2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: Curosurf® (poractant alfa) administered through a specific thin catheter, CHF 6440 (LISACATH®), for less invasive surfactant administration (LISA)	**Volume:**	
Name of Active Ingredient: Not applicable Product is comprised of 99% polar lipids and 1% hydrophobic low molecular weight proteins	**Page:**	

Title of Study: 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

Investigators: 25 Investigators in the United States of America (USA)

Study Centers: Multicenter, 25 initiated centers in the USA (15 centers randomized neonates)

Publication (Reference): None

Studied Period:	**Phase of Development:**
First Patient First Visit: 12/JUN/2021 Last Patient Last Visit: 11/AUG/2022	Phase III b

Objectives:

Primary Objective:

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 NIV (continuous positive airway pressure, nasal intermittent positive pressure ventilation, bi-level positive airway pressure), 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 was assessed: adverse events (AEs) and adverse drug reactions (ADRs) 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.

Secondary Objective:

The short-term and mid-term efficacy profile, which was assessed mainly in terms of: reduced oxygen requirement and ventilatory support, need for invasive mechanical ventilation (MV) 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.

Methodology *(Study Design):*

This was a phase III b, open-label, multicenter, randomized, controlled study conducted in the USA. The study included preterm neonates aged 25^{+0} to 28^{+6} weeks gestational age (GA) with a clinical course consistent with RDS, who were spontaneously breathing and stabilized on NIV, and receiving fraction of inspired oxygen (FiO_2) ≥0.30 to maintain preductal oxygen saturation (SpO_2) between 88% and 95%. The GA was restricted to 27^{+0} to 28^{+6} weeks until a safety evaluation by the Independent Safety Monitoring Board (ISMB) was performed for the first 15 neonates. Provided no safety concerns were raised, enrollment was then opened to the entire study population. Further ISMB meetings were to be held after the first 60, 105, and 150 neonates to ensure the safety of neonates in the study on an ongoing basis.

Neonates were randomized from ≥30 minutes to <24 hours after birth to receive a single dose of Curosurf® 200 mg/kg either via brief insertion of a thin catheter (CHF 6440) into the trachea (i.e., LISA administration group) while NIV was maintained, or via conventional intubation with an endotracheal tube (ETT) (i.e., Conventional administration group) during brief invasive ventilation, followed by rapid extubation (within 1 hour). It was planned to randomize 100 neonates to the LISA administration group and 50 neonates to the Conventional administration group. Randomization occurred as soon as a FiO_2 ≥0.30 was needed to maintain SpO_2, determined by pulse oximetry, between 88% and 95%.

In the case of lack of efficacy or clinical deterioration, as determined by FiO_2 ≥0.30 to maintain SpO_2 between 88% and 95%, a second dose of Curosurf® 100 mg/kg was administered using the same technique as the first dose within approximately 12 hours of the previous dose. Neonates could receive a third Curosurf® 100 mg/kg dose if needed, administered using a standard technique. Neonates in the LISA administration group could be intubated, and neonates in the Conventional administration group could be re-intubated for MV at the neonatologist's discretion, if one or more of the conditions for MV were satisfied.

The study included the following periods:

- Pre-randomization;
- Day 1: including randomization, the period between randomization and start of study procedure, treatment administration up to end of surfactant administration (Time 0 [T0]), and up to 24 hours (at 5, 15, 30 minutes and 1, 6, 12, 24 hours) after receiving study treatment;
- Day 2: from 24 to 48 hours post-treatment;
- Day 3: from 48 to 72 hours post-treatment;
- Day 5: from 96 to 120 hours post-treatment.

Follow-up visits occurred at 28 days post-natal age (PNA), 36 weeks PMA, and at discharge home or 40 weeks (whichever came first). If discharge occurred before 36 weeks, the last follow-up was to occur at 36 weeks. This represented the main phase of the study. A final follow-up is planned at 24 months (±3 months) corrected age as a separate standalone visit. The data from this visit will be analyzed and evaluated separately from the initial main part of the study and will become the object of an addendum to the present clinical study report.

