing), expiratory grunting, subcostal and intercostal retractions, cyanosis, nasal flaring, apnea and/or hypothermia in extremely immature neonates. In the pre-surfactant era, the disease led rapidly to progressive respiratory failure in the first 2-3 days of life [3] and, in the most severe cases, to the death of premature babies. Moreover, RDS can be followed by respiratory complications, such as bronchopulmonary dysplasia (BPD), most commonly in those neonates who required ventilatory support and/or oxygen therapy for RDS treatment [4].

The pathophysiology of RDS has been correlated to lung immaturity and surfactant deficiency. Surfactant, a macro-aggregate composed of highly organized lipids and specific proteins, is produced by type 2 cells in the alveoli and placed in the air liquid interface. It mainly reduces surface tension and prevents alveolar collapse, particularly at end-expiration, so that adequate gas exchange is maintained throughout the ventilatory cycle [5].

Surfactant therapy has become the standard of care in management of preterm neonates with RDS since it was able to reduce mortality and the incidence of pulmonary air leaks such as pneumothorax by about 50% [6,7].

The current American [8] and European [3] approach for treatment of neonatal RDS recommends a policy of early initiation of non-invasive ventilation, like Continuous Positive Airway Pressure (CPAP), immediately after birth and early selective surfactant administration. This strong recommendation derives from different studies that demonstrated the role of CPAP as first-step stabilization of preterm neonates with RDS in combination with early rescue surfactant therapy [9,10]. A new technique to deliver surfactant intratracheally in spontaneously-breathing neonates by using a thin catheter in combination with CPAP has been described in the literature in the last years [11].The development of this technique, most frequently called Less Invasive Surfactant Administration (LISA), has been based on the evidence from several studies that avoiding endotracheal MV and stabilizing very premature neonates on early CPAP in the delivery room may be one way of reducing BPD [12]. Indeed, even a short period of positive pressure ventilation could be harmful for the immature lung of

preterm neonates. Furthermore, LISA could allow administration of surfactant without the disadvantage of withholding non-invasive respiratory support [11].

A meta-analysis of seven randomized clinical trials (RCTs) comprising 3289 subjects confirmed that avoiding endotracheal MV reduces the combined outcome of death or BPD in preterm neonates <30 weeks' GA [12]. The early studies analyzed in the meta-analysis compared non- invasive respiratory support (e.g., CPAP) with standard intubation and rapid extubation after surfactant instillation, while more recent studies compared the LISA method with standard endotracheal intubation and surfactant administration. In spite of the differences of the study protocols and designs, the overall strategy of avoiding MV consistently led to a reduction in the incidence of death or BPD in all trials.

In Germany a first LISA technique with a soft, small diameter tube (gastric catheter) inserted through the nose into the pharynx with the use of Magill forceps has been described [13,14]. A second procedure, the Hobart method [15,16], has been proposed by an Australian group who uses a slightly stiffer vascular catheter, introduced through the mouth into the pharynx without the use of Magill forceps. In both procedures, the catheter is secured by the fingers of the neonatologist and surfactant slowly administered without withholding CPAP support. After surfactant instillation, the catheter is immediately removed. Maintaining the neonates on CPAP throughout the whole procedure seems helpful in reducing the incidence of desaturations.

The LISA method has only been evaluated in Investigator Initiated Trials (IITs) that showed promising results in terms of neonatal respiratory morbidity and seem to represent a significant improvement in the management of RDS [17,18].

The LISA method for porcine surfactant administration (poractant alfa, Curosurf®, Chiesi Farmaceutici S.p.A.) has been approved and added to the current authorized methods/techniques by European Authorities and other countries outside of Europe; moreover, the specific thin catheter (CHF 6440), developed by Chiesi Farmaceutici S.p.A. (Parma, Italy) for poractant alfa delivery through LISA technique and used in the present study, has been approved (CE mark) in Europe as well as other countries.

This Phase IIIb explorative study is mainly aimed at investigating the safety and efficacy profiles of porcine surfactant (poractant alfa, Curosurf®, Chiesi Farmaceutici S.p.A.) administered through LISA technique during a non-invasive respiratory support or conventional intubation with brief ventilation.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments), the current ICH E6 Good Clinical Practices and all other applicable laws and regulations.

1.2 Risk/benefit assessment

The application of LISA technique allows administration of surfactant without interrupting the non-invasive respiratory support, so avoiding the need for intubation and administration of

invasive positive pressure ventilation even for a short period.
The LISA technique, as well as other methods for less invasive surfactant administration through thin catheter, have been evaluated in several IIT and compared with conventional surfactant administration through endotracheal tube (including application of an intubation, surfactant administration and rapid extubation procedure). Even with limitations related to the heterogeneity and quality of the studies, recent meta-analysis showed that benefits associated with less invasive surfactant methods include reduced need for MV and reduced rate of mortality and BPD [17,18].
Moreover, some recent studies have also suggested a reduction in the incidence of Retinopathy of prematurity (ROP) and Intraventricular hemorrhage (IVH) in neonates receiving surfactant through LISA technique [19,20].
Some transient adverse events, including oxygen desaturation, apnea, bradycardia, coughing, chocking, sneezing, and surfactant reflux, have been observed more frequently during LISA procedure compared to conventional administration [17,21,22]. These events are usually mild and easily managed. In a recent large cohort study, an increased risk of focal intestinal perforation (FIP) (10% vs 7.4%) was observed in the subgroups of neonates <26 weeks GA [19]. The authors suggest that other factors, beside LISA, could contribute to the pathogenesis of FIP in this population of highly vulnerable neonates, including: early exposure to maximum CPAP levels, modulators of mucosal integrity (devices, bacterial colonization, nutrition, drugs), delayed meconium passage, and frequency of episodes of relevant desaturation (leading to temporary hypoxia of the gut).
Considering the above reported information, the safety profile of the treatment, the measures in place to ensure the patients' safety and the expected scientific value, the overall risk/benefit assessment can be considered acceptable for the proposed trial.

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

The main objective of this study is to evaluate the safety profile of the administration of porcine surfactant (poractant alfa, Curosurf®) through a less invasive method (LISA) using a thin catheter (CHF 6440) during non-invasive ventilation (NIV) (CPAP, NIPPV, BiPAP), 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). The short-term and mid-term safety will be assessed: adverse events and adverse drug reactions occurring during overall procedure for surfactant administration, neonatal pain assessment pre- and during surfactant administration, duration of surfactant administration, incidence of BPD at 36 weeks post menstrual age (PMA), major neonatal morbidities and vital signs.

2.2 Secondary Objective(s)

Moreover, short-term and mid-term efficacy profile will also be assessed mainly in terms of: reduced oxygen requirement and ventilatory support, need for invasive mechanical ventilation in the first 72 hours of life and throughout the study period, duration of invasive and non-

invasive ventilation and need for additional surfactant doses.

3. STUDY DESIGN

This is an open-label, multicenter, randomized and controlled study. Approximately 25 investigational sites will be involved in US. Neonates will be evaluated according to the selection criteria and then randomized to surfactant treatment via LISA or standard administration procedure (Table 1). 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 ISMB is performed for the first 15 neonates. Provided no safety concerns are raised, the enrollment will then be extended to the whole population (i.e. 25^{+0} weeks up to 28^{+6} completed weeks).

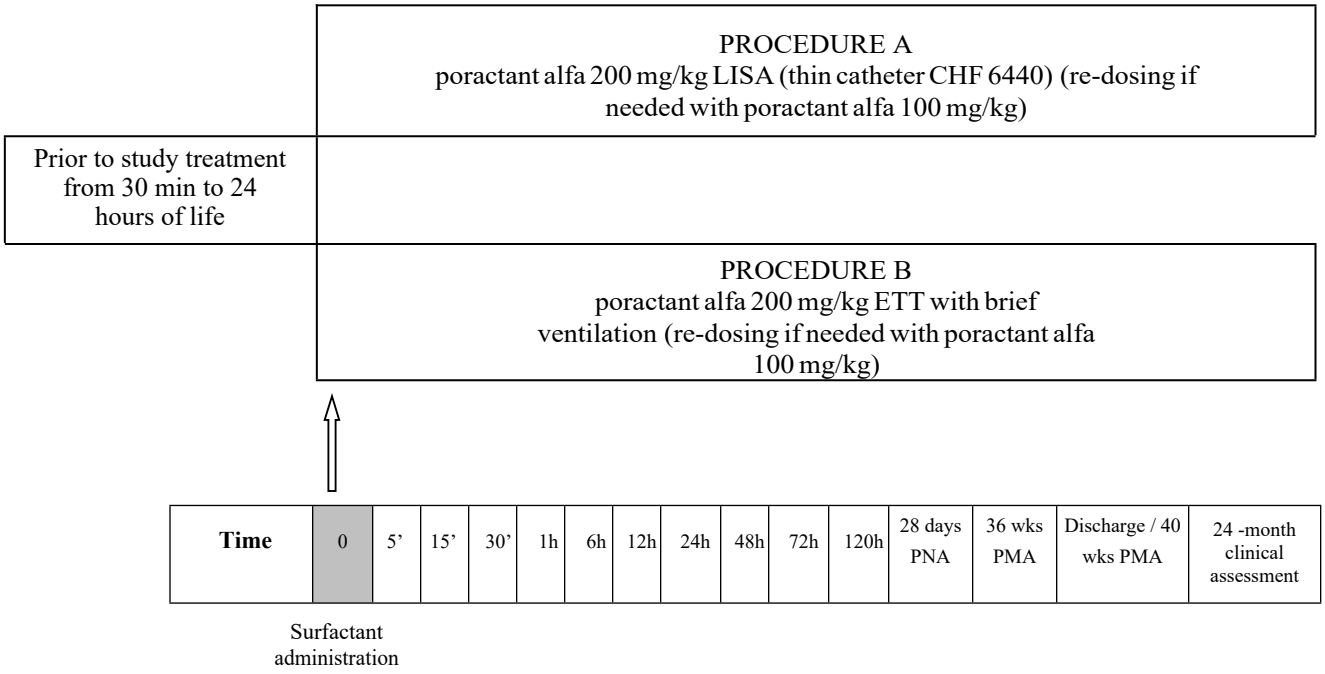
Enrolled neonates will be evaluated:

- until discharge,
- until 40 weeks 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 stand-alone 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



End of the trial

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 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).

