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)		
Name of Active Ingredient: Not applicable Product is comprised of 99% polar lipids and 1% hydrophobic low molecular weight proteins	**Volume:** **Page:**	

Title of Study: Multicenter, open-label, randomised trial to assess the efficacy and tolerability of poractant alfa (porcine surfactant, Curosurf®) in hospitalized patients with SARS-COV-19 acute respiratory distress syndrome (ARDS)

Investigators: 5 recruiting Investigators in 3 countries

Study Centres: Multicentre, 5 recruiting centres (6 initiated) in 3 countries (Italy, UK, USA)

Publication (*Reference*): None

Studied Period:	**Phase of Development:**
First Patient First Visit: 06/JAN/2021 Last Patient Last Visit: 17/MAR/2022	Phase II - Proof of Concept

Objectives:

Primary Objective:

To evaluate the efficacy and safety of poractant alfa (porcine surfactant, Curosurf®), administered by endotracheal (ET) instillation, in terms of ventilatory free days during the 21 days after randomisation, in adult patients with ARDS due to 2019 novel coronavirus (SARS-COV-19) infection.

Secondary Objective:

To evaluate the efficacy and safety of poractant alfa administered by ET instillation compared to control group, in terms of oxygenation (arterial partial pressure of oxygen/fraction of inspired oxygen [PaO_2/FiO_2]), FiO_2, free days from invasive and non-invasive mechanical ventilation, length of intensive care unit (ICU) stay, mortality at 28 days, Sequential Organ Failure Assessment (SOFA) score (overall organ failure measurement), incidence of adverse events (AEs), vital signs and laboratory parameters.

Exploratory Objective:

To investigate possible mechanism that could impact on surfactant functionality in Coronavirus 2019 Disease (COVID-19) infected patients requiring ventilator support: decreased concentration of surfactant phospholipid and protein, altered surfactant phospholipid composition, surfactant protein proteolysis and/or oedema protein inhibition of surfactant surface tension function as a consequence of inflammation.

These exploratory parameters were assessed only for UK patients enrolled in the study. Given the current pandemic situation and the samples delivery procedures within 48 hours, it was deemed appropriate to avoid additional burden for US sites.

Methodology *(Study Design):*

This was a multicentre, open-label, randomised, phase II proof-of-concept study assessing the mechanism of action and benefit/risk profile of poractant alfa (porcine-derived surfactant, Curosurf®) as an add-on to standard-of-care treatment in adult patients critically unwell with ARDS due to SARS-COV-19 infection.

Patients who successfully completed screening and still met the inclusion criteria and none of the exclusion criteria were randomised to one of two treatment arms:

- Poractant alfa;
- Standard-of-care control.

Dosing with the study treatment started within 2 hours of randomisation on Day 1, and within 48 hours of intubation. A total of three ET poractant alfa administrations were given, with a 24-hour dosing interval. Patients were monitored for up to 28 days following first administration/randomisation. Defined assessments were collected before randomisation and at 6, 12 and 24 hours after each poractant alfa administration in the treated group (or at equivalent timepoints in the control group) until 72 hours after the first administration/randomisation (Day 1–Day 3). From Day 4 to Day 27, assessment collection occurred every 24 hours until ICU discharge. Whenever ICU discharge occurred, additional defined assessments were performed. At Day 28, the last follow-up evaluation occurred (on ICU if the patient still required critical care or by telephone call if the patient had been discharged from ICU by that time).

Number of Patients *(Planned and Analysed)*:

It was planned to randomise a total of 70 patients in a 3:2 ratio (i.e. 42 patients in the poractant alfa arm and 28 patients in the control arm) in accordance with the inclusion and exclusion criteria. This number of patients was not finally achieved; owing to a global improvement in the pandemic situation in the countries where the study was ongoing (Italy, UK, US), patient recruitment was lower than expected (i.e. 22 patients randomised in total, 14 patients and 8 patients in the poractant alfa and control groups, respectively) and the study was terminated early before reaching the target sample size.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Participants were eligible to be included in the study if the following criteria applied:

1. Male or female ≥18 and ≤80 years of age;
2. Informed consent for participation in the study;
3. Positive SARS-COV-19 reverse transcription polymerase chain reaction (rt-PCR) before randomisation;
4. PaO_2/FiO_2 ratio <150 mmHg;
5. Lung compliance ≤45 mL/cmH_2O;
6. Intubated and artificially ventilated <48 hours before the first poractant alfa administration.