Note: The Sponsor issued an initial notification of an immediate enrollment hold to participating study sites on 01 June 2022 following the identification of issues related to the availability of the CHF 6440 catheter. An official notification of early termination of study recruitment was issued to all participating sites on 05 July 2022 following further assessment of supply issues with the CHF 6440 catheter. As the availability and provision of CHF 6440 catheter to participating sites could not be assured, the Sponsor decided to terminate the study early.

Number of Patients *(Planned and Analyzed)*:

A total of 150 neonates were planned to be randomized in a 2:1 ratio to either the LISA administration or the Conventional administration group (i.e., 100 and 50 neonates respectively). This number of neonates was not finally achieved owing to the early termination of the study (see note in the section above). A total of 33 neonates were randomized (i.e., 20 and 13 neonates in the LISA administration and Conventional administration groups, respectively).

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Neonates had to meet all the following inclusion criteria to be eligible for study enrollment:

1. Written informed consent obtained from parent/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. GA of 25^{+0} weeks up to 28^{+6} completed weeks; enrollment was restricted to neonates aged 27^{+0} weeks up to 28^{+6} GA weeks until safety evaluation of first 15 neonates was completed;
4. Clinical course consistent with RDS;
5. FiO_2 ≥0.30 to maintain SpO_2 in the target range of 88 to 95%.

Exclusion Criteria:

The presence of any of the following excluded a neonate from study enrollment:

1. Need for immediate endotracheal intubation for cardiopulmonary resuscitation or insufficient respiratory drive;
2. Use of nasal high frequency oscillatory ventilation 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 have caused 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 have placed 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 have been permitted following an agreement with the Sponsor. Non-interventional observational studies were allowed.

Test Product, Dose, and Mode of Administration, Batch Numbers:

Curosurf® (poractant alfa) sterile suspension in 3.0 mL glass vials with a total concentration of 80 mg/mL. 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 surfactant proteins B and C.

In the test therapy, the LISA procedure, Curosurf® was administered via brief insertion of a thin catheter (CHF 6440, LISACATH®) into the trachea while NIV was maintained in situ. The CHF 6440 catheter has a 1.7 mm outer and 1.1 mm internal diameter (corresponding to a 5 and 3.5 French gauge outer and internal diameter, respectively), and a soft rounded leading tip for atraumatic insertion via the mouth.

In both treatment arms, an initial single dose of Curosurf® 200 mg/kg was administered. In case of lack of efficacy or clinical deterioration, an additional dose of 100 mg/kg was administered using the same technique as the first dose. A third dose of Curosurf® 100 mg/kg could be administered if needed, using a standard technique.

Batch numbers for the investigational products (study treatment and LISA procedure catheter) are provided below.

	Clinical trial supply batch record number	Drug product or catheter batch number	Expiry date
Curosurf® (poractant alfa 80 mg/mL, 3 mL vial)	1084513	1121636	March 2022
	1092883	1131253	October 2022
CHF 6440 (LISACATH®)	1084514	DS19952	July 2022

Duration of Treatment:

An initial single dose of Curosurf® 200 mg/kg was administered within the time interval from 30 minutes after birth up to 24 hours after birth. Additional doses of 100 mg/kg were administered if needed, within approximately 12 hours of the previous dose. Up to two additional doses were allowed.

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

The reference therapy was Curosurf® administered via conventional intubation with an ETT (i.e., Conventional administration group) during brief invasive ventilation, followed by rapid extubation (within 1 hour). An approved endotracheal method of administration was used, i.e., either a 5-French end-hole catheter inserted into the ETT, or through 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 immediately extubated and placed again on NIV. If connected to the ventilator, extubation had to be performed within 1 hour after surfactant administration.