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

The study population consists of premature neonates with early clinical signs of RDS, spontaneously breathing and stabilized with NIV (CPAP, NIPPV, BiPAP). One hundred and fifty (150) subjects who meet all the inclusion and none of the exclusion criteria are expected to be randomized in the study. No limitation by ethnic origin or social status will be used. RDS is defined in this study population by the presence of respiratory symptoms and signs, associated to an increased inspired oxygen requirement, from 30 minutes up to the first 24 hours of life.

4.2 Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for enrolment into the study:

1. Written informed consent obtained by parents/legal representative (according to local regulation) prior to or after birth;
2. Preterm neonates of either sex aged ≥30 minutes and <24 hours, spontaneously breathing and stabilized on NIV;
3. Gestational age of 25^{+0} weeks up to 28^{+6} completed weeks; enrollment will be restricted to subjects aged 27^{+0} weeks up to 28^{+6} GA weeks until safety evaluation of first 15 subjects is completed;
4. Clinical course consistent with RDS;
5. Fraction of inspired Oxygen (FiO_2) ≥0.30 to maintain preductal SpO_2 in the target range of 88–95%.

4.3 Exclusion Criteria

The presence of any of the following criteria will exclude a subject from study enrollment:

1. Need for immediate endotracheal intubation for cardiopulmonary resuscitation or insufficient respiratory drive;

2. Use of nasal high frequency oscillatory ventilation (nHFOV) prior to study entry;
3. Use of surfactant prior to study entry and need for intratracheal administration of any other treatment (e.g. nitric oxide);
4. Known genetic or chromosomal disorders, major congenital anomalies (congenital heart diseases, myelomeningocele, etc.);
5. Mothers with prolonged premature rupture of the membranes (> 21 days duration) which could cause complications (in particular, severe pulmonary hypoplasia due to oligohydramnios);
6. Presence of air leaks if identified and known prior to study entry;
7. Evidence of severe birth asphyxia (e.g. continued need for resuscitation at 10 minutes after birth, altered neurological state or neonatal encephalopathy);
8. Neonatal seizures prior to study entry;
9. Any condition that, in the opinion of the Investigator, would place the neonate at undue risk;
10. Participation in another clinical trial of any medicinal product, placebo, experimental medical device or biological substance conducted under the provisions of a protocol on the same therapeutic target; the participation in studies involving diagnostic devices or studies with treatments for different conditions than lung and respiratory function impairments may be permitted following an agreement with the sponsor. Non-interventional observational studies are allowed.

4.4 Subject Withdrawals

Parents/legal representative have the right to withdraw the subject from the study at any time for any reason.

The Investigator also has the right to withdraw the subjects from the study in the event of:

- An adverse event which is considered intolerable by the Investigator prior to surfactant administration.
- An abnormal laboratory test result that the Investigator considers clinically significant and warranting the withdrawal of the subject prior to surfactant administration.
- A concomitant clinical condition/disorder/anomaly that necessitates pharmacological treatment with a drug which interacts in any way with the study treatment prior to surfactant administration.
- Hypersensitivity to the active substance or to any of the excipients with regards to the second and third possible treatments with poractant alfa (if needed).
- The development of any exclusion criterion prior to surfactant administration.

Detection of COVID-19 infection at the enrollment or during the study does not automatically lead to withdrawal of the subject. It will be up to the investigator's judgement to withdraw

the subject from the study if he/she deems that remaining in the study will place the subject and/or the clinical site at undue risk by continuing their participation. The investigator/site staff must take all necessary precautions to minimize and avoid the risk of transmission and exposure to study subjects and site staff, according to local guidelines.

The Investigator is responsible for the optimal individual treatment for the subject. The Investigator must complete the "Study Termination" page of the electronic case report form (eCRF) explaining the main reason for withdrawal.

5. CONCOMITANT MEDICATIONS

Subjects may be treated with other medications as needed in the critical care situation. The treating physician will manage neonates as he/she deems to be in their best interest.

Investigators are required to record all these medications in the eCRF with the only exception of the following drugs, when they are administered for prophylaxis only and not relative to any adverse event:

- Multivitamin or single vitamins (except for vitamin K and vitamin A which must be recorded);
- Probiotics and lactoferrin;
- Nystatin;
- Iron supplements;
- Folic acid;
- Calcium and phosphorus;
- Symeticon;
- Glycerine suppository.

5.1 Permitted concomitant Medications

Any concomitant medication required for the normal care of preterm neonates will be permitted during the study and recorded in the eCRF.

The use of sedative/analgesic medication, as well as the use of atropine, before / during surfactant administration, will be at investigator's discretion and according to each neonatal intensive care unit (NICU) internal standard practice. If premedication is used, the Investigator should define a protocol (with specification of drugs and dosages) before starting enrollment, which allows for a step-by-step management of pain and sedation for the endotracheal administration of surfactant. Each neonate will be managed according to the pre-defined protocol, and decision on which step of the protocol to apply should be based on neonate's needs. The same step-by-step protocol should be applied to both treatment arms. The protocol will be provided to the Sponsor.

If caffeine is administered, it should be used in both treatment arms.

5.2 Non-permitted previous and concomitant Medications

1. Surfactant treatment prior to randomization and study treatment administration;
2. Intratracheal administration of any other treatment (e.g. nitric oxide) prior to randomization and study treatment administration;
3. Other investigational drugs or investigational devices under the provisions of a protocol on the same therapeutic target. See exclusion criteria #10.

6. TREATMENT(S)

6.1 Appearance and Content

Poractant alfa (Curosurf®) is a standard natural surfactant treatment prepared from porcine lungs for intratracheal administration and containing almost exclusively polar lipids, in particular phosphatidylcholine (about 70% of the total phospholipid content), and about 1% of specific low molecular weight hydrophobic proteins SP-B and SP-C with a total concentration of 80 mg/ml. The drug product is filled in sealed 3.0 ml glass vials

Chiesi Farmaceutici S.p.A. will supply the study medication and also provide the Pharmacist/Investigator with appropriate certificates of analytical conformity.

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

Poractant alfa (Curosurf®) will be administered as 200 mg/kg for the first dose and 100 mg/kg for additional doses.

6.2.2 Dosage

Poractant alfa (Curosurf®) 2.5 ml/kg (200 mg/kg) sterile suspension in one single intratracheal administration from 30 minutes after birth up to 24 hours after birth.

Poractant alfa 1.25 ml/kg (100 mg/kg) will be used for further re-dosing in both arms (see section 6.2.3.6) up to two repeated doses.

6.2.3 Administration

6.2.3.1 Preparation for surfactant administration

Poractant alfa should be administered by, or under the supervision of, clinicians experienced in intubation, ventilator management, and general care of premature neonates. The neonate should be stabilized before surfactant administration.

Since poractant alfa suspension is refrigerated, before use each vial must be warmed up slowly to room temperature e.g. by placing it in an incubator for about 1 hour or keeping it in hands for 5-10 minutes and gently turned upside down, without shaking, avoiding the formation of foam. Artificial warming methods should not be used.

The entire contents of the vial of poractant alfa suspension should be slowly withdrawn into a 3 or 5mL plastic syringe through a large-gauge needle and the excess poractant alfa discarded. The syringe filled with poractant alfa suspension will be connected directly to LISA thin catheter (CHF 6440) in LISA cohort or attached to a 5-French catheter end-hole inserted into the endotracheal tube (ETT) or to the proximal end of the secondary lumen of a dual lumen ETT in the standard cohort, according to the approved delivery method.

Preparation should also include appropriate equipment such as an oxygen source, appropriately sized bags, face masks, stylet, laryngoscope and suction.

Neonatal team should include at least two people present during the maneuver: one performing the procedure and one additional person who can assist.

Before starting the procedure and throughout it, neonates must have cardiorespiratory monitoring: oxygen saturation and heart rate continuously through pulse oximetry, blood pressure measurement either continuously in presence of an arterial catheter or intermittently if no arterial line is in place.

6.2.3.2 Sedation and analgesia

The use of sedative/analgesic medication, as well as the use of atropine, before/during surfactant administration, will be at investigator's discretion and according to each neonatal intensive care unit (NICU) internal standard.

If premedication is used, the Investigator should define a protocol (with specification of drugs and dosages) before starting enrollment, which allows for a step-by-step management of pain and sedation for the endotracheal administration of surfactant. Each neonate will be managed according to the pre-defined protocol, and decision on which step of the protocol to apply should be based on neonate's needs. The same step-by-step protocol should be applied to both treatment arms. The protocol will be provided to the Sponsor.

A first step could be attempted with a non-pharmacological analgesic technique (sucrose, glucose, holding, swaddling and methods of sensorial saturation).

A pharmacological intervention could be given following a progression in the use of sedatives/analgesics, based on neonate's need. As a guidance, examples of pharmacological interventions which can be used (either alone or in combination) are the following:

- Vagolytic agents (e.g. atropine).
- Sedative/analgesics medications with rapid onset and short duration of action (e.g. fentanyl).

The use of sedation/analgesia and other medications will be carefully recorded along with related information (e.g. date and time of administration, dosage and route) in the relevant section of the eCRF.

6.2.3.3 LISA procedure

LISA-delivery of poractant alfa to the lung will be done via brief insertion of the thin catheter

(CHF 6440) through the mouth into the trachea, while the subject is being supported with NIV. The thin catheter will be provided by the Sponsor (Figure 1: CHF 6440).