Exclusion Criteria

Participants were excluded from the study if any of the following criteria applied:

1. Any contraindications to surfactant administration e.g. pulmonary haemorrhage and pneumothorax;
2. Weight <40 kg;
3. Stage 4 severe chronic kidney disease (i.e. estimated glomerular filtration rate <30);
4. Pregnancy;
5. Administration of any nebulised surfactant in the 48 hours before the first poractant alfa administration;
6. Extracorporeal membrane oxygenation (ECMO).

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

Curosurf® (poractant alfa) 240 mg/3 mL.

This sterile suspension was supplied in 3.0 mL glass vials at a total concentration of 80 mg/mL for ET administration. This is a standard natural surfactant, approved for marketing as treatment of premature neonates with respiratory distress syndrome (RDS) or at risk of RDS, 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 associated proteins (SPs), SP-B and SP-C.

Batch numbers used in the study were: 1108093, 1128229 and 1132607 (expiry dates: July 2021, August 2022 and October 2022, respectively).

Duration of Treatment:

Three administrations of poractant alfa, given with a 24-hour dosing interval.

Each administration consisted of 30 mg/kg (lean body weight [LBW]) poractant alfa, which was equal to 0.375 mL/kg LBW, diluted with normal saline up to approximately 2 mL/kg LBW.

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

Not applicable

Criteria for Evaluation:

Efficacy:

Primary Efficacy Variable:

- Number of days alive and ventilator-free (defined as the number of days the patient was alive and not receiving mechanical ventilation) over the **21 days** following randomisation.

  Mechanical ventilation was defined as invasive and non-invasive. The patient was defined as free of mechanical ventilation after 12 hours from the suspension of either invasive and non-invasive ventilation. Patients who died or were mechanically ventilated longer than this period were assessed as zero ventilator-free days.

Key Secondary Efficacy Variable:

- Percentage of patients alive and free of respiratory failure (i.e. need for mechanical ventilation, ECMO, non-invasive ventilation, or high-flow nasal cannula oxygen delivery) at **Day 28**.

Secondary Efficacy Variables:

- Number of days alive and ventilator-free at **Day 28**;
- Mortality at **Day 21** and **Day 28**;
- Number of days alive and free from invasive ventilation at **Day 21** and **Day 28**;
- Number of days alive and free from non-invasive ventilation at **Day 21** and **Day 28**;
- Percentage of patients with improvement in severity status, defined as a decrease in the severity score at **Day 28 or Discharge**, whichever came first. Severity score was defined as Mild, Moderate, Severe or Death based on PaO_2/FiO_2 ratio and patient status at Day 28 and numerically rated from 1-4, respectively:

Severity	Variable	Criteria
Mild: 1	PaO_2/FiO_2 ratio	200 mmHg < PaO_2/FiO_2 ratio ≤300 mmHg
Moderate: 2	PaO_2/FiO_2 ratio	100 mmHg < PaO_2/FiO_2 ratio ≤200 mmHg
Severe: 3	PaO_2/FiO_2 ratio	PaO_2/FiO_2 ratio ≤100 mmHg
Death: 4	Patient status	Yes/No

- Change from baseline in PaO_2/FiO_2 ratio at **6 and 12 hours following administration of each dose** in the treated group and at the similar timepoints in the control group (6, 12, 30, 36, 54 and 60 hours after randomisation);