Criteria for Evaluation:

Efficacy:

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

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

  Conventional administration 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 administration 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 T0 (study treatment administration end), 5, 15, 30 minutes, and 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 T0 (study treatment administration end), 5, 15, 30 minutes, and 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 T0 (study treatment administration end), 5, 15, 30 minutes, and 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 NIV during the study (days);
- Blood gas analysis, specifically acid-base balance parameters (i.e., pH, partial pressure of carbon dioxide [pCO_2] and oxygen [pO_2], bicarbonate [HCO_3-], base excess [BE], lactate) pre-surfactant administration (when applicable), at 1, 6, 24, 48, and 72 hours after study treatment.

Safety:

The following variables were 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 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) positive pressure ventilation (PPV) and related duration of ventilation (NIV);
- 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:

- Heart rate (HR) and respiratory (RR) at T0, 5, 15, and 30 minutes, and at 1, 6, and 12 hours after administration;
- Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) at 15 and 30 minutes, and at 1, 6, and 12 hours after administration;
- Premature Infant Pain Profile (PIPP) score at end of surfactant administration.

After first and second administration:

- Number and percentage of neonates with failed first attempt to insert the CHF 6440 catheter/ETT;
- Number of maneuvers discontinued due to neonate's severe destabilization;

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

During the study:

- AEs, including incidence of major neonatal complications of prematurity and ADRs;
- Blood pressure (SBP, DBP, MBP) at 24, 48, 72, and 120 hours post-administration;
- HR and RR at 24, 48, 72, and 120 hours post-administration and 28 days PNA, 36 weeks PMA, and discharge home or 40 weeks PMA (whichever came 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 28 days PNA and 36 weeks PMA;
- Oxygen use (alone and/or during invasive and NIV) at 28 days PNA and 36 weeks PMA;
- Weight, occipital-frontal circumference (OFC) and length at discharge home or 40 weeks PMA (whichever came first);
- Feeding and hearing status at discharge home or 40 weeks PMA (whichever came first);
- Incidence of major neonatal morbidities at discharge home or 40 weeks PMA (whichever came first);
- Neonates needing invasive ventilation or non-invasive respiratory support at discharge home or 40 weeks PMA (whichever came first);
- Neonates needing respiratory medications at discharge home or 40 weeks PMA (whichever came first).

At 24 months (±3 months) corrected age:

The results of this standalone assessment are not presented within the present report.

- 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).

Statistical Methods:

Efficacy Analyses:

Need for mechanical ventilation/intubation:

- The percentage of neonates needing invasive MV ventilation in the first 72 hours of life, in the first 28 days PNA, and within 36 weeks PMA was compared between the treatment groups using the Cochran-Mantel-Haenszel (CMH) test adjusted for GA group. The CMH adjusted difference and corresponding 95% confidence interval (CI) was presented;

- The 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 was compared between the treatment groups as per the need for invasive MV;
- Descriptive summaries of the percentage of neonates needing invasive MV or intubation in the first 72 hours of life, in the first 28 days PNA, and within 36 weeks PMA were repeated stratified by the use of sedation/analgesia (Yes/No) to explore the impact of use of sedation and/or analgesia.

SpO_2, FiO_2 and SpO_2/FiO_2 ratio:

- SpO_2, FiO_2, and the SpO_2/FiO_2 ratio were analyzed using a linear mixed model for repeated measures, including treatment, timepoint, treatment by timepoint interaction, and GA group as fixed effects, and pre-procedure value as a covariate. The adjusted means in each treatment group, the adjusted mean difference between treatment groups, and the corresponding 95% CIs at each timepoint and averaged over the first 120 hours post-treatment were estimated by the model;
- Time profile plots of mean SpO_2, FiO_2, and the SpO_2/FiO_2 ratio in the first 120 hours post-treatment were presented by treatment group. Forest plots for each parameter were also presented;
- SpO_2, FiO_2, and the SpO_2/FiO_2 ratio were summarized using descriptive statistics by treatment group for neonates still receiving respiratory support at 28 days (±2 days) PNA and 36 weeks PMA.

Blood gas analysis:

- Acid-base balance parameters (i.e., pH, pCO_2, pO_2, HCO_3^-, BE, lactate) were summarized using descriptive statistics by treatment group as absolute and change from pre-procedure values.

