STATISTICAL ANALYSIS PLAN

STUDY CODE No.: CLI-050000-04

NCT number: NCT04502433

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

Version No.: 1.0
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Contents

List of Abbreviations

ADaM	Analysis Dataset Model
ADR	Adverse Drug Reaction
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
Cdyn	Dynamic Compliance
CI	Confidence Interval
CSR	Clinical Study Report
Cstat	Static Compliance
CRP	C-Reactive Protein
DBP	Diastolic Blood Pressure
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
ET	Endotracheal
GCP	Good Clinical Practice
hrs	Hours
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
ITT	Intention-To-Treat
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NIV	Non-Invasive Ventilation
PEEP	Positive End-Expiratory Pressure
PIP	Peak Inspiratory Pressure
Pplat	Plateau Pressure
PT	Preferred Term
RR	Respiratory Rate
rtPCR	Real Time Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SARS	Severe Acute Respiratory Syndrome
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
TA	Tracheal Aspirate
TEAE	Treatment Emergent Adverse Event
TV	Tidal Volume
UK	United Kingdom
vvECMO	Veno-Venous Extracorporeal Membrane Oxygenation

WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

VERSION HISTORY

Version	Date	Change History
0.1	*07 Aug 2020*	*Not Applicable*
0.2	*01 Oct 2020*	*Updates following Chiesi review: Add of D21 mortality description, modification of Safety population definition.*
0.3 (Stable version)	*08 Oct 2020*	*Minor updates.*
0.4	*31 Aug 2021*	*Update according to protocol amendment. Protocol (protocol version 4.0, dated 02March2021.* - *The ECMO cohort has been removed* - *Central Laboratory assessments will be performed only for UK patients* - *Allowed Time windows have been identified and implemented* - *Clarify the inclusion of Death as intercurrent event in the primary endpoint* - *Key secondary endpoint added to comply with FDA request and guideline.* - *Additional timepoint for assessment added at Day 28 in line with FDA guideline.* - *New endpoints added to incorporate Death as intercurrent event in the evaluation*
0.5	*29 Jun 2022*	*Simplification of the analyses planned due to a lower recruitment. Slight update on footnotes and reference listings.*
1.0	*27 July 2022*	*Final version*

1 Introduction

This document presents the Statistical Analysis Plan (SAP) for Chiesi Farmaceutici S.p.A. protocol CLI-050000-04: Multicenter, open label, randomised trial to assess the efficacy and tolerability of poractant alfa (porcine surfactant, Curosurf®) in hospitalized subjects with SARS-COV-19 acute respiratory distress syndrome (ARDS).

This analysis plan is based on the protocol (version 4.0), dated 02March2021 and the final electronic case report form (eCRF) (version 4.0) dated 03Jun2021.

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

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

2 Study Design

This is a phase 2- proof of concept, multicentre, open-label, randomised study that includes a group of subjects treated with poractant alfa and a control group on standard of care.

Approximately 42 subjects with ARDS due to SARS-COV-19 will be randomized in the poractant alfa group and 28 subjects randomized in the control one.

Date of randomisation is considered Day 1 for both groups. This study consists a total of 28 days, as follows (refer to the Study Schedule in Table 1 for more details):

- Screening: from intubation to randomization (Day 1).
- Treatment period:
    - For poractant alfa group: from Day 1 till Day 3. Subjects receive three poractant alfa endotracheal administrations with a 24 hours interval.
    - For control group: standard of care from randomization on Day 1 till ICU discharge.
- Follow up period:
    - For poractant alfa group: from Day 4 to Day 28.
    - For control group: from ICU discharge to Day 28.

A participant is considered to have completed the study if he/she has completed the last scheduled procedure shown in the schedule of assessments, i.e., follow up at Day 28. The end of the study is defined as the date of the last follow up visit at Day 28 for the last participant in the trial.

Some recruited and treated subjects are likely to be transferred during the study period from the ICU to another hospital department for continuation of their clinical care. In this case the subject will remain in the study and relevant data will still be recorded through review of the medical chart or phone call by the Investigator to the physician of the other department also to check the occurrence of any adverse event as well as of any change in relevant concomitant medications.

The study schedule (Table 1) summarizes the study assessments by study day.

Table 1: Study Schedule

	ICU stay period					ICU discharge	Last FUP
Poractant alfa treated group	**Screening[7]**	**Day 1 (Randomisation)**	**Day 2**	**Day 3**	**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation/treatment and 6-12-24h after each administration up to 72 hours			Every 24h till ICU discharge	Whenever it occurs	
Control group	**Screening**	**Time 72 h**			**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation and at 6, 12, 24, 30, 36, 48, 54, 60, 72 h since randomisation			Every 24h till ICU discharge	Whenever it occurs	
Assessments							
Informed consent	X						
Inclusion and exclusion criteria	X						
Demography	X						

	ICU stay period					ICU discharge	Last FUP
Poractant alfa treated group	**Screening[7]**	**Day 1 (Randomisation)**	**Day 2**	**Day 3**	**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation/treatment and 6-12-24h after each administration up to 72 hours			Every 24h till ICU discharge	Whenever it occurs	
Control group	**Screening**	**Time 72 h**			**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation and at 6, 12, 24, 30, 36, 48, 54, 60, 72 h since randomisation			Every 24h till ICU discharge	Whenever it occurs	
Vital signs (blood pressure, heart rate)	X	Once Treated group: 24 - 48 - 72h post start of treatment Control group: 24 - 48 - 72h post randomisation			X	X	X
Full physical examination including height and weight	X						
Medical history (SARS COVID-19 ADRS, past and current relevant medical conditions)	X						
Arterial Blood Gas (ABG) Analysis[1]	X (If the screening assessment is done just before randomization no need to repeat the assessment)	Treated group: Before randomisation and 6-12-24h after each administration up to 72 hours Control group: Before randomisation and at 6, 12, 24, 30, 36, 48, 54, 60, 72h since randomisation			Every 24h	X	Once if not discharged from ICU
Respiratory support assessment Ventilator parameters[2]	X (If the screening assessment is done just before randomization no need to repeat the assessment)	Treated group: Before randomisation and 6-12-24h after each administration up to 72 hours Control group: Before randomisation and at 6, 12, 24, 30, 36, 48, 54, 60, 72h since randomisation			Every 24h	X	Once if not discharged from ICU