- Change from baseline in PaO_2/FiO_2 ratio at additional timepoints (i.e. every 24 hours after treatment/randomisation until the patient was discharged from the ICU);
- Percentage of patients alive and with PaO_2/FiO_2 ratio improvement of >20% at **6 and 12 hours following administration of each dose** in the treated group and at similar timepoints in the control group (6, 12, 30, 36, 54 and 60 hours after randomisation);
- Percentage of patients alive and with PaO_2/FiO_2 ratio improvement of >20% at additional timepoints (i.e. every 24 hours after treatment/randomisation until the patient was discharged from the ICU);
- Change from baseline in FiO_2 at **6 and 12 hours following administration of each dose** in the treated group and at similar timepoints in the control group (6, 12, 30, 36, 54 and 60 hours after randomisation);
- Change from baseline in FiO_2 at additional timepoints (i.e. every 24 hours after treatment/randomisation until the patient was discharged from the ICU);
- Length of ICU stay (days) at **Day 28**. Patients who died or were mechanically ventilated longer than this period were assigned with 28 days;
- Percentage of patients alive and out of ICU at **Day 28**;
- Delta SOFA score and sub-score components measured on **Day 3** and **Day 28 or Discharge**, whichever came first;
- Percentage of patients alive and organ failure free (SOFA score=0) at **Day 28 or Discharge**, whichever came first;
- Change from baseline in ventilatory parameters (i.e. tidal volume, respiratory rate, dynamic compliance, static compliance, positive end-expiratory pressure, peak inspiratory pressure, plateau pressure) measured at 6, 12 and 24 hours after each poractant alfa administration up to 72 hours and at similar timepoints in the control group (6, 12, 24, 30, 36, 48, 54, 60 and 72 hours after randomisation) and then every 24 hours until the patient was discharged from the ICU;
- Change from baseline in blood gas analysis acid-base balance parameters (i.e. potential of hydrogen, partial pressure of carbon dioxide, partial pressure of oxygen, bicarbonate, lactate) measured at 6, 12 and 24 hours after each poractant alfa administration up to 72 hours and at similar timepoints in the control group (6, 12, 24, 30, 36, 48, 54, 60 and 72 hours after randomisation) and then every 24 hours until the patient was discharged from the ICU.

Exploratory Efficacy Variables:

- Change from baseline in surfactant function measuring surface tension (mN/m) from tracheal aspirate (TA) samples;
- Change from baseline in mass spectrometric lipid analysis (%) from TA samples;
- Change from baseline in SP-D enzyme-linked immunosorbent assay (ELISA) (ng/mL) from TA samples;
- Change from baseline in SP-D ELISA (ng/mL) from blood samples.

Safety:

- AEs;
- Laboratory parameters;
- Vital signs.

Statistical Methods:

The following populations were considered for analysis:

- Safety population (SAF), defined as all randomised patients (who received at least one dose of the study treatment if poractant alfa-treated);
- Intention-to-treat population (ITT), defined as all randomised patients who had at least one available evaluation of efficacy after baseline.

All efficacy variables were analysed in the ITT. All safety variables were analysed in the SAF.

Efficacy Variables:

Primary Efficacy Variable:

- The number of days alive and ventilator-free at Day 21 was summarised by treatment group using descriptive statistics.

Key Secondary Efficacy Variable:

- The percentage of patients alive and free of respiratory failure at Day 28 was summarised by treatment group using descriptive statistics.

Secondary/Exploratory Efficacy Variables:

- All other efficacy variables values (and their change from baseline, if relevant) were summarised by timepoint (if relevant) and treatment group using descriptive statistics.

Safety Analysis:

All AEs were coded using Medical Dictionary for Regulatory Activities version 23.0.

Treatment-emergent adverse events (TEAEs) were defined as AEs that started at or after treatment start (for the poractant alfa group) or at or after randomisation (for the control group). Pre-treatment AEs were defined as those AEs that started before treatment start (for the poractant alfa group) or before randomisation (for the control group).

The number of events and the number and percentage of patients experiencing at least one TEAE, serious TEAE, non-serious TEAE, adverse drug reaction (ADR), serious ADR, severe TEAE, TEAE leading to treatment discontinuation or TEAE leading to death were summarised overall by treatment group. In addition, TEAEs, serious TEAEs, non-serious TEAEs, ADRs, serious ADRs, severe TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death were summarised overall by treatment group, system organ class (SOC) and preferred term (PT). TEAEs were also summarised overall by treatment group and PT. Pre-treatment AEs were listed.

Laboratory parameters values and their change from baseline were summarised by timepoint and treatment group using descriptive statistics.

Vital signs values and their change from baseline were summarised by timepoint and treatment group using descriptive statistics.

Summary – Results:

Study Population:

A total of 22 patients were randomised, 14 to poractant alfa and 8 to control. One patient randomised to poractant alfa was not treated. More than half of randomised patients completed the study (63.6% overall); the proportion was similar with both treatments.

Overall, most patients in the ITT were White (85.7%) and male (76.2%); the median (minimum [min] ; maximum [max]) age was 62.0 (25 ; 78) years. The majority of patients in the ITT were overweight (85.7%), baseline oxygenation status was of moderate severity (median [min ; max] PaO_2/FiO_2 ratio of 108.00 [49.00 ; 220.93] mmHg) and SOFA score was 6.0 (3 ; 17) points.