Use of additional surfactant doses:

- The percentage of neonates requiring at least one additional surfactant dose was compared between treatment group using a Fisher's exact test. The odds ratio and related exact 95% CI was also provided. Neonates with pulmonary hemorrhage (from AE form, occurring during the first procedure) were excluded from this analysis;
- The number of additional surfactant doses were summarized using descriptive statistics by treatment group.

Duration of ventilation/oxygen supplementation (alone):

- The median durations of invasive MV in the first 72 hours of life (in hours), in the first 28 days PNA (in days), and within 36 weeks PMA (in days) and standalone oxygen supplementation (in days) and NIV (in days) were compared between treatment groups using the Mann-Whitney U test. Estimates of median difference and the corresponding 95% CIs were presented.

Safety Analyses:

Parameters related to the first and second administration:

The following analyses were based on actual treatment received for the first administration. If the second administration actually received was not compliant with the first administration, the data were not analyzed.

- The number of first failed attempts to insert the catheter/ETT was summarized by treatment group. The percentage of neonates with first failed attempt was compared between treatment groups using the CMH adjusted for GA group. The CMH adjusted difference and corresponding 95% CI was presented;
- The number of maneuvers discontinued due to neonate's severe destabilization was summarized using descriptive statistics by treatment group;
- The number of device misallocation (i.e., esophageal intubation) was summarized, only for the LISA administration group, using descriptive statistics;
- The number of attempts to the first successful insertion was summarized using descriptive statistics by treatment group;
- The durations of surfactant administration (in minutes) and the overall procedure (in hours and minutes) for surfactant administration were compared between treatment groups using the Mann-Whitney U test.

Adverse events:

All AEs were coded using Medical Dictionary for Regulatory Activities Version 24.0. Treatment-emergent adverse events (TEAEs) were AEs that started on or after the date of first randomized treatment administration up to the end of the main phase of the study. TEAEs and pre-treatment AEs (only presented as listings) were presented separately.

The following were summarized by treatment group:

- The number and percentage of neonates with AEs starting during the overall procedure for surfactant administration by dose (first or second) and AEs starting during the overall procedure for surfactant administration dose (first or second) and judged related to the procedure;
- The number of AEs occurring during the 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;
    - Administration of manual (bag and mask) PPV and related duration of ventilation (NIV);
    - Endotracheal intubation and related duration of intubation (invasive ventilation);
    - Circulatory support including administration of crystalloids;
    - Cardiopulmonary resuscitation including administration of cardiac massage or adrenaline.

The frequency of neonates with at least one TEAE, ADR, serious TEAE, and TEAE leading to death event and the number of events in each category, was summarized by treatment group, system organ class (SOC) and preferred term (PT).

The frequency and percentage of neonates experiencing an AE indicating neonatal complications of prematurity was summarized for each complication along with the grade.

For AEs starting during the procedure, requiring either invasive or non-invasive (bag and mask) PPV, the related duration of invasive ventilation and PPV was summarized.

The incidence of Corona Virus Disease 2019 was summarized separately.

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

Vital signs:

Parameters (SBP, DBP, MBP, HR, and RR) were summarized using descriptive statistics by treatment group at each scheduled visit.

Pain assessment:

PIPP total score on Day 1 (calculated as the sum of pre-procedure total PIPP score and total PIPP score at T0) was summarized using descriptive statistics by treatment group.

Mortality and bronchopulmonary dysplasia:

- The number of deaths/BPD incidence at 36 weeks PMA was compared using the CMH test. The relative risk and related 95% CI were presented. Frequency and percentages under each GA group (25^{+0} to 26^{+6} weeks and 27^{+0} to 28^{+6} weeks) was also displayed;
- The incidence of BPD at 36 weeks PMA was compared by treatment as per the incidence of deaths/BPD. The severity of BPD was also summarized;
- Mortality and oxygen use (alone and/or during any kind of MV) at 28 days PNA and 36 weeks PMA was compared by treatment as per the incidence of deaths/BPD.