	ICU stay period					ICU discharge	Last FUP
Poractant alfa treated group	**Screening[7]**	**Day 1 (Randomisation)**	**Day 2**	**Day 3**	**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation/treatment and 6-12-24h after each administration up to 72 hours			Every 24h till ICU discharge	Whenever it occurs	
Control group	**Screening**	**Time 72 h**			**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation and at 6, 12, 24, 30, 36, 48, 54, 60, 72 h since randomisation			Every 24h till ICU discharge	Whenever it occurs	
Mechanics Laboratory assessments[3]		Treated group: Before randomisation and 12, 24, 48, 72, after first administration Control group: Before randomisation and 12, 24, 48, 72, after randomisation			Treated group: 96h after first administration Control group: 96h after randomisation		
Laboratory assessments[4]	X			Once Treated group: 24h post last treatment Control group: 72h post randomisation		X	Once if not discharged from ICU
SOFA score[5]	X			Once Treated group: 24h post last treatment Control group: 72h post randomisation		X	Once if not discharged from ICU
Thoracic CT scan or Chest XR[6]	X						
Curosurf administration (intreated group)		Three ET administrations with a 24 hours interval (Day 1, Day 2 and Day 3)					
Concomitant Medications	X	X	X	X	X	X	X

	ICU stay period					ICU discharge	Last FUP
Poractant alfa treated group	**Screening[7]**	**Day 1 (Randomisation)**	**Day 2**	**Day 3**	**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation/treatment and 6-12-24h after each administration up to 72 hours			Every 24h till ICU discharge	Whenever it occurs	
Control group	**Screening**	**Time 72 h**			**Day 4 – 27**	**Day X**	**Day 28**
		Before randomisation and at 6, 12, 24, 30, 36, 48, 54, 60, 72 h since randomisation			Every 24h till ICU discharge	Whenever it occurs	
Adverse Events	X	X	X	X	X	X	X
Ventilatory support	X	X	X	X	X	X	X
Concomitant procedures	X	X	X	X	X	X	X

- [1] Arterial blood gas (ABG) analysis: pH, pCO2, pO2, HCO3, lactate.
- [2] Ventilatory parameters: PaO2/FiO2, FiO2, TV (tidal volume), RR (respiratory rate), Cstat (static compliance), Cdyn (dynamic compliance), PEEP (positive end-expiratory pressure), PIP (peak inspiratory pressure), Pplat (plateau Pressure).
- [3] For mechanics assessments: blood sampling and tracheal aspirates (TA). Bronchoscopic washings performed as clinically indicated only, with surplus samples retrieved for mechanistic study as available. They are planned only for patients recruited in UK.
- [4] Blood count, bilirubin, creatinine, eGFR, glucose, AST, ALT, LDH, D-dimer, CRP (C-reactive protein), procalcitonin. Urine beta HCG at screening only.
- [5] SOFA score is calculated considering PaO2/FiO2, Glasgow coma scale, mean arterial pressure, and bilirubin, platelet and creatinine levels. SOFA score can be calculated only after the patient is included in the study (after the ICF signature) and in case not all the SOFA parameters are available before randomization, the calculation can be based on historical data collected (within 24 hours) as per standard practice.
- [6] Already available as part of the standard care procedures.
- [7] All screening procedures have to be completed/performed before the randomization.

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

Post-dose time assessments	Allowed deviations
≤ 72 hours	± 1 hour
>72 hours	± 2 hours

3 Study Objectives

3.1 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 randomization, in adult subjects with ARDS due to SARS-COV-19 infection.

3.2 Secondary Objectives

- To evaluate the efficacy and safety of poractant alfa administered by ET Instillation compared to control group, in terms of oxygenation (PaO_2/FiO_2), FiO_2, free days from invasive and non-invasive mechanical ventilation, length of ICU stay, mortality at 28 days, SOFA score (overall organ -failure measurement), incidence of AEs, vital signs and laboratory parameters.

3.3 Exploratory Objectives

- To investigate possible mechanism that could impact on surfactant functionality in COVID-19 infected subjects 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 will be assessed only for UK subject enrolled in the study. Given the current pandemic situation and the samples delivery procedures within 48h, it has been deemed appropriate to avoid additional burden for US sites.

4 Study Variables

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable

The primary efficacy variable is the number of days alive and ventilator-free defined as the number of days the subjects is alive and not receiving mechanical ventilation over the **21 days** following randomisation.

Mechanical ventilation is defined as invasive and non-invasive. Subject is defined as free of mechanical ventilation after 12 hours from the suspension of either invasive or non-invasive ventilation. Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days.

4.1.2 Secondary Efficacy Variables

4.1.2.1 Key Secondary Efficacy Variable

- Percentage of subjects 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.**

4.1.2.2 Others 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 (NIV) at **Day 21 and Day 28**
- Percentage of subjects with improvement in severity status defined as a decrease in the severity score at **Day 28 or Discharge**, whichever comes first. Severity score will be defined as Mild, Moderate, Severe or Death based on PaO2/FiO2 ratio and subject status at Day 28 and numerically rated from 1-4 respectively:

Severity	Variable	Criteria
Mild -1	PaO2/FiO2 Ratio	200 mmHg < PaO2/FIO2 ≤ 300 mmHg
Moderate - 2	PaO2/FiO2 Ratio	100 mmHg < PaO2/FIO2 ≤ 200 mmHg
Severe - 3	PaO2/FiO2	Ratio PaO2/FIO2 ≤ 100 mmHg
Death - 4	Patient Status	Yes/No