CHF 6440 is a sterile, single-use catheter. It has a working length of 130.0 mm, presents a 1.7 mm Outer Diameter (corresponding to a 5 French OD), with a 1.1 mm Internal Diameter (corresponding to 3.5 French ID) through which the surfactant is delivered. The hole at the distal edge has a diameter of 0.8 mm. It includes a standard polycarbonate mono Luer connection at the proximal end. The Luer is bonded to a reinforced shaft, with the shaft consisting of composite assembly of an overcoat / jacket, a braided woven stainless steel, and a Pebax liner. The Pebax leading tip of the device presents a rounded and soft distal edge to provide an atraumatic lead for the catheter during insertion via mouth. Printed depth markings on the outer surface of the shaft provide visual guide to the depth of device insertion during clinical procedure. Do not manipulate, kink and bend the catheter prior to its insertion. Check the presence of the ring markings prior to the insertion of this catheter.

The neonate will be placed supine with the head in neutral position before the onset of the procedure. The procedure should be performed with the NIV remaining in situ during surfactant administration. Poractant alfa should be administered by, or under the supervision of clinicians experienced in intubation of premature neonates. The investigators' site staff will be trained during the Investigators' meeting and site initiation visits in performing the LISA technique through a specific informative video as well as the provision of a specific mannequin**Error! Hyperlink reference not valid.** designed to facilitate the training of healthcare professionals in the initiation of proper care and resuscitation of preterm infants.

Following direct laryngoscopy, the catheter will be introduced orally and inserted though the vocal cords into the trachea to the desired depth of 1-2 cm, the laryngoscope will be carefully removed while the catheter is secured by the fingers of the neonatologist/investigator, who will finally close the neonate's mouth. The correct position of the catheter into the trachea will be confirmed by the visualization of tip depth markings and by the tip- to-lip measurement. The thin catheter presents three different ring markings close to the tip, equal to 1, 2 and 3 cm (Figure 1C) and helpful to address the depth of insertion beyond the vocal cords. Moreover, the catheter presents markings going from 5 to 9 cm for the tip-to-lip measurement, which represents the standard method to estimate the correct position also of the ETT [23].

After having confirmed the correct position of the catheter into the trachea, the syringe filled with poractant alfa suspension will be connected to the Luer of the catheter and poractant alfa will be instilled over 0.5-3 minutes with careful observation of the neonate's continuous spontaneous breathing. Once the surfactant is administered, the catheter will be removed. Before removing the LISA catheter, it should be fully cleared of surfactant with some additional air. After completion of surfactant administration, ventilatory support may require transient adjustments. Airways suction should not be performed for 1 hour after surfactant instillation, unless signs of significant airway obstruction occur.

If on the first attempt the catheterization of the trachea is not possible within 30 seconds, the laryngoscope should be removed and if required neonate's recovery allowed. Then a second

attempt should be performed for a total number of 3 attempts.

Details of the procedure as well as neonate's vital signs and any occurring adverse event will be recorded according to the time points of the protocol by the team member assisting or observing the procedure.

Figure 1: CHF 6440

Figure 1A
CHF 6440 Full View

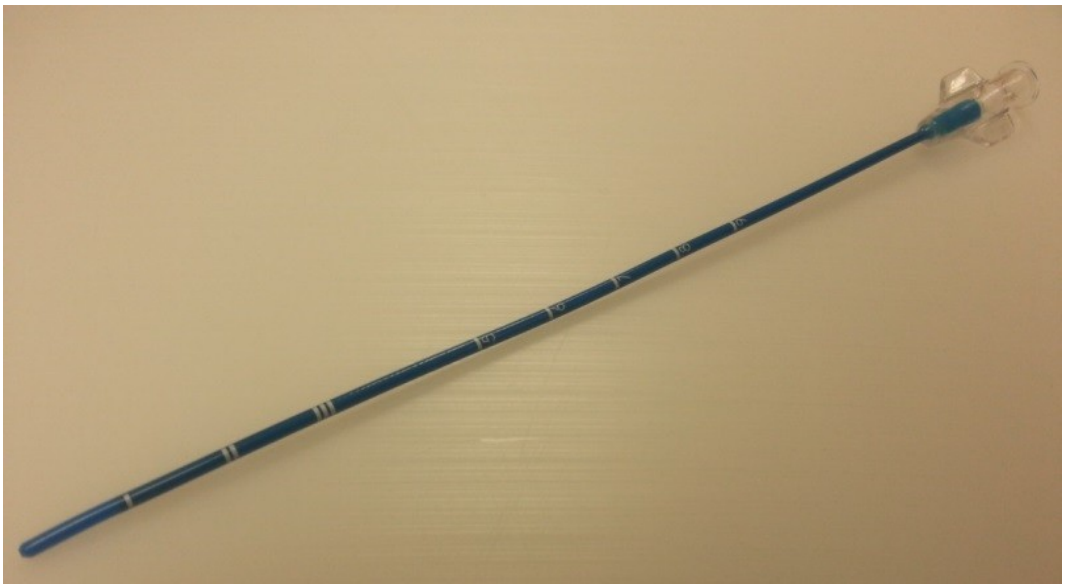
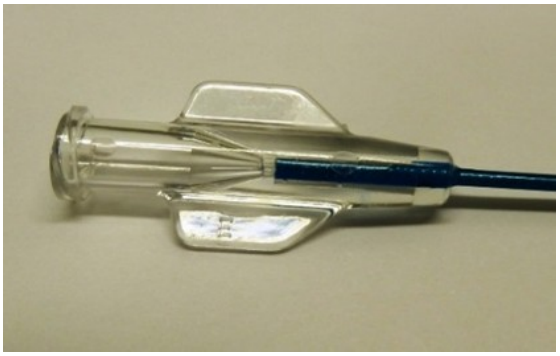


Figure 1B
Close-up on CHF 6440 Components

a) Standard Luer



b) Rounded and Soft Tip

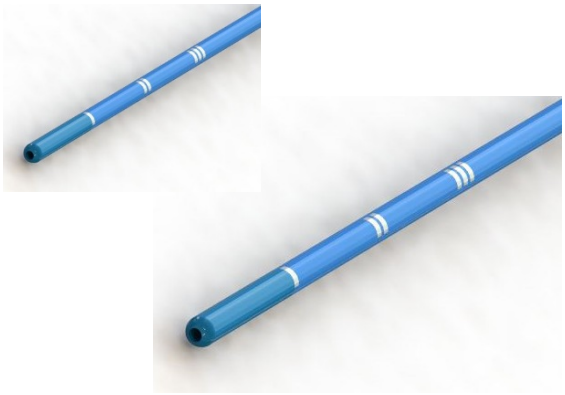


Figure 1C

Close-up of Markings Present on CHF 6440 Shaft

6.2.3.4 Conventional Intubation, surfactant administration and brief ventilation

As standard control treatment, neonates spontaneously breathing and stabilized on NIV will receive surfactant via ETT using an approved method of administration, connecting the syringe filled with poractant alfa suspension to:

- a 5-French end-hole catheter inserted into the ETT

  or
- the proximal end of the secondary lumen of a dual lumen ETT.

The standard ETT has markings along the side to help identifying the correct distance from the tip of the tube.

Following direct laryngoscopy, the ETT will be inserted through the vocal cords into the trachea to the desired depth. The laryngoscope will be then carefully removed. The correct ETT position into the trachea will be confirmed by the visualization of tip depth markings and by the tip-to-lip measurement. The tube position could be checked by auscultation of the chest to ensure equal aeration of both lungs, observation of chest movement synchronous with positive pressure inflation, enhancement of vital signs, absence of stomach distension while ventilation, and where possible, with the measurement of end tidal CO_2 by colorimetric system on the ETT. Once the tube position is confirmed, the ETT will be secured with adhesive tape or other ways according to the NICU policy.

After administration, manual ventilation can be continued, or the neonate can be connected to the ventilator, or the neonate can be immediately extubated and placed again on NIV. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur.

If connected to the ventilator, extubation should be performed within one hour after surfactant administration and then the neonate placed again on NIV.

Details of the procedure as well as neonate's vital signs and any occurring adverse event will be recorded according to the time points of the protocol by the team member assisting or observing the procedure.

6.2.3.5 Need for resuscitation during surfactant administration

In both arms of the study, if a life-threatening event requiring resuscitation occurs during poractant alfa administration, the procedure of surfactant administration will be stopped and resuscitation provided starting from supplying Positive Pressure Ventilation (PPV) and following step-by-step the American Guidelines for Neonatal Resuscitation [24,25].

6.2.3.6 Additional surfactant treatment

Up to two repeated doses could be administered at 100 mg/kg.

A second surfactant dose (poractant alfa 100 mg/kg) will be administered using the same technique as the first dose administration in case of lack of efficacy, or clinical deterioration,

as per randomization criteria (FiO_2 ≥0.30 to maintain preductal oxygen saturation (SpO_2) in the target range 88–95%), within approximately 12 hours from the initial dose.

After the first and the second surfactant administration, neonates could receive a third surfactant dose (poractant alfa 100 mg/kg). If a third dose is administered, it will be provided through a standard technique. Neonates could be intubated (LISA group) or re-intubated (control group) for MV at neonatologist's discretion, if one or more of the below detailed conditions for MV in section 6.2.3.7 are satisfied.

6.2.3.7 Intubation and extubation criteria

Intubation for mechanical ventilation and further surfactant doses could happen if one or more of the following criteria are satisfied:

- FiO_2 ≥0.45 to maintain preductal SpO_2 of 88-95% for at least 30 minutes, unless rapid clinical deterioration occurs;
- 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);
- Respiratory acidosis (pCO_2 >65 mmHg/8.5 kPa and pH <7.20 identified by either arterial or capillary blood gas monitoring).

These criteria will be applied during the first 3 days of life (72 hours).

