2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A. (Chiesi)	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: Curosurf® (poractant alfa) administered via [redacted]	**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: A randomized, open, multinational, multicentre, 2-part study in spontaneously breathing preterm neonates with mild to moderate respiratory distress syndrome to investigate the safety, tolerability and efficacy of inhaled nebulised poractant alfa (porcine surfactant, Curosurf®) in comparison with nCPAP alone

Investigators:
Part I: 9 recruiting investigators in 4 countries

Study Centres:
Part I: Multicentre, 9 recruiting centres (11 initiated) in 4 countries

Publication (*Reference*): None

Studied Period: Part I: ***Initial Core Study:*** First Patient First Visit (FPFV): 28/AUG/2017 Last Patient Last Visit (LPLV): 21/JUN/2018 ***Clinical Assessment at 24 Months:*** FPFV: 10/NOV/2019 LPLV: 05/OCT/2020	**Phase of Development:** Phase II

Background and Rationale for the Clinical Study Report (CSR) Addendum:

The initial core part of this study was conducted in two phases (Part I and Part II), both of which had follow-up periods until discharge home, 36 weeks post-menstrual age or between 28 and 56 days post-natal age depending on gestational age (GA).

For patients treated during Part I, further standalone clinical assessment was performed at 24 months (±3 months) corrected age to check the neurological and general health status related to the condition of prematurity.

This addendum describes the results of the standalone clinical assessment done for patients treated during Part I to evaluate the long-term safety profile of the study treatment.

Previous long-term follow-up studies conducted in surviving preterm infants treated with surfactant have not identified any increases in major neurodevelopmental or pulmonary sequelae. A meta-analysis systematic review including randomised controlled trials of surfactant replacement therapy with follow-up outcomes did not show any concerns[1]. Moreover, in more than 25 years of post-marketing experience with Curosurf®, with more than 3 million patients treated worldwide, no long-term effects have been notified to Chiesi[2]. Therefore, a different safety profile based on the way of administration was not expected. Importantly, no major safety issues were observed with Curosurf® compared with the control group for Part I of this study. Therefore, the 24-month clinical assessment originally also planned for patients treated during Part II will not be done.

[redacted]

Objectives:

The main objective of the initial phase of study Part I was to assess the safety and tolerability of three single ascending doses of nebulised Curosurf®.

The objective of this standalone assessment was to check cognitive and language development, to evaluate cerebral palsy, seizure and feeding method and to evaluate functional disability of the senses and communication, growth, respiratory morbidity and general health status related to the condition of prematurity at birth.

Methodology *(Study Design):*

Study Part I was conducted according to a multicentre, randomised, open-label, ascending dose, controlled design in 3 cohorts of preterm neonates.

In each of the 3 cohorts, 12 neonates were randomised to receive the active treatment (nebulised Curosurf®) from 60 minutes up to 12 hours from birth or to remain on nasal continuous positive airway pressure (nCPAP) alone. Each cohort was comprised of:

- 9 neonates on active treatment (27 neonates in total across all cohorts): neonates received Curosurf® as a single dose administration of 200 mg/kg in the first cohort, 400 mg/kg in the second cohort and 600 mg/kg in the third cohort, according to a dose escalation scheme;
- 3 neonates as control (9 neonates in total across all cohorts): neonates remained on nCPAP alone.

As soon as the last neonate of each cohort (active treatment and control) was enrolled, the recruitment was stopped until an Independent Safety Monitoring Board (ISMB) evaluated the

[1] Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. J Paediatr Child Health 2002;38(6):597-600.

[2] Investigator's Brochure of product CHF01534CA1 ([redacted]): CUROSURF (Poractant Alfa) administered by nebulisation. [redacted]

first 7-day safety data of all 12 neonates. As no major safety concerns were raised, the ISMB's decision triggered the continuation of the dose escalation scheme to the next dose.