Other safety variables:

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

Summary – Results:

Study Population:

In this study, a total of 33 neonates were randomized: 20 to LISA administration and 13 to Conventional administration. Two neonates (one randomized to each treatment group) were not treated and were therefore not included in study analyses. The majority of randomized neonates completed the study (90.0% and 84.6% of neonates with LISA administration and Conventional administration, respectively).

Overall, the mean GA for neonates included in the Intention-to-treat population was 27.76 weeks (only 3 neonates with GA from 25^{+0} to 26^{+6} weeks were included) and the median Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 5 minutes after birth was 8.0 points. More than half of the neonates were male (58.1%) and White (58.1%). The mean birth weight was 0.995 kg, ranging from 0.52 kg to 1.67 kg.

The demographic and baseline characteristics, and medical history, of neonates and their mothers were generally balanced between the LISA administration and Conventional administration groups; however, noteworthy differences were observed in terms of the mean age of mothers (30.0 versus [vs.] 25.8 years) and the percentage of mothers who received corticosteroids antenatally (73.7% vs. 91.7%).

Efficacy Results:

Evaluation of efficacy formed the secondary objective of this study; as such, no primary efficacy variable was defined.

In spontaneously breathing preterm neonates, with a clinical course consistent with RDS, and stabilized on NIV, administration of Curosurf® via LISA administration, compared to Conventional administration (with ETT, followed by rapid extubation), favorable trends were observed in some of the efficacy outcomes (oxygenation in the first 72 hours post-administration, need for MV in the first 72 hours of life, and

duration of MV in the short- and mid-term), without statistically significant differences. No clinically meaningful benefit was observed in the other efficacy parameters.

The percentage of neonates needing invasive MV in the first 72 hours of life, in the first 28 days PNA, and within 36 weeks PMA was numerically lower with LISA administration than with Conventional administration. However, there was no statistically significant difference between treatment groups in this parameter at any of those timepoints.

In line with the numerically lower percentage of neonates needing invasive MV with LISA administration during the study, the duration of invasive ventilation in the first 72 hours of life, in the first 28 days PNA, and within 36 weeks PMA was also numerically lower with LISA administration than with Conventional administration. However, similarly, there was no statistically significant difference between treatment groups in this parameter at any of those timepoints.

For SpO_2, despite an initial drop from pre-procedure SpO_2 at T0 with LISA administration, a positive trend for a better oxygenation profile with LISA administration than with Conventional administration was observed from 30 minutes post-treatment to 120 hours post-treatment. However, no statistically significant differences were observed in SpO_2 at any individual timepoint, nor considering the first 120 hours post-treatment overall.

For FiO_2, despite an initial spike from pre-procedure FiO_2 at T0 with LISA administration, a positive trend for a reduced oxygen requirement with LISA administration than with Conventional administration was observed from 5 minutes post-treatment up to 72 hours post-treatment; subsequently, oxygen requirement was similar between treatments. No statistically significant differences were observed in FiO_2 at any individual timepoint, nor considering the first 120 hours post-treatment overall.

When considering the parameters together via the SpO_2/FiO_2 ratio, despite an initial drop from pre-procedure SpO_2/FiO_2 ratio at T0 with LISA administration, a positive trend for a better oxygenation profile with LISA administration than with Conventional administration was observed from 5 minutes post-treatment up to 72 hours post-treatment; subsequently, oxygenation was similar between treatments. Statistically significant differences in SpO_2/FiO_2 ratio were not observed at any individual timepoint except 1 hour post-treatment (when the SpO_2/FiO_2 ratio was statistically significantly higher with LISA administration, p=0.040), nor considering the first 120 hours post-treatment overall.

Among the neonates still receiving respiratory support at Day 28 PNA and 36 weeks PMA with available data, mean SpO_2, FiO_2, and SpO_2/FiO_2 ratio values were generally similar with LISA administration and Conventional administration.

The percentage of neonates needing at least one additional dose of surfactant during the study was numerically lower with Conventional administration than with LISA administration. However, no statistically significant difference between treatment groups was observed.