After the first 3 days of life, intubation and mechanical ventilation can happen as per Investigator's clinical judgement.

FiO_2 and SpO_2 values should be collected at time of decision for intubation and recorded in eCRF as well as the criterion for intubation.

Criteria for termination of Mechanical Ventilation and Extubation are defined as follows:

- Clinical improvement, e.g. presence of a good respiratory drive;
- Ability to wean FiO_2, e.g. FiO_2 <0.30 to maintain SpO_2 between 88 and 95%.
- Ability to wean ventilatory pressures, e.g. MAP ≤7 in conventional ventilation or MAP ≤8 in HFOV;
- Normalization of blood gases' values, e.g. pCO_2 < 65 mmHg and pH ≥7.20.

6.2.4 Subject Training

Not Applicable.

6.3 Packaging

Chiesi Farmaceutici S.p.A. will supply the study medication for both groups as well as the thin catheter (CHF 6440) for the administration in the relevant LISA treatment group.

The study medication kit is composed of a single glass vials of 3 ml of Poractant alfa for initial dosing or possible re-dosing; the vial will be packed in an outer box and will be provided to

the investigational sites. Each vial is for single use only. Any need for dosing and re-dosing will require a vial to be issued via IRT (see Section 6.6).

CHF 6440 catheters will be packed and provided separately.

6.3.1 Primary packaging

Poractant alfa:

Labeled glass vial containing 3 ml of Poractant alfa at a concentration of 80 mg/ml for respectively initial dosing and possible re-dosing.

CHF 6440 catheters:

A sterile labeled tyvek pouch containing CHF 6440 catheter.

6.3.2 Secondary packaging

Poractant alfa:

A holder containing one labelled glass vial containing 3 ml of Poractant alfa.

CHF 6440 catheter:

A labeled carton containing a tyvek pouch .

6.3.3 Tertiary packaging

Not applicable.

6.4 Labeling

The supplies (Poractant alfa and CHF 6440 catheters, in primary and secondary packaging) will be labeled in English and according to US law and FDA regulatory requirements in compliance with Annex 13 of Volume 4 of the GMPs and in compliance with 21 CFR 312.6 “Labelling of an Investigational New Drug”, for US Trials.

The tear-off sticker from the vial box and the tear off sticker from the catheter carton will be applied in the appropriate section of the surfactant accountability log.

6.5 Treatment allocation

A balanced block randomization scheme stratified by investigational site and gestational age group (i.e. from 25^{+0} to 26^{+6} weeks and from 27^{+0} to 28^{+6} weeks) will be prepared via a computerized system. Once the neonate’s eligibility to take part in the study is confirmed, neonates will be centrally assigned to one of the two treatment arms (LISA/Poractant alfa or ETT/Poractant alfa) through an IRT system (Interactive Response Technology, combination of voice and web response system and also referred as IVRS/IWRS). Enrollment will be staggered: the gestational age will be restricted to 27^{+0} to 28^{+6} weeks for at least the first 15 randomized neonates. After ISMB evaluation of safety data from the first 15 neonates, provided no safety concerns are raised, the enrolment will be extended to the whole population (25^{+0} to 26^{+6} weeks and from 27^{+0} to 28^{+6} weeks).

The IRT will allocate the subject to a certain treatment group using a list-based randomization algorithm and assign the unique screening number of eight digits: the country will be the first three digits (according to ISO 3166 Numeric Country Code), the investigational site number will be the second two digits and the following three digits will be the progressive numbering of the subject within each site (e.g. for the first USA site the screening numbers will be 84001001, 84001002 etc.). The IRT will also generate a confirmation after every IRT transaction is performed.

The Investigator will call the IRT on admission to receive the subject screening number and randomize the subject and obtain the medication (Poractant alfa) kit numbers. Detailed instructions for use of IRT will be provided to the site.

In the LISA group, the relevant catheter provided by the Sponsor (CHF 6440) will be dispensed and used for administration. In the control group, the endotracheal tubes available at the investigational sites for clinical practice will be used for administration.

The LISA catheter (CHF 6440) will be dispensed by the IRT system.

6.6 Treatment Code

The study medication (Poractant alfa) will be packaged and uniquely numbered. The IRT will be used to assign both initial and subsequent kits in order to have an inventory control and subject dosing tracking. The IRT will also maintain quantities, kit numbers, drug types, batch/code numbers, expiration dates and do not dispense after these dates. The IRT will monitor inventory levels at all sites and manage the study drug re-supply.

6.7 Treatment compliance

The actual volume of poractant alfa administered will be entered in eCRF. The evaluation of compliance will be done based on the actual volume administered in relation to the neonates' weight using the following formula:

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

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 following doses.

6.8 Drug and Device Storage

The Pharmacist/Investigator will be responsible for the safe storage of all medications and catheters assigned to this study, in a secure place with restricted access, and maintained within the appropriate ranges of temperature.

Poractant alfa will have to be stored between 2° and 8°C (36° to 46°F), protected from light, until the moment of use.

CHF 6440 catheter does not require any special storage condition. Keep in a cool dry place.

Please refer to CTS Instructions for Use.

6.9 Drug Accountability

The Investigator or pharmacist is responsible for the management of all the study treatments and thin catheters CHF 6440 to be used for the study. Study treatments should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the study drugs.

An inventory will be maintained by the Investigator or pharmacist (or other nominated individual), to include a signed account of all the study treatment(s) and LISA catheters received and used for each subject. The actual volume of instilled study treatment will be reported in the relevant section of the eCRF.

At the conclusion or termination of the study, the Investigator or the pharmacist shall conduct and document a final drug supply (used and unused) inventory. An explanation should be given for any discrepancies.

No surfactant material or catheters for this trial are to be used for any other purpose.

In addition, a signed account shall be kept of all study treatments administered to each subject.

All the study treatments supplied, used or unused, will be returned for destruction to the designated Clinical Trial Supply (CTS) vendor/depot under Sponsor's responsibility or destroyed directly by the Pharmacy of the involved investigational site upon provision of destruction certificate and documentation assuring the occurred destruction according to standard procedures and filed both at investigator's site file and at Sponsor/CRO trial master file.

6.10 Provision of additional care

At study completion, it is the Investigator's responsibility to prescribe the more appropriate treatment for the subject.

7. STUDY PLAN

7.1 Study Schedule

This study will include the following periods and visits:

Periods:

- Pre-randomization period: on admission to the study prior to study treatment;
- Day 1: randomization, before start of study procedure, treatment administration up to end of surfactant administration (T0); up to 24 hours after receiving study treatment (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 Post-Menstrual Age (PMA);
- Discharge home or 40 weeks PMA, whichever comes first;
- 24 months (±3 months) corrected age visit.

Details are reported in the following sections and summarized in the following flowchart (Table 2):

Table 2: 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

The following time deviations from theoretical post-dose times will be allowed:

Table 3: ALLOWED TIME DEVIATIONS

Post-dose time assessments	Allowed deviations
5, 15 minutes	± 1 minute
30 minutes	± 5 minutes
1 hour	± 10 minutes
6, 12 and 24 hours	± 30 minutes
48, 72, and 120 hours	± 2 hours
28 days PNA	± 2 days
36 wks PMA	± 4 days
40 wks PMA (if still in hospital)	± 2 days
24 months clinical assessment	± 3 months

7.1.1 Pre-randomization Period - On admission prior to study treatment administration

The study will be explained to the parents of a potentially eligible neonate prior to birth, if possible, giving the parents the maximum time to make an informed choice. Once parental/ maternal written informed consent has been obtained either prior to or after birth, the neonate's eligibility to take part in the study will be assessed according to the post-birth inclusion and exclusion criteria. If the neonate becomes eligible, then the medical history of the mother, the complications during pregnancy and the prenatal use of corticosteroids will be collected.

If the neonate becomes eligible, then the following information will be collected:

- Birth weight, occipital-frontal circumference (OFC), length;
- Apgar score at 1 and 5 min from birth;
- All medical conditions diagnosed before treatment drug administration, to be reported as "Medical History". To this group should be added thereafter those congenital conditions that, even if already present at birth, could be diagnosed after study treatment administration (including: major organ malformations, genetic diseases and/or chromosomal abnormalities);
- Concomitant medications;
- Clinical signs of RDS, such as tachypnea, retractions, nasal flaring, expiratory grunt;
- SpO_2 along with vital signs (systolic, diastolic and mean blood pressure, heart rate, respiratory rate);

- Fraction of inspired oxygen (FiO_2);
- Type of respiratory support (CPAP, BiPAP, NIPPV);
- Blood gas analysis (values of pH, pCO_2, pO_2, HCO_3, BE, lactate), when feasible.

7.1.2 Day 1 - From study treatment administration to 24 hours post-treatment

Once the neonate's eligibility to take part in the study is confirmed, the Investigator will have to call/check the IRT to randomize the neonate to the treatment group (LISA or ETT).

Before starting the procedure:

Within 15 minutes before starting the procedure (before laryngoscope insertion), the following information will be collected:

- SpO_2 along with vital signs (systolic, diastolic and mean blood pressure, heart rate, respiratory rate);
- Fraction of inspired oxygen (FiO_2);
- Type of respiratory support (CPAP, BiPAP, NIPPV);
- Non-invasive ventilation parameters (CPAP pressure, BiPAP pressures, NIPPV peak pressure, PEEP, mean airway pressure);
- Pain score assessment (PIPP score) [26] by observing the subject for 15 seconds (see APPENDIX IV);
- Blood gas analysis (values of pH, pCO_2, pO_2, HCO_3, BE, lactate), unless the time from the blood gas analysis at screening is less than 1 hour. In this case only one blood gas analysis is acceptable;
- All medical conditions diagnosed before treatment drug administration, to be reported as "Medical History", including congenital conditions that could be diagnosed after study treatment administration;
- Concomitant Medications.