- Change from baseline in PaO2/FiO2 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 PaO2/FiO2 ratio at additional timepoints (i.e. every 24 hours after treatment/randomisation until the subject is discharged from the ICU)
- Percentage of subjects alive and with PaO2/FiO2 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 subjects alive and with PaO2/FiO2 improvement of >20% at the additional timepoints (i.e. every 24 hours after treatment/randomisation till the subject is discharged from the ICU)
- Change from baseline in FiO2 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 FiO2 at additional timepoints (i.e. every 24 hours after treatment/randomisation until the subject is discharged from the ICU)
- Length of ICU stay (days) **at Day 28**. Subjects who die or are mechanically ventilated longer than this period are assigned with 28 days
- Percentage of subjects alive and out of ICU **at Day 28**
- Delta SOFA Score and sub-score component measured on **Day 3** and **Day 28 or Discharge** whichever comes first
- Percentage of subjects alive and organ failure free (SOFA score=0) at **Day 28 or Discharge** whichever comes first
- Change from baseline in ventilatory parameters [tidal volume (TV), respiratory rate (RR),dynamic compliance (Cdyn), static compliance (Cstat), positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), plateau pressure (Pplat)] measured at 6-12-24h 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 till the subject is discharged from the ICU

- Change from baseline in blood gas analysis acid-base balance parameters (i.e. pH, pCO2, pO2, HCO3, lactate) measured at 6-12-24h 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 till the subject is discharged from the ICU

4.1.3 Exploratory Efficacy Variables

The following parameters will be measured only on UK subjects at 12, 24, 48, 72 and 96 hrs after start of treatment (first dose in the poractant alfa group) or after randomisation (in the control group):

- Change from baseline in Surfactant Function measuring surface tension (mN/m) from TA samples.
- Change from baseline in Mass spec lipid analysis (%) from TA samples.
- Change from baseline in Surfactant Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from TA samples.
- Change from baseline in Surfactant Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from Blood samples.

4.2 Safety Variables

- Adverse events (AEs).
- Laboratory parameters.
- Vital signs (blood pressures and pulse rate).

5 Sample Size

A total of 70 subjects will be randomised in the study with a ratio 3:2 (i.e. 42 subjects randomised to the poractant alfa group and 28 in the control group). Assuming subjects in the control arm being free from ventilation on average 1 week (i.e. 7 days), this sample size achieves 84% power to detect a difference of 4 days (i.e. on average 11 ventilation-free days for subjects treated with poractant alfa), assuming a standard deviation of 5.5 and a two-sided significance level (alpha) of 0.05 using a two-sample t-test.

6 Analysis Set

The definition of the analysis set is summarized below. A final agreement on the subjects to be included in or excluded from the analysis set will be reached during the review of the data

before database lock. Inclusions and exclusions from the analysis set will be fully documented in the Data Review Report.

6.1 Safety Set

All randomised subjects and receive at least one dose of the study treatment (Curosurf treated patients) (analysed as treated). The Safety Set will be used for all safety analyses.

6.2 Intention-To-Treat Set

All randomised subjects who have at least one post baseline efficacy data analysed as randomised. The ITT Set will be used for all efficacy analysis.

6.3 Other Populations Defined for Tables and Listings

For the purposes of tables and listings the following population is defined:

- Enrolled Set: all subjects who have a signed informed consent for the study.

Note: the informed consent can be signed by subject himself when feasible or, in case of unconscious subject, by a third party (legal representative or by the physician only) according to the local regulations and the pre-defined rules suitable for a trial conducted at Intensive Care Units. In case the subject is consented to the study by a third party and they regain capacity, the participant was informed and their consent was requested to continue the participation in the trial.

7 General Considerations for Statistical Analysis

7.1 Statistical Significance

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

7.2 Intercurrent Events

Death and Early discontinuation from study drug can be anticipated as intercurrent events:

- Death will be incorporated as a failure outcome for binary endpoints using composite strategy;
- Early discontinuation from study drug will be handled using treatment policy strategy: all data collected after discontinuation from study drug till Day 28 or death will be included;
- Change in respiratory parameters will be analysed using while-alive strategy.

7.3 Multiplicity

No multiplicity adjustment will be performed.

7.4 Handling of Missing Data

In general, except as described below, missing data will not be imputed.

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

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

Other critical missing data, if any, will be discussed during the review of the data before database lock. Decisions will be fully documented in the Data Review Report.

Medications: Missing/Incomplete Date
In case of missing or incomplete dates not directly allowing allocation to any category of medications, a worst-case allocation will be done according to the available parts of the start and the stop dates. The medications will be allocated to the first category allowed by the available data, according to the following order: 1. Concomitant medication; 2. Maintained medication; 3. Prior medication.
Procedures: Missing/Incomplete Date
In case of missing or incomplete dates not directly allowing allocation to any category of procedure, a worst-case allocation will be done according to the available parts of the start and the stop dates. The procedure will be allocated to the first category allowed by the available data, according to the following order: 1. Concomitant procedure; 2. Maintained procedure; 3. Prior procedure.

Adverse Events (AEs): Missing/Incomplete Date
In case of missing or incomplete date/time not directly allowing allocation to any of the category of AEs, a worst-case allocation will be done according to the available parts of the start and the stop dates/times. The AE will be allocated to the first category allowed by the available data, according to the following order: 1. Treatment emergent; 2. Pre-treatment.
Adverse Events (AEs): Missing Severity
In case of missing severity, the severity will not be imputed and will be reported as "Missing". For the table of TEAEs by maximum severity, the maximum severity will be considered as the maximum of the non-missing severities for the relevant subject and preferred term.

7.5 Covariates

Not applicable. All data will be summarized by means of descriptive statistics.

7.6 Interim Analyses

No interim analysis will be performed.

7.7 Examinations of Subgroups

Exploratory parameters from TA aspirates and blood samples will only be analysed for UK subjects.