No statistically significant differences between LISA administration and Conventional administration were observed considering the durations of oxygen alone supplementation and NIV during the study (median duration and mean duration, respectively, were numerically longer with LISA administration than with Conventional administration).

The mean changes from pre-procedure in blood gas analysis acid-base balance parameters (pH, pCO_2, pO_2, HCO_3^-, BE, lactate) were generally similar between treatment groups.

Safety Results:

Administration of the first dose of study treatment was completed successfully in all neonates. The majority of neonates received only the first dose of study treatment; overall, nearly 20% of neonates received two doses, and 10% of neonates received three doses. The percentage of neonates who received one, two, or three doses was not remarkably different between treatment groups; accordingly, study treatment exposure was similar with each treatment. Considering the first administration, while the first attempt to insert the CHF 6440 catheter/ETT failed in a numerically lower percentage of neonates with LISA administration than with Conventional administration, no statistically significant difference between groups was observed. Duration of surfactant administration was numerically shorter with LISA administration, but the difference was not statistically significant, while duration of the whole procedure was statistically significantly shorter with LISA administration for the first administration. In 2 neonates

with LISA administration (1 unique neonate at each administration), the procedure had to be temporarily discontinued due to neonate's severe destabilization; however, in both cases it could be re-started and completed after proper management (neither neonate required major interventions like endotracheal intubation, circulatory support, or cardiopulmonary resuscitation). Device misallocation was assessed with LISA administration only and was reported in 3 neonates at first administration.

One device deficiency (also recorded as a TEAE [PT: device occlusion]) was reported during the first study treatment administration of a neonate with LISA administration. The study staff reported difficulties in the use of a straight catheter and the catheter was removed, slightly bent, and re-inserted, after which the administration was completed successfully using the same catheter. The device deficiency was reported as leading to a TEAE (PT: laryngeal haemorrhage), which was mild in intensity, non-serious, and resolved within 5 minutes of onset without intervention. During the same procedure, a desaturation was also reported (PT: neonatal hypoxia), considered as an ADR, which is described in more detail below.

The incidence of AEs starting during the overall procedure for surfactant administration was higher with LISA administration than with Conventional administration: 18 AEs were reported in 11 (57.9%) neonates with LISA administration and 6 AEs were reported in 3 (25.0%) neonates with Conventional administration; all AEs starting during the procedure, except 1 with Conventional administration, were judged as related to the procedure, none were serious AEs. With both treatments, the majority of AEs starting during the procedure by PT were reported in <2 neonates; those reported in ≥2 neonates with either treatment were: neonatal hypoxia, infantile apnoea, and bradycardia neonatal. Of the AEs starting during the procedure, 9 events in 7 (36.8%) neonates with LISA administration and 2 events in 2 (16.7%) neonates with Conventional administration required treatment with either oxygen alone or an increase in FiO_2 without the need for escalation of invasive or non-invasive ventilator support; a further 3 events in 2 (10.5%) neonates with LISA administration required administration of manual (bag and mask) PPV; none of the AEs required endotracheal intubation, circulatory support, or cardiopulmonary resuscitation. All AEs starting during the procedure were transient and resolved without sequelae.

All neonates were reported with at least 1 TEAE during the study. The total number of TEAEs reported was higher with LISA administration (139 TEAEs) than with Conventional administration (69 TEAEs); the numerical difference observed was driven by a difference in the number of mild events only. Most of the TEAEs reported with LISA administration and with Conventional administration were mild or moderate in intensity and the majority had resolved by the end of the main phase of the study. The incidence of severe TEAEs was low and similar with LISA administration (6 events in 2 [10.5%] neonates) and with Conventional administration (5 events in 1 [8.3%] neonate). No individual severe TEAE by PT was reported in >1 neonate with LISA administration or Conventional administration. Overall, AEs indicating neonatal complications of prematurity accounted for almost one-quarter of TEAEs (50/208 TEAEs). With both treatments, the majority of TEAEs by PT were reported in ≤50% neonates; those reported in >50% neonates with either treatment were: infantile apnoea (in 13 [68.4%] and 5 [41.7%] neonates with LISA administration and Conventional administration, respectively), hyperbilirubinaemia neonatal (in 11 [57.9%] and 5 [41.7%] neonates with LISA administration and Conventional administration, respectively), and anaemia neonatal (in 10 [52.6%] and 4 [33.3%] neonates with LISA administration and Conventional administration, respectively).