After Starting the Procedure:

From the start of the procedure (laryngoscope insertion) through the first 24 hours from administration, the following information will be collected:

- SpO_2 and FiO_2 at time 0 (end of surfactant administration), and at 5, 15, 30 min, 1 hour, 6, 12 and 24 hours after the end of study treatment administration;
- Vital signs (SDB, DBP, MBP, HR, RR): 15, 30 min, 1 hour, 6, 12 and 24 hours after the end of study treatment administration; HR and RR to be reported also at time 0 and 5 min (as showed in flow chart Table 2);
- Evaluation of respiratory support: any change in non-invasive ventilation, need for intubation and invasive mechanical ventilation with the relevant dates and times;
- If applicable, NIV parameters (as specified above) at 30 minutes, 1 hour, 6, 12 and 24

hours after the end of treatment administration;

- Evaluation of oxygen alone use: duration of needing supplementary oxygen with the relevant dates and times;
- PIPP score immediately following surfactant administration after observing the neonates for 30 seconds (see APPENDIX IV);
- Capillary or arterial blood gas analysis (values of pH, pCO_2, pO_2, HCO_3, BE, lactate) at 1 hour, 6 hours and 24 hours after the end of study treatment administration;
- Surfactant- and procedure-related adverse events will be strictly monitored during the whole procedure for surfactant administration (see section 10.8);
- Adverse events diagnosed after treatment administration (including worsening of conditions pre-existing to treatment); major complications of prematurity (listed in APPENDIX III) to be recorded among adverse events;
- Further neonatal concomitant medications.

7.1.3 48 hrs after study treatment administration

The following information will be collected:

- FiO_2, SpO_2, vital signs (SBP, DBP, MBP, HR and RR) and, if applicable, NIV parameters (as specified above) at the same time;
- Evaluation of respiratory support: any change in non-invasive ventilation, need for intubation and invasive mechanical ventilation with the relevant dates and times;
- Evaluation of oxygen alone use: duration of needing supplementary oxygen with the relevant dates and times;
- Blood gas analysis (values of pH, pCO_2, pO_2, HCO_3, BE, lactate);
- Further neonatal concomitant medications and adverse events (including worsening of conditions pre-existing to treatment), as well as changes in those already reported; major complications of prematurity (listed in APPENDIX III) to be recorded among adverse events.

7.1.4 72 hrs after study treatment administration

The following information will be collected:

- FiO_2, SpO_2, vital signs (SBP, DBP, MBP, HR and RR) and, if applicable, NIV parameters (as specified above) at the same time;
- Evaluation of respiratory support: any change in non-invasive ventilation, need for intubation and invasive mechanical ventilation with the relevant dates and times;
- Evaluation of oxygen alone use: duration of needing supplementary oxygen with the relevant dates and times;
- Blood gas analysis (values of pH, pCO_2, pO_2, HCO_3, BE, lactate);

- Further neonatal concomitant medications and adverse events (including worsening of conditions pre-existing to treatment) as well as changes in those already reported; major complications of prematurity (listed in APPENDIX III) to be recorded among adverse events.

7.1.5 120 hrs after study treatment administration

The following information will be collected:

- FiO_2, SpO_2 and vital signs (SBP, DBP, MBP, HR and RR) at the same time;
- Evaluation of respiratory support: any change in non-invasive ventilation, need for intubation and invasive mechanical ventilation with the relevant dates and times;
- Evaluation of oxygen alone use: duration of needing supplementary oxygen with the relevant dates and times;
- Further neonatal concomitant medications and adverse events (including worsening of conditions pre-existing to treatment) as well as changes in those already reported; major complications of prematurity (listed in APPENDIX III) to be recorded among adverse events.

7.1.6 28 days PNA

The following information will be collected:

- FiO_2 (highest recorded value), SpO_2, HR and RR at the same time;
- Evaluation of respiratory support: any change in non-invasive ventilation, need for intubation and invasive mechanical ventilation with the relevant dates and times;
- Evaluation of oxygen alone use: duration of needing supplementary oxygen with the relevant dates and times;
- Further neonatal concomitant medications and adverse events (including worsening of conditions pre-existing to treatment) as well as changes in those already reported; major complications of prematurity (listed in APPENDIX III) to be recorded among adverse events.

In case the neonate was discharged home (either by the recruiting site or by a continuing care site) prior to 28 days of life, the neonate should be recalled for an on-site clinic visit at the recruiting site. If not feasible, any effort should be made to collect information about the occurrence of any adverse events as well as about any change in concomitant medications. The Investigator should contact the family pediatrician to collect the relevant information.

In case the treated neonate was transferred to a continuing care site prior to 28 days PNA and the neonate is still hospitalized there, the neonate should be recalled at the recruiting site for the visit. If this is not feasible, the visit can be replaced by a contact/phone call by the Investigator to the physician of the continuing care site to collect relevant information and check the occurrence of any other adverse event as well as of any change in concomitant medications.

7.1.7 36 weeks PMA

The following information will be collected:

- Weight
- FiO_2 (highest recorded value) SpO_2, HR and RR at the same time;
- Evaluation of respiratory support: any change in non-invasive respiratory support, need for intubation and invasive mechanical ventilation with the relevant dates and times;
- Evaluation of oxygen use alone: duration of needing supplementary oxygen with the relevant dates and times;
- If receiving respiratory support via nasal cannulae: evaluation if flow rate ≤2 l/min or >2 l/min
- BPD assessment: breathing room air or on oxygen, if neonate has received oxygen for at least 28 days, need of positive-pressure respiratory support (see Section 7.2.3);
- Further neonatal concomitant medications and adverse events (including worsening of conditions pre-existing to treatment) as well as changes in those already reported; major complications of prematurity (listed in APPENDIX III) to be recorded among adverse events.

In case the subject is discharged home or transferred to a continuing care site prior to this visit, the subject should be recalled as soon as possible for an on-site clinic visit at the recruiting site. If not feasible, any effort should be made to collect relevant information for BPD assessment, adverse events as well as any change in concomitant medications. The investigator should therefore contact the physician of the continuing care site or the family pediatrician to collect the relevant information. In case study visits or procedures are modified or missed due to COVID-19, the relevant information will be recorded in the eCRF. If the subject was discharged without any supplemental oxygen or respiratory support, an on-site visit is not mandatory, but the Investigator should contact the family pediatrician to collect the relevant information to complete BPD evaluation.

7.1.8 Discharge home or 40 weeks PMA (whichever comes first)

The below assessments will be performed at discharge, or at 40 weeks PMA if the infant is still in hospital. The following information will be collected:

- SpO_2, HR and RR at the same time;
- Weight, OFC and length;
- Evaluation of respiratory support (if present): non-invasive respiratory support, or invasive mechanical ventilation and related FiO_2;
- If receiving respiratory support via nasal cannulae: evaluation if flow rate ≤2 l/min or >2 l/min
- Evaluation of feeding status, hearing screen status, medications for respiratory problems;

- Assessment of relevant neonatal co-morbidities, their severity and treatment;
- Further neonatal concomitant medications and adverse events (including worsening of conditions pre-existing to treatment) as well as changes in those already reported.

In case the infant had been transferred to a continuing care site, the recruiting site is responsible for the proper continuation of data collection and documentation of the primary and secondary outcomes. The investigator of the recruiting site should keep contacts and provide the continuing care site with written instruction about management of the above as well as for the reporting of serious AE, if any. The recruiting site should receive a discharge letter clarifying as much detailed information as possible the progress in subject's conditions.

Routine clinical safety data included in the discharge home summary letter should be sought to complete data collection.

If the discharge home coincides with the 36 weeks PMA visit, both assessments should be completed and recorded in the eCRF.

7.1.9 Clinical assessment at 24 months (±3 months) corrected age

A further clinical assessment will be performed at 24 months (±3 months) corrected age at the participating study centers. In this occasion, age and age corrected for prematurity will be collected. This clinical assessment will be based on:

- Bayley Scales of Infant Development Edition III or IV (see Section 7.2.4);
- Health status questionnaire (additional evaluation of growth and development, respiratory assessment);
- Vital signs (SBP, DBP, MBP, HR and RR);
- Body weight, length and OFC.

7.2 Investigations

7.2.1 Neonatal pain assessment by Premature Infant Pain Profile (PIPP) score [26]

This is a composite score system based on the following indicators:

- Gestational age;
- Behavioral state before painful stimulus;
- Change in heart rate during painful stimulus;
- Change in oxygen saturation during painful stimulus;
- Brow bulge during painful stimulus;
- Eye squeeze during painful stimulus;
- Nasolabial furrow during painful stimulus.

The interpretation can vary from a minimum score of 0 to a maximum score of 21. The higher the score the greater the pain behavior (APPENDIX IV).

7.2.2 Vital signs and Blood tests

- Heart rate and pre-ductal SpO_2 are measured by pulse oximetry;
- Respiratory rate is shown on the cardiorespiratory monitor and can be measured by bioimpedance electrode sensors or chest wall motion sensors;
- Systolic, diastolic and/or mean blood pressures are measured either in a non-invasive or in invasive way, depending on the availability of an arterial catheter;
- Blood gas analysis (values of pH, pCO_2, pO_2, HCO_3, BE, lactate) will be performed either with arterial or capillary samples. Small volumes of blood (e.g. some droplets) will be collected in pre-heparinized tubes or syringes. When collected through an arterial line, at least 1.6 ml of blood should be withdrawn before collection of the blood gas sample to avoid contamination errors.

7.2.3 Assessment of Bronchopulmonary Dysplasia

To define presence and severity of BPD, the definition from the National Institute of Child Health and Human Development (NICHD) will be used, with some adaptation [4] (Table 4). According to this definition, BPD is diagnosed if treatment with >21% oxygen is required for at least 28 days; for subjects with GA at birth <32 weeks (including our study population); severity of BPD is assessed at discharge or at 36 weeks PMA, whichever comes first, and is based on requirement of oxygen and/or positive pressure ventilation (Table 4). It is classified as mild, if at the time point of assessment the subject is breathing room air, moderate if still needs for supplemental oxygen less than 30%, severe if needs oxygen greater than or equal to 30% and/or positive pressure (PPV or nCPAP).