7.8 Descriptive Statistics

General descriptive statistics for quantitative variables will include the n (the number of non-missing values), the mean, the standard deviation (SD), the median, the minimum (min) and the maximum values (max).

For categorical variables, the number (n) and percentage (%) of subjects with a specific level of the variable will be presented. The number of missing values will be displayed as a "Missing" category, where appropriate. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the analysis set and treatment group.

7.9 Definitions

7.9.1 Baseline

Baseline is defined as the last non-missing value available before randomisation (for control group)/first treatment dose (for poractant alfa group).

Change from baseline will be derived as follows:

Assessment value at the timepoint - Assessment value at baseline

7.9.2 Date of First and Last Study Medication Administration

The date of first study medication administration is the earliest date of study medication administrated considering the eCRF data, corresponding to the date part of the variable RFXSTDTC in the study data tabulation model (SDTM) dataset DM.

The date of last study medication administration is the latest date of study medication administrated considering the eCRF data, corresponding to the date part of the variable RFXENDTC in the study data tabulation model (SDTM) dataset DM.

7.9.3 Study Day

If not otherwise specified, all assessment days will be related to date of randomization.

The randomization date is referred to as Day 1.

- If the date of the assessment is on or after the randomisation, then

  Study Day = (date of assessment – randomisation date) + 1.
- If the date of the assessment is prior to the randomisation, then

  Study Day = (date of assessment – randomisation date).

7.9.4 Visit Dates

For each visit, the variable SVSTDTC in the SDTM SV dataset will be considered as the visit date in all the algorithms and the listings. SVSTDTC corresponds to the minimum of all assessment dates performed for a visit.

ATPT variable derived in ADaM datasets will be considered for the timepoint analyses. In the listings, --TPT variables of SDTM datasets will be used unless specified otherwise.

For the end of randomized treatment date, if the visit end date (SVENDTC) is different from the visit start date (i.e. at least one day after) (SVSTDTC) and if the subject is still under randomized treatment, the end of randomized treatment date will be SVENDTC.

7.9.5 Duration of Adverse Events or Medications

The duration of an AE or medication will be calculated as follows:

- AE/Medication End date – AE/Medication Start date + 1 (when both dates are completely known);
- Date of study completion/discontinuation – AE/Medication Start date + 1 (when the start date is fully known but the AE or medication still ongoing at the end of the trial): in this case the duration will be presented as “>x” days in the listing rather than “x” days;

- Missing (when the start date is incomplete or unknown, or when the AE or medication ended but with an incomplete or unknown end date, or when the start date is greater than date of study completion/discontinuation).

7.10 Diary Data

Not applicable. Diary data are not collected in this study.

7.11 Data Re-allocation and duplication

In general, for by timepoint summaries, data recorded at the nominal timepoint will be presented. Data collected at unscheduled timepoints will be reviewed during the review of the data before database lock. Any re-allocation of unscheduled data will be described and justified in the Data Review Report, which will be finalized prior to database lock. In any case, listings will include scheduled, unscheduled and early discontinuation data.

Duplicated data reported twice at 2 different timepoints will be reported only once in both listings and tables at the first occurrence for post dose/post randomization and the last occurrence for pre dose/ pre randomisation.

7.12 Exclusion of Data from the Statistical Analyses

All data collected in the database will be used in all statistical analyses.

7.13 Listings

All data collected in the eCRF will be presented in the individual listings. All listing will be presented for the ITT set (equal to the randomised set), unless otherwise specified.

7.14 Coding

Medical and surgical history, concomitant diseases, procedures and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or higher.

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version March 2020 or later.

8 Study Population

8.1 Disposition of Subjects and Discontinuations

8.1.1 Disposition of Subjects

The number of subjects screened, randomised will be presented by country, site and treatment group.

A flow chart will be produced.

8.1.2 Discontinuation from the Study

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

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

8.1.3 Protocol Deviations and Analysis Sets

All important clinical deviations, including Good clinical Practice (GCP) ones, will be discussed during Data Review meeting to evaluate impact on analyses population and described in the Data Review Report.

The following categories will be classified as important protocol deviations:

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

Other categories may be added and will be discussed during the DRM and documented in the DRR before the data base lock.

All important clinical deviations will be summarized by treatment group and overall.

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

8.2 Demographic and Baseline Characteristics

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

8.2.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall using descriptive statistics for ITT Set. These will include age, age category, gender, and childbearing potential or not, race, height, weight at baseline and body mass index (BMI) at baseline.

Notes:

- BMI will be calculated as: weight (kg) / height (m^2).
- Age categories are: 18-64 (years); 65 + (years). All categories must be reported even if there are no subjects under a particular category.

An individual subject listing will also be provided for demographic and baseline characteristics data.

8.2.2 SAS COVID-19 ARDS History

Days between screening positive SARS-COV-19 rt-PCR test and start of intubation, days between ICU admission date and start of intubation, and SARS COVID-19 ARDS medication categories recorded at Screening Visit will be presented by treatment group and overall for Safety Set.

In addition, SAS COVID-19 ARDS history data will be presented in an individual listing.

Notes:

- Days between screening positive SARS-COV-19 rt-PCR test and start of intubation = Start date of intubation – Date of screening positive SARS-COV-19 rt-PCR test + 1.
- For subject with intubation done after ICU admission: Days between ICU admission: date and start of intubation = Start date of intubation – Date of ICU admission + 1.
- For subject with intubation done before ICU admission (transfer from another hospital): Days between ICU admission date and start of intubation = Start date of intubation – Date of ICU admission.

8.2.3 Other Baseline and Disease Characteristics

The following baseline and disease characteristics parameters will be summarised using descriptive statistics by treatment group and overall based on ITT Set:

- Vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate) at baseline;
- Ventilatory parameters at baseline (PaO_2/FiO_2 ratio and FiO_2);
- SOFA score at baseline.

8.3 Medical History and Concomitant Diseases

Medical/surgical history and concomitant diseases will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall, using Safety Set.