The median (min ; max) number of days between a positive SARS-COV-19 rt-PCR test and the start of intubation was 12.0 (1 ; 47) days in the SAF. The most common concomitant diseases overall were hypertension (38.1%), obesity (28.6%) and pulmonary embolism (28.6%).

All patients received standard-of-care treatment. According to the standard-of-care for COVID-19 at the time, all patients in the SAF were treated concomitantly with systemic corticosteroids and treatment with anticoagulants, antiviral drugs and antibiotics was common (in 90.5%, 66.7% and 66.7% of patients overall, respectively).

Demographic and baseline characteristics, and medical history, were generally balanced between the poractant alfa and control groups; however, noteworthy differences were observed in terms of: median age (63.0 versus [vs.] 53.0 years), PaO_2/FiO_2 ratio (112.62 vs. 90.00 mmHg), FiO_2 (60.0% vs. 72.5%), days between a positive SARS-COV-19 rt-PCR test and the start of intubation (14.0 vs. 4.5 days), concomitant use of antiviral drugs and monoclonal antibodies (antiviral drugs: 76.9% vs. 50.0%; monoclonal antibodies: 23.1% vs. 0.0%) and concomitant diseases (hypertension: 46.2% vs. 25.0%; myocardial ischaemia: 30.8% vs. 0.0%). In addition, at baseline, median lymphocyte count and platelet count were lower and median leukocyte count, C-reactive protein value and lactate dehydrogenase value were higher in the poractant alfa group than in the control group.

Efficacy Results:

In patients critically unwell with ARDS due to SARS-COV-19 infection, treatment with poractant alfa on top of standard-of-care did not appear to show any clinically meaningful improvement in efficacy parameters vs. standard-of-care alone as assessed by the primary, key secondary or other secondary efficacy variables.

Considering the number of days alive and ventilator-free at Day 21 (primary efficacy variable), the median was 0.0 days with both treatments.

All secondary efficacy variables appeared to confirm the absence of benefit from poractant alfa treatment; no meaningful differences favouring poractant alfa over control were observed when considering:

- The percentage of patients alive and free of respiratory failure at Day 28 (key secondary efficacy variable; 15.4% vs. 25.0%);
- The number of days alive and ventilator-free at Day 28 (median of 0.0 days with both treatments);
- Mortality at Day 21 and at Day 28 (30.8% vs. 25.0% at both timepoints);
- The number of days alive and free from invasive ventilation at Day 21 and at Day 28 (median of 0.0 days with both treatments at both timepoints);
- The number of days alive and free from non-invasive ventilation at Day 21 and at Day 28 (Day 21 median: 21.0 vs. 12.5 days; Day 28 median: 28.0 vs. 19.5 days);
- The percentage of patients with improvement in severity status at Day 28/Discharge (25.0% vs. 50.0%);
- Change from baseline in PaO_2/FiO_2 ratio at each timepoint (the median increased [i.e. improved] from baseline with both treatments; increases from baseline were observed from the first post-baseline timepoint and were maintained until 60 hours post-baseline with poractant alfa and until 54 hours post-baseline with control);
- The percentage of patients with PaO_2/FiO_2 ratio improvement >20% compared to baseline at each timepoint (which was generally similar with both treatments at timepoints up to and including 72 hours post-baseline);
- Change from baseline in FiO_2 (%) at each timepoint (the median showed small decreases or no change from baseline with poractant alfa and small decreases, no change or small increases from baseline with control at timepoints up to and including 72 hours post-baseline);
- The length of ICU stay at Day 28 (median of 28.0 days with both treatments);
- The percentage of patients alive and out of ICU at Day 28 (7.7% vs. 37.5%);
- Delta SOFA score at Day 3 and Day 28/Discharge (median change from baseline of 0.0 points at both timepoints vs. an increase of 0.5 points and a decrease of -1.0 points, respectively);
- The percentage of patients alive and organ failure free at Day 28/Discharge (0.0% with both treatments).

As a result of the low number of patients with available data, data observed for other ventilatory parameters and blood gas analysis acid-base balance parameters tended to be highly variable and no clear trends over time or differences between treatments were found.

With regard to exploratory efficacy parameters, sparse laboratory data for patients enrolled in the UK made it difficult to speculate on mechanism of action of poractant alfa in the study population. However, surfactant behaviour observed in the 6 patients treated with poractant alfa with available data seemed to be in line with known findings on its biophysical profile in ARDS:

- Three administrations allowed a stable maintenance of lipids, despite ARDS;
- Exogenous surfactant did not significantly improve surface tension; this could be caused by its rapid inactivation under inflammatory conditions;
- SP-D was not present in exogenous surfactant and it was also impacted by ARDS; indeed in TA of these patients, it was diminished from 24–72 hours post-baseline despite multiple surfactant administrations.