When the last enrolled neonate of the third cohort (the highest dose of nebulised Curosurf®) completed the 7-day assessment period, a final ISMB meeting was carried out. Considering the final ISMB advice and the study results until the end of Part I of the study for all 36 neonates, Chiesi selected the 2 doses to be tested in Part II of the study.

After the completion of the initial core study phase, at 24 months (±3 months) corrected age, the families of the surviving treated patients were contacted to attend an on-site clinic visit (at the recruiting site) to perform the following clinical assessments:

- Bayley Scales of Infant Development (BSID): mental development index (MDI) (BSID-II) or language and cognitive scores (BSID-III) according to the version in use at the participating investigational sites;
- Vital signs: systolic, diastolic and mean blood pressure (SBP, DBP, MBP), heart rate (HR), respiratory rate (RR);
- Health status questionnaire, including:
  - Anthropometric measures: body weight, height and head circumference;
  - Cerebral palsy evaluation;
  - Seizure evaluation;
  - Feeding method: spoon, nasogastric tube or gastrostomy;
  - Functional disability: sensory and communication evaluation;
  - Clinical assessment of respiratory conditions and morbidity;
  - Physical examination and last cardiological diagnosis and timing (on the basis of electrocardiogram and/or echography).

When not feasible for reasons related to the parent's and patient's availability or to COVID-19 restrictions, the on-site visit was replaced by a contact/phone call by the Investigator to the parents or to the family's paediatrician to attempt to retrieve the key information on health status.

[redacted]

Number of Patients *(Planned and Analysed)*:

Part I: A total of 36 neonates were to be randomised. Only neonates of 28^{+0} to 32^{+6} weeks GA were planned to be included in the study, according to clinical study protocol (CSP) Version 3.0. However, a neonate with a lower GA was randomly allocated to the 200 mg/kg cohort as per a previous version of the CSP. This neonate was not included in the analysis populations, but relative data were presented in the data listings. This neonate was started on nebulised Curosurf® but did not complete nebulisation successfully.

Excluding the neonate described above, a total of 36 neonates received active treatment or nCPAP alone and were included in the Safety population (SAF). All 36 neonates included in the analyses completed Part I of the study (excluding assessments at 24 months corrected age).

Of these, 27 (75.0%) patients were examined for the 24-month clinical assessment and another 4 (11.1%) patients' parents were interviewed (the total number comprised the Completers analysis set [CAS]); this included 9 patients from the 200 mg/kg group (all examined), 8 patients from the 400 mg/kg group (all examined), 9 patients from the 600 mg/kg group (6 examined/3 parent interviews) and 5 patients from the nCPAP group (4 examined/1 parent interview). Data from these 31 patients form the basis of the CSR addendum.

Main Criteria for Inclusion:

Inborn preterm neonates of either sex with a GA of 28^{+0} to 32^{+6} weeks and a clinical course consistent with respiratory distress syndrome (RDS), receiving continuous positive airway pressure 5 to 8 cmH_2O and fraction of inspired oxygen between 0.25 and 0.40 to maintain peripheral oxygen saturation between 88% and 95% for at least 30 minutes were eligible for inclusion in the initial core part of study no. CCD-01534CA1-01. Any surviving patients who completed the core part of the study were eligible to undergo the standalone clinical assessment at 24 months (±3 months) corrected age.

[redacted]

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

Curosurf® 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 proteins SP-B and SP-C.

Curosurf® was administered through a customised vibrating membrane nebuliser ([redacted]) which is placed between the nasal prongs and the connection of the ventilator circuit.

In Part I of the study, three ascending single doses of Curosurf® at 200 mg/kg (first cohort), 400 mg/kg (second cohort), and 600 mg/kg (third cohort) were administered. The doses to be used in Part II were defined based on Part I results.

[redacted]

Duration of Treatment:

A single administration of nebulised Curosurf® between 60 minutes and 12 hours after birth whilst nCPAP was ongoing. The total duration of the nebulisation was variable considering the neonate's body weight, but was not to last more than 30, 60 and 90 minutes for the 200, 400 and 600 mg/kg groups, respectively.