Notes:

- Medical/surgical history is defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are not ongoing at Screening (even if end date is missing);
- Concomitant diseases are defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are ongoing at Screening.

In addition, medical, surgical and concomitant diseases data will be listed.

8.4 Medications

Prior medications, medications maintained during the treatment period, and concomitant medications will be summarized by treatment group, using Safety Set through frequency

distributions and percentages by Anatomical Main Group [1st level of the Anatomical Therapeutic Chemical (ATC) classification], Therapeutic Subgroup (2nd level of the ATC classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

The medications will be classified according to the following rules:

- For poractant alfa group:
    - Prior medication: start date < date of first study medication administration and stop date ≤ date of first study medication administration;
    - Medication maintained during the treatment period: start date < date of first study medication administration and stop date > date of first study medication administration or ongoing;
    - Concomitant medication: start date ≥ date of first study medication administration.
- For control group:
    - Prior medication: start date < start date of randomization and stop date ≤ start date of randomisation;
    - Medication maintained during the treatment period: start date < start date of randomisation and stop date > start date of randomisation or ongoing;
    - Concomitant medication: start date ≥ start date of randomisation.

8.5 Procedures

Prior procedures, procedures maintained during the treatment period and concomitant procedures will be summarized (including intubation) by treatment group, using Safety Set through frequency distributions and percentages by SOC and PT.

The procedures will be classified according to the following rules:

- For poractant alfa group:
    - Prior procedure: start date/time (if time is available) < date/time of first study medication administration and stop date/time (if time is available) ≤ date/time of first study medication administration;
    - Procedure maintained during the treatment period: start date/time (if time is available) < date/time of first study medication administration and stop date/time (if time is available) > date/time of first study medication administration or ongoing;
    - Concomitant procedure: start date/time (if time is available) ≥ date/time of first study medication administration.
- For control group:
    - Prior procedure: start date/time (if time is available) < start date/time of randomization and stop date/time (if time is available) ≤ start date/time of randomization;

- Procedure maintained during the treatment period: start date/time (if time is available) < start date/time of randomization and stop date/time (if time is available) > start date/time of randomization or ongoing;
- Concomitant procedure: start date/time (if time is available) ≥ start date/time of randomization.

8.6 Compliance

Not Applicable.

9 Efficacy Analyses

All the efficacy comparisons between the treatment groups will be based on the ITT Set.

9.1 Primary Efficacy Variable

The primary efficacy variable is the number of days alive and ventilator-free days, defined as the number of days the subject is not receiving mechanical ventilation over the 21 days following randomization. Mechanical ventilation is defined as invasive and non-invasive. Subject is defined free of mechanical ventilation after 12 hours from the suspension of either invasive or non-invasive ventilation.

Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days.

Notes:

Subjects with at least 12 hours of suspension of ventilation either invasive or non-invasive ventilation will be flagged. Then duration will be calculated within the flagged subject's subset, as below:

- Ventilator-free days = 21-[MAX (End date of invasive ventilation; End date of non-invasive ventilation)] – Date of randomisation + 1.

Descriptive summaries of the number of ventilator-free days will be presented by treatment group.

9.2 Key Secondary Efficacy Variable

The key secondary efficacy variable is the percentage of subjects 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.**

Notes:
The subject will be defined alive and free of respiratory failure if:

- On Patient Status form at "D28-FU" visit, the subject is still alive

AND

- On Ventilatory Support form, if start date is not missing, max (end date) for any ventilator type > date of "D28 – FU" visit

The percentage will be summarized.

9.3 Others Secondary Efficacy Variables

9.3.1 Number of Days Alive and Ventilator-free at Day 28

First, within subject with a start date filled in the ventilator support form, subjects with at least 12 hours of suspension of ventilation either invasive or non-invasive ventilation will be flagged. Then duration will be calculated within the flagged subject's subset, as below:

- Ventilator-free days = 28-[MAX (End date of invasive ventilation; End date of non-invasive ventilation)] – Date of randomisation + 1].

Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days.
Number of ventilator-free days will be described at Day 28.

9.3.2 Mortality at Day 21 and Day 28

The number and proportion of deaths at Day 21 and Day 28 will be presented for both groups.

9.3.3 Number of Days Alive and Free from invasive and Non-Invasive ventilation at Day 21 and Day 28

For Day 21:

First, subjects with at least 12 hours of suspension of ventilation will be flagged by type (i.e. one flag for Non-Invasive, and one for Invasive). Then duration will be calculated within the flagged subject's subsets, as below:

- Invasive ventilation-free days = 21-(End date of invasive ventilation) – Date of randomisation + 1].
- Non-invasive ventilation-free days = 21-(End date of non-invasive ventilation) – Date of randomisation + 1].

If subject never started a non-invasive ventilation then the value will be set to 21 days.

For Day 28:

First, subjects with at least 12 hours of suspension of ventilation will be flagged by type (i.e. one flag for Non-Invasive, and one for Invasive). Then duration will be calculated within the flagged subject's subsets, as below:

- Invasive ventilation-free days = 28-(End date of invasive ventilation) – Date of randomisation + 1].

- Non-invasive ventilation-free days = 28-(End date of non-invasive ventilation) – Date of randomisation + 1].

If subject never started a non-invasive then the value will be set to 28 days.

Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days.

9.3.4 Improvement in Severity Status at Day 28 or Discharge

The severity status will be based on the ventilatory parameters form for PaO2/FiO2 ratio at baseline and at Day 28 or Discharge (whichever comes first) and on Study Termination form for the death, according to the scale below:

Severity	Variable	Criteria
Mild -1	PaO2/FiO2 Ratio	200 mmHg < PaO2/FIO2 ≤ 300 mmHg
Moderate - 2	PaO2/FiO2 Ratio	100 mmHg < PaO2/FIO2 ≤ 200 mmHg
Severe - 3	PaO2/FiO2	Ratio PaO2/FIO2 ≤ 100 mmHg
Death - 4	Patient Status	Yes/No

In case of multiple assessments done on same date, the last assessment will be taken into account for the severity status definition.