In this clinical study, BPD assessment will be performed at 36 weeks PMA for all treated subjects. If the discharge home is before the 36 weeks PMA and the subject is discharged with supplemental oxygen and/or positive pressure, a further visit will be required at 36 weeks PMA. If the discharge home is before 36 weeks PMA and the subject is discharged without supplemental oxygen or any respiratory support, an on-site visit is not mandatory, but the Investigator should contact the caring pediatrician to collect the relevant information and complete the evaluation.

Table 4
Definition of bronchopulmonary dysplasia for infants with GA at birth < 32 weeks: Diagnostic criteria adapted from 2001 NICHD consensus workshop [4]

Gestational Age	**< 32 wks**
Time point of assessment*	36 wks PMA
Treatment with oxygen >21% for at least 28 days plus	
Mild BPD	Breathing room air
Moderate BPD	Need for <30% oxygen
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP)

* Assessed at 36 weeks timepoint for all the study subjects when possible

7.2.4 Clinical assessment of growth and development and respiratory morbidity, using a health status questionnaire

The Clinical assessment of growth and development and respiratory morbidity will be done through a questionnaire to record weight, length and head circumference, result of the last cardiological evaluation and timing, the feeding method, the cerebral palsy, seizures, functional disability (vision, hearing, and communication), respiratory conditions and morbidity. This latter is mainly addressed to test the BPD severity (if any) at two-year corrected age.

To measure cognitive and language development, the score from the related sections of the Bayley Scales III and IV (i.e. cognitive and language domains) will be reported in the questionnaire. Bayley Scales of Infant Development is a standard series of measurements used primarily to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers, aged 0-3. This measure consists of a series of developmental play tasks and takes between 45 - 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores (recorded in the eCRF) are used to determine the child's neurodevelopmental performance compared with norms taken from typically developing children of their age (in months).

8. EFFICACY ASSESSMENTS

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:

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, pCO_2, pO_2, HCO_3, BE, lactate) pre-surfactant administration (when applicable), at 1 hour, 6 hours, 24, 48 and 72 hours after study treatment.

9. SAFETY ASSESSMENTS

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

During procedure for surfactant administration

- Number and percentage of neonates with 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 1st attempt to insert the CHF6440/ETT;
- Number of attempts to the first successful insertion;
- Number of device misallocation (esophageal insertion);
- Number of maneuvers discontinued due to neonate's severe destabilization;
- Duration of the whole procedure (starting from the insertion of laryngoscope up to the removal of the catheter or ETT);
- Duration of surfactant administration (min);
- 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 [26] (end of surfactant administration).

During the study

- AEs, including incidence of major neonatal complications of prematurity (listed in APPENDIX III) and adverse drug reactions (ADRs);
- Blood pressure (SBP, DBP, MBP) at 24, 48, 72, 120 hours post-administration;
- Heart Rate (HR) and respiratory rate (RR), at 24, 48, 72, 120 hours post-administration and 28 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, 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

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

- 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).

10. ADVERSE EVENTS REPORTING

10.1. Definitions

An **Adverse Event** is "any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment".

An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

An **Adverse Drug Reaction** is an "untoward and unintended responses to an investigational medicinal product related to any dose administered".

All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction** is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- ***Results in death***

  Death is not an adverse event but an outcome. It is the cause of death that should be regarded as the adverse event. The only exception to this rule is "sudden death" where no cause has been established; in this latter instance, "sudden death" should be regarded as the adverse event and "fatal" as its reason for being serious.

- ***Is life-threatening***

  Life-threatening refers to an event in which the subject was at risk of death at the time of the event (e.g., aplastic anemia, acute renal failure and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.

- ***Requires hospitalization or prolongation of existing hospitalization***

  Hospitalization refers to a situation whereby an AE is associated with unplanned overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as an AE. Complications that occur during the hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.

  Emergency room visits that do not result in a formal admission into hospital should be evaluated for one of the other seriousness criteria (e.g., life-threatening; persistent or significant disability or incapacity; medically significant).

- ***Results in persistent or significant disability or incapacity***

  The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the subject's physical or psychological well-being to the extent that the subject is unable to function normally.

- ***Is a congenital anomaly or birth defect*** *(not applicable for this study)*

- ***Is a medically significant adverse event***

  This criterion allows for any situations in which important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalization may jeopardize the subject's health or may require intervention to prevent one of the above outcomes.

  Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

  Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A **Non-Serious Adverse Event/Non-Serious Adverse Drug Reaction** is an adverse event or adverse drug reaction that does not meet the criteria listed above for a serious adverse event/serious adverse drug reaction.

A **Device Deficiency**, for the purpose of this trial, is any inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction.

An **Unanticipated Adverse Device Effect (UADE)** is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2. Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (included in the Poractant alfa/CHF 6440 catheter Investigator's Brochure), otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the above relevant documentations would be considered as "unexpected". General examples of such events are: (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

10.3. Intensity of Adverse Event

The investigator is asked to assess the intensity of all the adverse events and to report them in the eCRF.

Each Adverse Event must be rated on a 3-point scale of increasing intensity:

- *Mild*: asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior (e.g. oral feeding behavior, voluntary movements and activity). The event does not lead to establishment of a correcting treatment.
- *Moderate*: resulting in minor changes of baseline age appropriate behavior; requiring minor changes in baseline care or monitoring (e.g. oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning). The event leads to establishment of a correcting treatment.
- *Severe*: resulting in severe discomfort with major changes of baseline age-appropriate behavior; requiring major change in baseline care or monitoring (e.g. brief, local, non-invasive or symptomatic treatments).

For the classification of AEs intensity, the 'INC Neonatal Adverse Event Severity Scale (NAESS) v1.0''[27] may be used as a guidance.

Since the above-mentioned guidance is based on a 5-grade table, the following conversion will be performed:

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

In order to guarantee objectivity and consistency in the evaluation of AEs (including classification of intensity), the proposed guidance should be followed in alignment with best medical practice. Moreover, clinical abnormalities and other abnormal assessments will be reported as AEs if are judged by the Investigator as being clinically significant.

10.4. Causality Assessment

The following "binary" decision choice will be used by the Investigator to describe the causality assessment with the study medication/device/procedure:

- Reasonable possibility of a relatedness with study medication/device/procedure
- No reasonable possibility of relatedness with study medication/device/procedure

Each AE will be evaluated for its relationship with the study drug (Poractant alfa), and also with the specific procedure for surfactant administration in both treatment groups. Moreover, for baby randomized to the LISA group, causal relationship to CHF 6440 medical device will be also assessed.

An AE will be assessed as related to the medical device (i.e. CHF 6440 catheter) if associated with its technical features or with any defect/malfunction.

An AE will be assessed as related to the procedure (i.e. LISA or intubation, surfactant administration and brief ventilation) if connected with the technique, including user difficulties in applying it.

An AE can be assessed as related to multiple choices.

The expression "reasonable possibility of relatedness" is meant to convey, in general, that there are facts (evidence) or arguments meant to suggest a causal relationship.

The Investigator will be asked to consider the following before reaching a decision on causality assessment:

- Time relationship between study drug intake/device use/procedure for administration and event's onset;
- Medical history;
- Lack of efficacy/worsening of existing condition;
- Study treatment(s);
- Mechanism of action of the study drug/device;
- Class effects of the study drug;
- Other treatments-concomitant or previous;
- Erroneous treatment with study medication (or concomitant)/device/procedure for

administration;

- Protocol related process.

10.5. Action taken with study drug due to AE

Since subjects will receive a single dose of study drug, "action taken with study drug" will be not applicable.

10.6. Other actions taken

- Specific therapy/medication;
- Concomitant procedure;
- Supplementary oxygen alone;
- FiO_2 increase;
- Manual Positive Pressure Ventilation;
- Endotracheal intubation and invasive ventilation;
- Administration of adrenaline, crystalloids or colloids;
- Not applicable.

10.7. Outcome

Each Adverse Event outcome must be described by choosing among:

- Recovered/resolved;
- Recovering/resolving;
- Not recovered/not resolved;
- Recovered with sequelae/resolved with sequelae;
- Fatal;
- Unknown.

10.8. Recording Adverse Events

All AEs occurring during the course of the study must be documented in the Adverse Event page of the eCRF. Moreover, if the Adverse Event is serious, the Serious Adverse Event Form must also be completed.

It is responsibility of the Investigator to collect all adverse events (both serious and non-serious).

The recording period for Adverse Events is the period starting from the beginning of the procedure until the subject's study participation ends.

Given the significant amount of possible comorbidities in the study population, any condition diagnosed before the start of the procedure will be considered a baseline condition and will be recorded in the Medical History page of the eCRF. The occurrence or worsening of these conditions during and after the study procedure must be recorded as an AE in the eCRF.

The only exception to this rule is represented by congenital anomalies including major organ malformations, genetic diseases and/or chromosomal abnormalities, that should be reported as baseline conditions even if diagnosed after treatment.

If a clinically significant abnormal laboratory finding or other abnormal assessment detected during the study period meets the definition of an AE and is not assessed as pre-existing, then the AE eCRF page must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on the AE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded as adverse event.

Occurrence of COVID-19 infection during the study will be reported in the Adverse Events section of the eCRF if symptoms judged related to the infection are present. Every effort should be made by the site to confirm all suspected incidences of COVID-19 in accordance with local diagnostic guidelines. Tests for detecting SARS-CoV-2 infection, as well as their results, will be reported in the eCRF. Documentation of testing and results obtained outside the clinical site, should be collected within 14 days of confirmed diagnosis (or whenever possible) and recorded in the eCRF. For all confirmed cases of COVID-19/SARS-CoV-2 the investigator must follow the standard of care in accordance with local treatment guidelines. All concomitant treatments must be recorded in the eCRF as well.