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

The reference therapy was nCPAP alone.

[redacted]

Criteria for Evaluation:

Safety:

- BSID; patients had either:
  - BSID-II MDI scaled score;
  - BSID-III language and cognitive composite scores;
  - Overall evaluation of child development in case no formal developmental assessment was performed (i.e. normal development, mild delay, moderate delay, severe delay).
- Vital signs: SBP, DBP, MBP, HR, RR;
- Health status questionnaire, evaluating the following:
  - Anthropometric measures: body weight, height, head circumference;
  - Cerebral palsy evaluation: presence of cerebral palsy, gross motor ability observed using the Gross Motor Function Classification Scale for Cerebral Palsy (GMFCS),

presence of ventricular shunt, recurrent seizures, presence of other neurological problems;

- Feeding method: spoon, nasogastric tube or gastrostomy;
- Functional disability – sensory and communication: vision problems or eye defects, hearing problems, speech or language problems;
- Clinical assessment of respiratory conditions and morbidity: requirement of oxygen at home, current use of medicine for chest problems, current medication, need of chest physical therapy, attacks of wheezing or gasping in the last 12 months under various conditions, re-hospitalisation;
- Physical examination: presence of congenital malformation or pulmonary hypertension, last cardiological evaluation.

Statistical Methods:

The analyses were performed on the CAS, consisting of all patients in SAF who were alive and examined for the 24–month clinical assessment, or for whom contact and interview with the parents was possible.

All BSID, vital signs and health status questionnaire items were summarised by treatment group and overall using appropriate descriptive statistics.

For patients with BSID assessment, patients were classified as below normal range in the following cases:

- BSID-II: if MDI < 70;
- BSID-III: if language AND cognitive composite scores both < 85. If either score was missing, development was not defined. If both scores were available, both values had to be ≥ 85 for development to be considered normal.

Patients with either BSID-II MDI ≥ 70 or available BSID-III score (language OR cognitive) ≥ 85 were also identified. If language or cognitive score was missing development was defined based on the available score. If both language and cognitive scores were available both should have been ≥ 85 for development to be considered normal.

The number and percentage of patients with BSID scores below the normal range were summarised by treatment group and overall. In addition, the number and percentage of patients with BSID-II MDI scaled score ≥ 70 and available BSID-III composite score(s) ≥ 85 were summarised by treatment group and overall.

Sensitivity analysis was performed excluding patients meeting exclusion criterion #5 (major congenital anomalies) in the main study phase from the BSID analyses.

Summary – Results:

Efficacy Results:

Not applicable.

Safety Results:

Of the 31 patients in the CAS, 9 (100.0%), 8 (100.0%), 5 (55.6%) and 4 (80.0%) patients underwent any BSID assessment with nebulised Curosurf® 200 mg/kg, nebulised Curosurf® 400 mg/kg, nebulised Curosurf® 600 mg/kg and nCPAP, respectively, and, of the patients with full BSID assessment, a similar percentage of patients with each treatment were considered to be normal: 4 (44.4%), 5 (62.5%), 3 (60.0%) and 2 (50.0%) patients, respectively. To be considered normal the BSID-II MDI scaled score had to be ≥ 70 or both BSID-III language and cognitive composite scores had to be ≥ 85. If one BSID-III score was missing, development was not defined. Considering patients with any BSID assessment, 7 (77.8%), 5 (62.5%), 4 (80.0%) and 2 (50.0%) patients had BSID-II MDI scaled score ≥ 70 or available BSID-III composite score(s) ≥ 85 with nebulised Curosurf® 200 mg/kg, nebulised Curosurf® 400 mg/kg, nebulised Curosurf® 600 mg/kg and nCPAP. A further 5 patients (4 with nebulised Curosurf® 600 mg/kg and 1 with nCPAP) did not undergo any BSID assessment. Among those patients, 2 patients (1 each with nebulised Curosurf® 600 mg/kg and nCPAP) were considered developmentally normal based on clinical judgement of information collected from parents, without formal neurodevelopmental assessment.