The severity status, the number and percentage of subjects with an improvement (i.e. a decrease of at least one point of severity) from baseline to Day 28 or Discharge will be summarized.
A shift table displaying the severity at baseline and at day 28 or Discharge will also be provided.

9.3.5 Change from Baseline in PaO2/FiO2 Ratio at each Timepoint After Treatment

Actuals values and change from baseline in PaO2/FiO2 ratio at 6 and 12 hours following each treatment medication administration and then each 24 hours till the subject is discharged from the ICU in the poractant alfa group and similar timepoints in the control group (defined as 6 and 12 hours post randomization for Day 1, 30 and 36 hours post randomization for Day 2 and 54 and 60 hours post randomization for Day 3 and then each 24 hours till the subject is discharged from the ICU) will be described by treatment group.
A graph displaying the mean value and SD for each timepoint will be also provided for each treatment group.

9.3.6 Percentage of Subjects with PaO_2/FiO_2 Ratio Improvement of >20% Compared to Baseline at each Timepoint After Treatment

The number and percentage of subjects with PaO_2/FiO_2 ratio improvement of >20% compared to baseline at 6 and 12 hours following each dose administration and then each 24 hours till the subject is discharged from the ICU in the poractant alfa group and similar timepoints in the control group (defined as 6 and 12 hours post randomization for Day 1, 30 and 36 hours post

randomization for Day 2 and 54 and 60 hours post randomization for Day 3 and then each 24 hours till the subject is discharged from the ICU) will be described.

Subjects who die before the analysis timepoint will be considered as a failure.

Notes:

- % change in PaO_2/FiO_2 ratio = [(Value – baseline)/baseline]x100
- If % change in the ratio >20%, then PaO_2/FiO_2 ratio improvement='>20%', else '<=20%'

9.3.7 Change from Baseline in FiO_2 at each Timepoint After Treatment

Actual values and change from baseline in FiO_2 at 6 and 12 hours following each treatment medication administration in the poractant alfa group and then each 24 hours till the subject is discharged from the ICU and similar timepoints in the control group (defined as 6 and 12 hours after randomization for Day 1, 30 and 36 hours after randomization for Day 2 and 54 and 60 hours post randomization for Day 3 and then each 24 hours till the subject is discharged from the ICU) will be described.

9.3.8 Length of ICU Stay at Day 28

The length of ICU stay (in days) will be calculated as: MIN (date of ICU discharge, date of Day 28) – date of ICU entrance + 1.

In case of readmission in ICU, the duration of the primary one and the readmission will be added. Lengths of ICU stay will be presented in total.

Subjects who die or are mechanically ventilated longer than this period will be assigned with a 28 days length value.

Those subjects will be identified using:

- On Study Completion form, death date is filled and < MIN (date of ICU discharge, date of Day 28)
- On Ventilatory Support form the subtype Invasive- Mechanical ventilation is ticked and (End Date – Start Date) +1 > 28 Days or if Ongoing is ticked (i.e. subject still under mechanical ventilation at the end of the Study).

In case of multiple sessions of Invasive- Mechanical ventilator support without any discharge in between the MIN start date and the MAX end date will be taken into account.

It will be presented using descriptive statistics by treatment group.

A graph displaying the mean and SD for each timepoint (until the subject is discharged form ICU) will be also provided for each treatment group.

9.3.9 Percentage of Subjects Alive and Out of ICU at Day 28

The subject will be defined alive and out of ICU at Day 28 if:

- On Patient Status form at "D28 – FU" visit, the subject is still alive

AND

- Date of ICU discharge Visit < Date of "Day 28 – FU" visit

The percentage will be summarized.

9.3.10 Change from Baseline in SOFA Score

SOFA sub-score and total score actual values and change from baseline will be presented using descriptive statistics at Day 3, ICU discharge or Day 28 (whichever comes first).by treatment group. The change from baseline to Day 3 and to ICU Discharge or Day 28 difference between the two groups for each sub-score and for total score will be described.

A graph displaying the means and SD for each timepoint (until the subject is discharged form ICU) will be also provided for each treatment group.

9.3.11 Percentage of Subjects Alive and Organ Failure Free (SOFA score=0) at Day 28 or Discharge

The subject will be defined alive and organ failure free at Day 28 or Discharge if:

- Date of Death is missing or > MIN (Date of Day 28 or Date of Discharge)

AND

- Total SOFA Score = 0 at Day 28 or at Discharge

The percentage will be summarized.

9.3.12 Change from Baseline in Ventilatory Parameters

Ventilatory parameters actual values and change from baseline (TV, RR, Cdyn, Cstat, PEEP, PIP, and Pplat) will be presented using descriptive statistics by timepoint and treatment group.

A graph displaying the means and SD for each timepoint (until the subject is discharged form ICU) will be also provided for each treatment group and parameter.

9.3.13 Change from Baseline in Blood Gas Analysis Parameters

Acid-base balance blood gas analysis parameters actual values and change from baseline (pH, pCO_2, paO_2, HCO_3, lactate) will be presented using descriptive statistics by time point and treatment group.

9.4 Exploratory Efficacy Variables

Only for the UK subgroup of subjects:
Exploratory parameters from tracheal aspirates and blood samples:

- Surfactant Function measuring surface tension (mN/m) from TA samples.
- Mass spec lipid analysis (%) from TA samples.

- Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from TA samples.
- Surfactant Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from Blood samples.

will be summarized by actual and change from baseline values by treatment group at each time point using descriptive statistics on ITT set.

Cytospin values will only be listed.

In case of sample not done or if some values are under the lower limit of quantitation (BLOQ), the values will be considered as missing data.

10 Safety Analyses

Safety analysis will be based on the Safety Set.