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or until the subject is lost to follow-up. Follow-up may therefore continue after the subject has left the study. In this case, the follow-up will continue with no timelines for related SAEs, while for unrelated SAEs the type and extent of follow-up undertaken will be determined for each individual case and will depend upon the nature (e.g. events with poor prognosis or which do not resolve), severity and medical significance of the event.

AEs related to the procedure for surfactant administration

The procedure for surfactant administration will last from the application of the laryngoscope up to the removal of the CHF 6440 catheter in the LISA treatment group or the ETT in the comparator arm within one hour after the instillation of poractant alfa.

All AEs during procedures for surfactant administration will be carefully monitored and recorded in both arms. Specific focus will have to be paid on the following AEs:

- Obstruction of the CHF 6440 catheter or ETT;
- Bradycardia;
- Neonatal oxygen desaturation;

- Apnoea;
- Hypotension requiring treatment;
- Any episodes of cough, sneezing, choking, laryngospasm, surfactant reflux, vomiting.

A complete qualitative risk assessment has been conducted to identify and mitigate potential safety risks associated with use of CHF 6440 medical device. The results provide evidence that the benefits of using the device outweigh the residual risks and do not highlight any specific additional risk or safety issue than the ones listed above.

10.9. Reporting Serious Adverse Events to the Sponsor

The Investigator (or delegate) must report all Serious Adverse Events and any UADE to the [redacted] Safety Contact listed below within 24 hours of awareness.

Information on SAE (including UADE) must be sent by providing the completed, dated and signed paper Serious Adverse Event form. At a later date, the [redacted] Safety Contact will report all information to Chiesi Global Pharmacovigilance, the Clinical Project Manager and the Clinical Research Physician.

Name and Title	Telephone no.	E-mail
[redacted] Safety [redacted]	Toll free numbers provided separately	[redacted]
[redacted] Global Pharmacovigilance Chiesi Farmaceutici S.p.A., Parma (Italy)	Phone: [redacted] Fax: [redacted]	[redacted] ct_cds@chiesi.com

- Reporting of SAEs from the investigator site is from the start of the procedure until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, related SAEs occurring to a subject should be reported if the investigator becomes aware of them.
- Up to the closure of the site, SAEs/UADEs reports should be reported to the [redacted] Safety Contact. New related serious adverse events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10. Reporting Serious Adverse Events/Unanticipated Adverse Device Effects to Regulatory Authorities/ IRB

The Sponsor or designated CRO will report adverse events to the regulatory authorities in compliance with the timelines and standards of reporting according to local regulations (Guidance for industry and Investigators-Safety Reporting Requirements for INDs and BA/BE studies, December 2012) as well as to the Investigators and Central IRB, if applicable, by MedWatch/CIOMS form. The Investigator (or Sponsor/CRO where required) must inform the IRB per Sponsor instruction upon receipt of the SUSAR notification. An IND and/or NDA Safety Report will be submitted to regulatory authorities unblinded. Participating Investigators and IRB will receive a blinded IND Safety Report, unless otherwise specified.

All UADEs which occur with the medical device will be reported by the sponsor or designated CRO to regulatory authorities, as required, as well as to the Investigators and Central IRB, if applicable, as IND Safety Reports.

The Investigator (or Sponsor/ [redacted] where required) must ensure that the IRB receives a copy of the report and that a copy is also filed within their study files.

10.11. General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and provided to the [redacted] Safety Contact together with the Serious Adverse Event form, retaining a copy on site;
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and provided to the [redacted] Safety Contact as soon as available,

retaining a copy on site;

- All source documents provided by the Investigator or site staff to the [redacted] Safety Contact must be carefully checked for respect of confidentiality. All personal subject's data must be redacted.
- Any Adverse Drug Reaction (ADR) occurring with any marketed non-investigational medicinal product and/or concomitant medication during the study must be reported by the Investigator to his/her concerned Health Authority according to the applicable laws. The Investigator is also recommended to report all adverse drug reactions to the relevant Marketing Authorization Holders of the involved medicinal products. Additionally, also conditions of use outside the marketing authorization of the medicinal products (i.e. off-label, overdose, misuse, abuse and medication errors) or from occupational exposure, as well as cases of suspected drug interaction and lack of efficacy should be reported.
- If a neonate is transferred to a continuing care site prior to end of the main phase of the trial, the investigator should ensure that the receiving hospital site is aware that the neonate is participating to the present study and communication should be maintained in order to record any adverse event. Moreover, the investigator of the recruiting site will have to provide the continuing care site with written instruction about management and reporting of SERIOUS AE. After discharge home from the continuing care site a copy of the discharge summary letter should be requested in order to cross reference any adverse events and to contribute to BPD assessment.

10.12. Independent Safety Monitoring Board

An Independent Safety Monitoring Board (ISMB) will be established to ensure the safety of study subjects on an on-going basis. The involvement of independent expert advisors will provide an unbiased evaluation of the overall safety in the study, with particular regard to the incidence of major adverse outcomes (i.e. Serious Adverse Events) following study treatment administration.

The ISMB will be composed by independent Clinicians and one independent Biostatistician.

The ISMB will have periodical face-to face or telephone meetings, as appropriate, and a Safety Assessment Report will be issued after each meeting.

An ISMB meeting will be scheduled after the first 15 neonates will have been enrolled. If no safety concerns will be raised, enrollment will continue and will be extended to newborns with GA at birth between 25^{+0} weeks up to 28^{+6}. Before obtaining a favorable opinion from the ISMB, only newborns with GA from 27^{+0} to 28^{+6} weeks will be enrolled. Further ISMB meetings will be scheduled after the first 60, 105 and 150 subjects, respectively. *Ad-hoc* ISMB meetings can be scheduled, if needed, in case of unexpected safety issues.

The Sponsor (and other study personnel) may be involved in some parts of the ISMB meetings.

All ISMB members will keep as confidential all information and data deriving from the

ISMB activity, without disclosing them to others.

The complete ISMB guidelines including details regarding the members, duties and responsibilities, work and communication processes, frequency of meetings will be established by the ISMB members during the first meeting and reported in a separate charter.

11. DATA MANAGEMENT

An electronic case report form (eCRF) to be filled in by the investigator and/or his/her designee will be used. Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

Front-end edit checks will run at the time of data collection and back-end edit checks will be run by the CRO Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Conditions pre-existing to the start of the procedure, concomitant procedures (even if recorded in a different form) and adverse events will be coded using the MedDRA dictionary while medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification (ATC). The same dictionaries will be used to code mother's medical history, complications during pregnancy and mother's prenatal medications.

After cleaning of the data, a review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis.

Once the database of the main phase study has been declared to be complete and accurate, the eCRF forms will be locked and the planned statistical analysis will be performed. Only authorized and well-documented updates to the study data are possible after eCRF forms lock.

The Investigators will receive electronic copies of the subject data for retention at the investigational sites.

The 24-month clinical assessment data will be collected and recorded in a separate visit of the database: once all the data of the 24-month clinical assessment has been declared to be complete and accurate, the complete database will be locked and the planned statistical analysis for this assessment will be performed.

The complete database, including the main phase data, will be newly transferred. Comparing procedures documenting anything hasn't been changed in the main phase study data, will be prepared and archived in the TMF.

12. STATISTICAL METHODS

12.1. 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).

12.2. Populations for analysis

The following populations will be considered for the analysis:

- **Intention-to-Treat population (ITT):** all randomized subjects who will receive at least one dose of study medication.
- **Safety population:** all randomized subjects who will take at least one dose of study medication.

The efficacy analyses population will be performed in the ITT population. 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).

12.3. Statistical analysis

A detailed statistical analysis plan (SAP) will be described in a separate document. The plan might be reviewed and updated as result of the review of the data before database locking.

12.3.1. Descriptive Statistics

General descriptive statistics for numeric variables will include the n (number of observed values), the mean, the standard deviation, 95% CI, the median, the minimum, and the maximum values. For categorical variables, the number and percent of subjects with a specific level of the variable will be presented.

12.3.2. Missing data

Details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP. Critical missing data, if any, will be discussed during the review of the data before database locking. Decisions will be fully documented in the Data Review Report.

12.3.3. Description of the population-description of baseline characteristics

Demographics and baseline variables will be summarized by treatment group using descriptive statistics for the ITT population.

The following variables will be summarized by treatment group and overall in order to describe the study population: neonate baseline characteristics and demographics (birth weight, gestational age, sex, race, APGAR score), maternal history including the mother's age, race, medical and pregnancy history, current and pre-birth medications and delivery conditions.

The sex, GA, weight, age and age corrected for prematurity will be summarized at 24 months corrected age.

12.3.4. Efficacy variables

Need for mechanical ventilation/intubation

- Percentage of neonates needing invasive mechanical ventilation in the first 72 hours of life, in the first 28 days PNA and within 36 weeks PMA will be compared between group using the Cochran-Mantel-Haenszel (CMH) test adjusted for gestational age group. The CMH adjusted difference with its 95% CI will be presented. Additional analysis will be performed to explore the impact of use of sedation and/or analgesia.
- Percentage of neonates needing any intubation procedure, outside the initial surfactant administration period, in the first 72 hours of life, 28 days PNA and within 36 weeks PMA will be compared between treatments as need for IMV.

SpO_2

- SpO_2 will be analyzed using 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. 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 in the first 120 hours post-administration will be presented by treatment group.
- SpO_2 will be summarized by treatments on neonates still receiving respiratory support at 28±2 PNA and 36 weeks PMA by means of descriptive statistics.

FiO_2

- FiO_2 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 FiO_2 as covariate. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) at each time point and averaged over the first 120 hours post-treatment will be estimated by the model. Time profile plot of mean FiO_2 in the 120 hours post-treatment will be presented by treatment group.
- FiO_2 will be summarized by treatments on neonates still receiving respiratory support at 28±2 PNA and 36 weeks PMA by means of descriptive statistics.