In terms of neurological conditions, none of the patients had cerebral palsy at 24-month clinical assessment, nor were any of the patients reported with a ventricular shunt or other neurological problems. A total of 2 patients overall (both with nebulised Curosurf® 400 mg/kg) were reported as suffering recurrent seizures; for 1 patient seizures were febrile. All patients were reported to eat solid food with a fork and drink by cup without problems except 1 patient with nebulised Curosurf® 400 mg/kg ([redacted]) who used a nasogastric tube to feed.

Considering sensory and communication ability, 3 patients overall were reported with a visual or eye defect/problem of any type at 24-month clinical assessment (1 each with nebulised Curosurf® 400 mg/kg, nebulised Curosurf® 600 mg/kg and nCPAP). In addition, 3 patients with nebulised Curosurf® 200 mg/kg and 1 patient with nCPAP were reported with retinopathy of prematurity. Despite this, all patients were reported with normal to mildly reduced vision except 1 patient with nebulised Curosurf® 400 mg/kg ([redacted]) whose vision was considerably reduced. A total of 2 patients overall (1 with nebulised Curosurf® 400 mg/kg [[redacted]] and 1 with nebulised Curosurf® 600 mg/kg) were reported with hearing impairment which was not normalised by use of hearing aids. In addition, 6 patients overall (1 with nebulised Curosurf® 200 mg/kg, 3 with nebulised Curosurf® 400 mg/kg [[redacted]] and 2 with nebulised Curosurf® 600 mg/kg) were reported as having communication difficulties.

Respiratory problems at 24-month clinical assessment appeared to be minimal. None of the patients had required oxygen at home since discharge nor were they reported with any wheezing or gasping after exercise during the last 12 months. Two patients with nebulised Curosurf® 400 mg/kg were reported as needing chest physical therapy ([redacted]). In addition, 4 patients overall were reported as having had attacks of wheezing or gasping during the last 12 months (2 with nebulised Curosurf® 400 mg/kg [[redacted]] and 1 each with nebulised Curosurf® 600 mg/kg and nCPAP).

By the 24-month clinical assessment, 10 patients overall had been re-hospitalised since discharge from the neonatal unit with 21 events: 1 patient with 2 events with nebulised

Curosurf® 200 mg/kg, 5 patients with 13 events with nebulised Curosurf® 400 mg/kg, 2 patients with 2 events with nebulised Curosurf® 600 mg/kg and 2 patients with 4 events with nCPAP. Of the re-hospitalisations which occurred with nebulised Curosurf® 400 mg/kg, 5 of the 13 events were experienced by 1 patient ([redacted]). Overall, the majority of events which led to re-hospitalisation were caused by infection (11 of 21 events) or by seizure (4 of 21 events). The mean number of times patients needed re-hospitalisation was similar between treatments: 2.0, 2.6, 1.0 and 2.0 with nebulised Curosurf® 200 mg/kg nebulised Curosurf® 400 mg/kg, nebulised Curosurf® 600 mg/kg and nCPAP, respectively.

With nebulised Curosurf® 400 mg/kg, 1 patient was reported with congenital malformation ([redacted]) and 1 patient was reported with hypertension. None of the patients were reported with pulmonary hypertension.

Vital signs and anthropometric measures were similar with all treatments considering available data at 24-month clinical assessment.

Conclusion:

At 24-month clinical follow-up, preterm neonates aged 28^{+0} to 32^{+6} weeks GA and with mild to moderate RDS at randomisation, treated with a single dose of nebulised Curosurf® at 200 mg/kg, 400 mg/kg or 600 mg/kg alongside nCPAP were not subject to an increased likelihood of major neurodevelopmental or pulmonary sequelae compared to preterm neonates treated with nCPAP alone.

Date of report: 11 March 2021