10.1 Extent of Exposure

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

10.2 Adverse Events

An adverse event (AE) will be classified as follow:

- For poractant alfa group:
  - Pre-treatment AE: if it starts before the first study medication administration (AE onset date/time < date/time of first study medication administration);
  - Treatment emergent AE (TEAE): if it starts on or after the first dose of study medication administration (AE onset date/time $\geq$ date/time of first study medication administration).
- For control group:
  - Pre-treatment AE: if it starts before the randomisation date (AE onset date/time < start date/time of randomisation);
  - Treatment emergent AE (TEAE): if it starts on or after the randomization date (AE onset date/time $\geq$ start date/time of randomisation).

An adverse drug reaction (ADR) is an AE related to study medication. A serious ADR is a serious AE (SAE) related to study medication.

A severe AE is an AE with severe intensity. Refer to Section 7.3 for missing severity.

An AE leading to discontinuation is an AE with action taken with study drug equal to “Drug Permanently Withdrawn”.

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

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

Two AEs with the same PT and classified in the same category (pre-treatment AE or TEAE) will be considered as two different events when calculating the "number of events" in the tables.

A summary table displaying the number and the percentage of subjects experiencing at least one TEAE, serious TEAEs, non-serious TEAEs, ADRs/drug-related TEAE, serious ADRs, severe TEAEs, TEAEs leading to study drug discontinuation and TEAEs leading to death, as well as the number of events, will be presented by treatment group.

The SOC and PT will also be used for tabulation using the MedDRA dictionary. The number and percentage of subjects with at least one AE and the number of events will be presented by SOC and PT by treatment group for treatment emergent AEs, non-serious TEAEs, serious TEAEs, ADRs, serious ADRs, severe TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death.

A table presenting the number and percentage of subjects with at least one TEAE will be provided by PT. The number of subjects with TEAEs will be also displayed by SOC and PT and maximum severity. The number of events will be also included in these analyses.

Tables will be presented by SOC and then by PT, alphabetically sorted.

In addition, TEAEs that are presented by PT will be sorted by decreasing overall frequency.

An individual subject listing will also be provided for AEs.

10.3 Vital Signs

Vital signs parameters actual values and change from baseline (pulse rate, systolic blood pressure, and diastolic blood pressure) will be presented using descriptive statistics by timepoint for each treatment group.

An individual subject listing will also be provided for vital signs data.

10.4 Laboratory Parameters

Laboratory parameters actual values and change from baseline will be presented using descriptive statistics by timepoint for each treatment group.

An individual subject listing will also be provided for laboratory data.

11 Other Analyses

No other analyses planned. All other data collected in the eCRF will be listed.

12 Changes in the Planned Analyses from Study Protocol

As this study is specifically linked to the COVID-19 pandemic situation, as there was a global improvement in the countries (US, UK, Italy) where the study was done during 2021 (vaccines against COVID-19, better treatment, variant less contagious…), the recruitment was lower than expected and the study was closed before reaching the target sample size of 70 subjects.

As a consequence all statistical analysis planned in the protocol were not done considering the low sample size:

- Statistical Analysis of Days Alive and Free from Ventilation at Day 21
- Subjects alive and free of respiratory failure at Day 28.
- Statistical Analysis of Days Alive and Free from Invasive Ventilation Day 28
- Statistical Analysis of Days Alive and Free from Invasive Ventilation at Day 21 and Day 28
- Statistical Analysis of Days Alive and Free from Non-Invasive Ventilation at Day 21 and Day 28
- Statistical Analysis of Mortality at Day 21 and Day 28
- Statistical Analysis of Proportion of Subjects with Improvement in Severity Status at Day 28/Discharge
- Statistical Analysis of Change from Baseline in pao2/fio2 Ratio at Each Timepoint
- Statistical Analysis of Proportion of Subjects with pao2/fio2 Ratio Improvement >20% Compared to Baseline at Each Timepoint
- Statistical Analysis of Change from Baseline in fio2 at Each Timepoint
- Statistical Analysis of Length of ICU Stay (Days) at Day 28
- Statistical Analysis of Proportion of Subjects Alive and Out of ICU at Day 28
- Statistical Analysis of Delta SOFA Score at Day 3 and Day 28/ Discharge
- Statistical Analysis of Delta SOFA Sub Score at Day 3 and Day 28/Discharge
- Statistical Analysis of Proportion of Subjects Alive and Organ Failure Free at Day 28/Discharge

ITT definition was changed from “all randomised patients (analysed as randomised)” to “all randomised subjects who have at least one post baseline efficacy data analysed as randomised”.

Cytospin analysis was not done by central laboratory University College London (UCL) due to freeze of the samples. Freezing destroys the cells in the TA samples and hence it has not been possible to do this analysis. Cytospin data won’t be summarized in the tables and will be listed as missing in the listings.

Data on inflammatory indices such as cellular and cytokine (pg/ml) inflammatory markers (e.g. IL-1, IL-6, TNF alpha, IFN gamma and lymphocyte markers) from TA and blood samples were not provided (i.e., not analysed by the time of DB lock). As a consequence, these won’t be summarised and listed.

13 Output

13.1 Software

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

13.2 Reporting Conventions

13.2.1 Treatment and Timepoints Descriptors

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

Treatment group (as displayed in outputs)	**Descriptor for treatment**
Poractant Alfa	One or two or three doses of poractant alfa (Curosurf®)
Control	Standard of care

Output	**Descriptor for timepoints**
Tables and Figures	<u>For poractant alfa group:</u> Visits: Screening, Day 1, Day 2, …, Day 28, ICU Discharge. Timepoints: At intubation, Baseline, 6 hours post first dose, 12 hours post first dose, 18 hours post first dose, 24 hours post first dose, 30 hours post first dose, 36 hours post first dose, 42 hours post first dose, 48 hours post first dose, 54 hours post first dose, 60 hours post first dose, 66 hours post first dose, 72 post first dose. <u>For control group:</u> Visits: Screening, Baseline, Day 2, … Day 28, ICU Discharge. Timepoints: At intubation, Baseline, 6 hours post randomisation, 12 hours post randomisation, 18 hours post randomisation, 24 hours post randomisation, 30 hours post randomisation, 36 hours post randomisation, 42 hours post randomisation, 48 hours post randomisation, 54 hours post randomisation, 60 hours post randomisation, 66 hours post randomisation, 72 hours post randomisation.
Listings and Figures	<u>For poractant alfa and control groups:</u> Visits: Screening, Day 1, Day 2, … Day 28, ICU Discharge. Timepoints: At intubation, Baseline, 6 hours, 12 hours, 18 hours, 24 hours, 30 hours, 36 hours, 42 hours, 48 hours, 54 hours, 60 hours, 66 hours, 72 hours.