Only 1 ADR was reported. The ADR (PT: neonatal hypoxia), which occurred with LISA administration, was non-serious and moderate in intensity. The ADR started during study treatment administration and was temporally associated with a device deficiency that occurred at the outset of the study treatment administration procedure (described above). The ADR was managed by transient increase in oxygen delivery and had resolved by 30 minutes post-administration.

The incidence of TEAEs leading to death was similar with LISA administration (2 events in 1 [5.3%] neonate) and with Conventional administration (1 event in 1 [8.3%] neonate). Both neonates with TEAEs leading to death were from the GA group '25^{+0} to 26^{+6} weeks'. None of the TEAEs leading to death were considered related to the study treatment.

A total of 2 serious TEAEs were reported in 1 (5.3%) neonate with LISA administration and 5 serious TEAEs were reported in 2 (16.7%) neonates with Conventional administration. No individual serious TEAE by PT was reported in >1 neonate. Overall, 3 of the 7 serious TEAEs were fatal (see above);

2 of the non-fatal events resolved and 2 other non-fatal events resolved with sequelae. None of the serious TEAEs were considered related to the study treatment.

No meaningful safety signals emerged from vital signs assessments; the majority of neonates did not show changes of clinical concern with treatment. Changes in HR and/or RR were observed in some neonates at timepoints shortly after administration, largely corresponding to the AEs starting during the procedure.

Median (minimum ; maximum) Day 1 PIPP total score was similar with both treatment groups: 6.0 (3 ; 12) points with LISA administration and 5.5 (2 ; 15) points with Conventional administration, suggesting that the LISA procedure was not associated with more pain/discomfort.

At 36 weeks PMA, BPD was reported in 9 (50.0%) and 7 (70.0%) neonates with LISA administration and Conventional administration, respectively. While the relative risk was in favor of LISA administration, no statistically significant difference between treatment groups was observed (CMH relative risk: 71.4% [95% CI: 38.6; 132.1], p=0.314). Similar results were observed considering the category 'death or BPD'. Severity of BPD was evaluated based on the requirement for oxygen and respiratory support at 36 weeks PMA. No statistically significant differences between treatment groups were observed considering any of the CMH test comparisons (mild BPD: relative risk: 166.7% [95% CI: 19.9; 1398.4], p=0.635; moderate BPD: relative risk: 27.8% [95% CI: 6.1; 125.9], p=0.080; severe BPD: relative risk: 111.1% [95% CI: 24.5; 503.5], p=0.893).

When growth, neonatal comorbidities, and respiratory morbidity were assessed at discharge home or 40 weeks PMA, no relevant difference between treatments were observed. A total of 3 (16.7%) and 4 (36.4%) neonates were receiving supplemental oxygen via nasal cannula with LISA administration and Conventional administration, respectively.

Conclusion:

This phase III b randomized, controlled study showed that in preterm neonates with RDS, aged 25^{+0} to 28^{+6} weeks GA, the administration of Curosurf® via LISA administration did not cause any unexpected safety issues when compared to Conventional administration. While a higher number of peri-procedural AEs were reported with LISA administration vs. Conventional administration, mid-term safety profile, as assessed by incidence of BPD at 36 weeks PMA, showed a more favorable trend. In terms of efficacy parameters, trends favoring LISA administration over Conventional administration were observed in some of the efficacy outcomes, particularly during the first 72 hours of life, without statistically significant differences. However, the relatively low number of neonates included in the study as a result of its early termination allows only limited conclusions to be drawn regarding the impact of surfactant administration procedure on the pre-defined endpoints.

Date of Report: 18 April 2023