SpO_2/FiO_2 ratio

- SpO_2/FiO_2 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 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 in the first 120 hours post-treatment will be presented by treatment group.

- SpO_2/FiO_2 will be summarized between treatments at 28±2 Days PNA and at 36 weeks PMA by means of descriptive statistics.

Blood gas analysis

- Acid-base balance parameters (i.e. pH, pCO_2, pO_2, HCO_3, BE, lactate) will be summarized by treatments group as absolute and change from pre-treatment values by means of descriptive statistics.

Use of additional surfactant doses

- 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 at 5% significance interval. Odds ratio (OR) and related exact 95% CI will be also provided. Subjects with pulmonary hemorrhage will be excluded from this summary.
- The number of additional surfactant doses will be summarized by treatment group by means of descriptive statistics.

Duration of ventilation/oxygen supplementation (alone)

- The median duration time of invasive mechanical ventilation in the first 72 hours of life (hours), in the first 28 days PNA and within 36 weeks PMA (days), stand-alone oxygen supplementation (days), non-invasive ventilation (days) will be compared between treatment groups by using the Mann-Whitney U-test.

12.3.5. Safety variables

Adverse Events and Neonatal Morbidities

- Number and percent of neonates reporting AEs started during procedure for surfactant administration as well as AEs started during the procedure and judged related to the procedure will be summarized by treatment group.

  For LISA group, any AE assessed as related to CHF 6440 catheter will be considered procedure-related.

  These events will be also summarized by treatment group based on action required, if any (i.e. supplementary oxygen or transient increase in FiO_2, manual positive pressure ventilation, endotracheal intubation, administration of, crystalloids, or cardiopulmonary resuscitation or administration of adrenaline). The duration of endotracheal intubation and positive pressure ventilation will be

summarized as well.

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

- Incidence of AEs including neonatal complications of prematurity (see APPENDIX III for complete list), 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 System organ Class (SOC) and Preferred Term (PT).
- Frequency of neonates with major neonatal morbidities at discharge or 40 weeks PMA (whichever comes first) will be summarized by treatment group.

Vital Sign

- Vital signs parameters (SBP, DBP MBP, HR and RR) will be summarized as absolute and the change from baseline (pre-procedure) by treatment group using descriptive statistics.

Pain assessment

- PIPP score will be summarized by treatment group by means of descriptive statistics.

First administration

- 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 group using the Cochran-Mantel-Haenszel adjusted for gestational age group. The CMH adjusted difference with its 95% CI will be presented.
- Number of attempts to the first successful insertion will be summarized by treatment group by means of descriptive statistics.
- Number of device misallocation (i.e., esophageal intubation) will be summarized by treatment group by means of descriptive statistics.
- Number of maneuvers discontinued due to neonate's severe destabilization will be summarized by treatment group by means of descriptive statistics.
- Duration of surfactant administration (min) and overall procedure for surfactant administration will be compared between treatment groups by using the Mann-Whitney U- test.

Mortality and BPD

- Death/BPD incidence at 36 weeks PMA will be compared by treatment by means of CMH test, adjusting for GA group and related 95% confidence interval will be provided.

- The incidence of BPD at 36 weeks PMA will be compared by treatment as for Death/BPD incidence.
- 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 (alone and / or during any kind of MV) will be compared by treatment as for Death/BPD incidence.

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.
- Weight, OFC and length 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 respiratory medications at discharge home or 40 weeks PMA will be summarized by treatment group by frequency distribution

Health status questionnaire at 24 months (±3 months) corrected age

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

- Bayley Scales of Infant Development (cognitive and language scores) will be summarized using descriptive statistics by treatment group and BSID version (III or IV).
- Vital signs and all other variables collected through the questionnaire (i.e., anthropometric measures, cerebral palsy, seizures, feeding method, functional disability and respiratory morbidity) will be summarized by treatment group by frequency distribution or descriptive statistics, as appropriate.

12.3.6. Interim Analysis

No interim analysis is planned in this study.

13. INSTITUTIONAL REVIEW BOARD APPROVAL

The study proposal will be submitted to the Institutional Review Board (IRB) in accordance with US requirements.

The IRB shall give its opinion in writing -clearly identifying the study number, study title and informed consent form approved-, before the clinical trial commences.

A copy of all communications with the IRB will be provided to the Sponsor.

The Investigator should provide written reports to the IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the subjects (according to the requirements of each country).

14. REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorized by) according to the legal requirements in the US. In the case of a substantial amendment, approval from the Health Authority will be sought before implementation.

Selection of the subjects will not start before the approval of the IRB has been obtained and the study notified to Health Authorities (or authorized by).

The study will be conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practices guidelines and following all other requirements of local laws.

15. INFORMED CONSENT

It is the responsibility of the Investigator to obtain written consent from each subject's parent or the parents' legal representative prior to any study related procedures taking place, by using the latest IRB approved version of the Informed Consent document.

If the subject's parents or the parents' legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g. a person independent of the study who will read the informed consent form and the written information for the parents.

Adequate time shall be given to the subjects' parents or legal representative to ask the PI about any clarifications needed and to consider parents' decision to enroll the subject in the study.

Consent must be documented by the dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the informed consent form.

Each signed informed consent must be kept on file by the Investigator. One copy must be given to the subject.

16. SOURCE DOCUMENTS/DATA

16.1. Recording of source data

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents (APPENDIX II).

16.2. Direct access to source document/data

The Investigators or designated must permit trial-related monitoring, audits, IRB review or regulatory inspection, providing direct access to source data/documents.

17. STUDY MONITORING

Monitoring will be performed by the CRO, [redacted], who has been designated by Chiesi Farmaceutici S.p.A.

It is understood that the monitor(s) will contact and visit the Investigator/center before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and source data, provided that subject confidentiality is respected.

The purposes of these visits are:

- to assess the progress of the study;
- to review the compliance with the study protocol;
- to discuss any emergent problem;
- to check the eCRFs for accuracy and completeness;
- to validate the contents of the CRFs against the source documents;
- to assess the status of drug storage, dispensing and retrieval.

Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the eCRF. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

The R&D Quality Assurance Department of Chiesi Farmaceutici S.p.A may perform an audit at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with Good Clinical Practices and protocol.

19. INSURANCE AND INDEMNITY

Chiesi Farmaceutici S.p.A. holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.

Chiesi Farmaceutici S.p.A. will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.

The Investigator must notify Chiesi Farmaceutici S.p.A. immediately upon notice of any claims or lawsuits.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi Farmaceutici S.p.A.

The Investigator must assure the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names, addresses and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi Farmaceutici S.p.A.

21. PREMATURE TERMINATION OF THE STUDY

The Sponsor, Competent Authorities and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.

The Sponsor should submit a written notification to the Regulatory Authority concerned and the IRB providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

The clinical study report, including the statistical and clinical evaluations, shall be prepared and sent to the Lead Investigator for agreement and signature.

At the end of the trial a summary of the clinical study report will be provided to all IRBs, to the Competent Authority of the US and to the Investigators.

23. RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.

Regulations require that essential documents must be retained for at least two years after the final marketing approval in an ICH region or until two years have elapsed since the formal interruption of the clinical development of the product under study.

It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. The Investigator must contact Chiesi Farmaceutici S.p.A. before destroying any trial- related documentation. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the institution.

24. PUBLICATION OF RESULTS

Chiesi Farmaceutici S.p.A. is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical trial data to national and international Regulatory Authorities, and if they fall under the Chiesi commitments on Clinical Trial Transparency, to make them available on www.chiesi.com website. Furthermore, Chiesi Farmaceutici S.p.A. reserves the right to use such data for industrial purposes.

In the absence of a Study Steering Committee, Investigators will inform Chiesi Farmaceutici S.p.A. before using the results of the study for publication or presentation and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites must not be published separately.

Negative as well as positive results should be published or otherwise made publicly available.

25. REFERENCES

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APPENDIX I

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.

Acronym: **LISPAP (Less Invasive Surfactant** administration combined with nCPAP**)**

Product: Poractant alfa (porcine derived surfactant, Curosurf®, Chiesi Farmaceutici S.p.A.)

Pharmaceutical Form: Sterile suspension

Test device: Thin catheter (CHF 6440, Chiesi Farmaceutici S.p.A.), specific for delivery of poractant alfa through LISA technique

Approval of Clinical Study Protocol by the Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this trial will not be initiated without Ethics Committee/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Informed written consent will be obtained from the parents/legal representative of all participating subjects and appropriately documented, prior to the enrolment in the study.

The undersigned agrees that the trial will be carried out in conformity with the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Investigator's Name: _____, MD

Center No.:_____

_____ _____
Signature Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A, 43122 Parma, Italy

APPENDIX II

MINIMUM LIST OF SOURCE DATA REQUIRED

- Date of informed consent signature
- Demographic data
- Study number
- Subject identity/number
- Randomization number
- Complications during pregnancy
- Neonatal comorbidities
- Neonatal Concomitant Medications
- Date of specific study visits
- Labels of study drugs
- Examination or assessments carried out during the study (please refer to Table 2)
- Laboratory reports (blood gas analysis)
- Adverse events / serious adverse events
- 24-month clinical assessment (Bayley scales, health status questionnaire)
- If subject is withdrawn, reason for withdrawal

APPENDIX III

COMPLICATIONS OF PREMATURITY

- **Air leaks** (pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum)
- **Apnea of prematurity**
- **Focal intestinal perforation (Neonatal spontaneous intestinal perforation)**
- **Germinal matrix hemorrhage/Intraventricular hemorrhage:** to be classified according to the following [28,29]:
  - 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 [30,31]
- **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" [32,33]

APPENDIX IV

PIPP SCORE ASSESSMENT TOOL