Safety Results:

The majority of patients with poractant alfa received all three planned poractant alfa administrations (11 [(84.6%] patients) while the remaining 2 (15.4%) patients received two administrations. Control patients received standard-of-care treatment.

A total of 46 TEAEs were reported in 12 (92.3%) patients with poractant alfa and 25 TEAEs in 6 (75.0%) patients with control. The most common TEAEs were from the SOCs Infections and Infestations (9 [69.2%] patients with poractant alfa and 5 [62.5%] patients with control) and Respiratory, Thoracic and Mediastinal Disorders (6 [46.2%] patients with poractant alfa and 2 [25.0%] patients with control). The most common TEAE by PT with poractant alfa was decubitus ulcer (3 [23.1%] patients). Additionally, a total of 5 (38.5%) patients with poractant alfa were reported with PTs indicating pneumonia (PTs: pneumonia, pneumonia bacterial and pneumonia klebsiella). The only TEAE by PT reported in >1 patient with control was pneumonia (in 2 [25.0%] patients). The majority of TEAEs with poractant alfa and with control were mild or moderate in intensity and around half of the reported TEAEs resolved or were resolving by the end of the study. Around half of patients experienced severe TEAEs, with a similar incidence with poractant alfa (12 events in 7 [53.8%] patients) and control (11 events in 4 [50.0%] patients). The most common severe TEAEs were from the SOCs Infections and Infestations (3 [23.1%] patients with poractant alfa and 2 [25.0%] patients with control) and Cardiac Disorders (3 [23.1%] patients with poractant alfa and in 1 [12.5%] patient with control). No individual severe TEAE by PT was reported in >1 patient with poractant alfa or control.

About one-quarter of patients experienced TEAEs leading to death, with a similar incidence with poractant alfa (4 events in 3 [23.1%] patients) and control (2 events in 2 [25.0%] patients). The majority of patients with TEAEs leading to death were male (4 of 5 patients), aged ≥65 years (3 of 5 patients) and overweight or obese (4 of 5 patients). None of the TEAEs leading to death were considered related to study treatment. The most common TEAEs leading to death were from the Cardiac Disorders SOC (in 2 [15.4%] patients with poractant alfa and 1 [12.5%] patient with control). There were 2 patients with pre-treatment AEs leading to death; one of them also had a TEAE leading to death. Both pre-treatment AEs leading to death were ongoing at the time of randomisation and the deaths occurred after randomisation.

Over one-third of patients experienced serious TEAEs, with a similar incidence with poractant alfa (9 events in 5 [38.5%] patients) and control (10 events in 3 [37.5%] patients). One serious TEAE (PT: atrioventricular block) resulted in study treatment discontinuation and a concomitant procedure and resolved with sequelae on the same day. This event was not considered related to study treatment. The majority of serious TEAEs had not resolved by the end of the study.

The incidence of serious ADRs was low, with 2 serious ADRs reported in 1 (7.7%) patient with poractant alfa. These events (PTs: hypotension and hypoxia) occurred shortly after study treatment administration, were moderate in intensity, did not lead to a study treatment dose change, and resolved within 15-20 minutes. The patient, who had relevant concomitant cardiac disorders, received the third administration of study treatment and no further ADRs were reported.

The incidence of TEAEs leading to study treatment discontinuation was also low, with only 1 event in 1 (7.7%) patient with poractant alfa (serious TEAE of atrioventricular block described above).

No meaningful safety signals emerged from haematological, biochemical or vital signs assessments. With the exception of 1 serious TEAE of bicytopenia (not considered related to study treatment) and 1 serious ADR of hypotension, no serious TEAEs or ADRs related to haematological, biochemical or vital signs assessments were reported.

Conclusion:

Treatment with poractant alfa on top of standard-of-care did not appear to show any clinically meaningful improvement in adult patients critically unwell with ARDS due to SARS-COV-19 infection vs. standard-of-care alone. However, imbalances between treatment groups at baseline, resulting from poor recruitment, do not allow a straightforward analysis of the impact of surfactant treatment on the pre-defined endpoints. No particular safety concerns were raised with poractant alfa treatment when compared to control treatment.

Date of Report: 16 December 2022