13.2.2 Decimal Places

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

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

Variables	**Decimal Places**
• Number of ventilator-free days	0 decimal

Variables	Decimal Places
• Duration of AE, medication (days) • Length of ICU stay (days) • Days between screening positive SARS-COV-19 rt-PCR test and start of intubation • Days between ICU admission date and start of intubation	
• BMI (kg/m2) • Ventilatory Parameters: TV, RR, Cdyn, Cstat, PEEP, PIP, and Pplat	1 decimal
• PaO2/FiO2 ratio	2 decimals

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

All summary statistics will be rounded (using the SAS® function ROUND) and wherever possible data will be decimal aligned.

Statistic	Number of decimal places for reporting
Counts (n)	None
Percentages (%)/Proportion	1 decimal place *Note:* *If the calculated percentage is >0.0% but <0.1% then <0.1% is to be presented in the relevant table and/or listing.* *If the calculated percentage is >99.9% but <100.0% then >99.9% is to be presented in the relevant table and/or listing.*
Mean, Median, SD, Confidence intervals	Actual data + 1 decimal place
Difference between percentages (%)/ Proportions, Mean and difference between means	Actual data + 1 decimal place
Min, Max	Same as actual data
p-values	3 decimal places. *Note:* *If the p-value is less than 0.001, it will be presented as <0.001.* *If the rounded result is a value of 1.000, it will be displayed as >0.999.*

13.2.3 Other Reporting Conventions

UK English will be used for all outputs.

Treatments will be presented with the following order in the tables: poractant alfa, control.

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

In the listings, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. All figures will include the source table in a footnote. Listings should be sorted by subject ID and visit (unless otherwise specified) and have the SDTM and/or ADaM source data referenced in a footnote. The columns of each listing should fit into one page and should not be split into different pages.

When an output is split in multiple pages, page-break should be adequately controlled.

When a table is split in multiple pages, breaking of a block information in different pages is not allowed.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number and any other relevant information which is split between 2 pages) must be presented at the beginning of that page.

When a listing contains a lot of information, in order to optimize space on the page, some columns can be merged (e.g. "reported term" and "indication" may be presented in the same column.

13.3 Format

The following information should always be presented:

- 'Clinical Study Code No.:<Study Code No.>' followed by Chiesi denomination in the top portion of each page. Chiesi denomination is 'Chiesi Farmaceutici S.p.A'.
- The table/listing/figure number followed by the title, the analysis set used and the output page number in the format of 'Page x of Y' in the top portion of each page of any table/listing/figure.
- The SAS program name followed by the date time of the output production and the analysis type (e.g. Dry Run; Draft Version; Final Version) in the bottom portion of each page of any table/listing/figure. The source listing/table/dataset will appear bottom left for every table/figure/listing.
- Tables and listings will be produced in rich text format (i.e., they will be tabular in format). Individual outputs must be provided in both portable format document (.pdf) and rich text format (.rtf).

- Combined PDF and RTF documents must also be provided, including a table of contents with hyperlinks. The combined documents should be divided by document type (tables, figures, listings).
- SAS outputs will be provided to the Sponsor in a similar manner (PDF and RTF; combined and with hyperlinked table of contents). The SAS outputs will be a separate deliverable to the Sponsor and are not intended for inclusion within the CSR.
- The combined documents page number in the format of 'Page n of N' will be presented bottom right corner.

The following should be followed for the tables:

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

The following should be followed for the listings:

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

The following should be followed for the figures:

- A portrait layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Figures will be produced in RTF and PDF formats (as described above), including relevant titles and footnotes as separate elements on the page (not within the body of the figure).

- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The size of the figures will be: width=16.3 cm, height=12.2 cm. The resolution will be set using the option IMAGE_DPI=400. Figures will have a footer specifying the source table or listing. Figures should clearly identify each treatment arm and require care of colours/symbols.
- The left margin will be a minimum of 2.5 cm, the right margin will be a minimum of 2 cm. The top and bottom margins will be a minimum 0.8 cm.

13.4 Quality Control

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

14 SAS Code

Not applicable: data will be summarized by means of descriptive statistics.

15 References

1. Chiesi Farmaceutici S.p.A. TLFs_Library_v1.0_signed. 10 Sep 2019.
2. Chiesi Farmaceutici S.p.A. Instructions for Producing Statistical Analysis Plan & Statistical Output. 25 Jan 2016.
3. ICH E9: Statistical Principles for Clinical Trials. Sept 1998.
4. [redacted] Statistical Analysis Plan v3.0.

16 List of Tables, Listings and Figures

16.1 Tables

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.1	Disposition by Treatment (Enrolled Set)	DST002	- Overall column should be displayed - Study discontinuation/completion status and reason for discontinuation to be displayed	Source: Listing 16.2.1.1
Table 14.1.1.2	Disposition of Subjects by Country and Site (Enrolled Set)	DST004	Overall column should be displayed. Display first Country and then all site within the country. All countries and sites sorted by alphabetical order.	Source: Listing 16.2.1.1
Table 14.1.1.3	Important Protocol Deviations (Enrolled Set)	DVT001	Overall column should be displayed. Display only important deviation, discard non important and no deviations lines.	Source: Listing 16.2.2.2
Table 14.1.1.4	Analysis Sets (Enrolled set)	DST005	- Overall column should be displayed - Safety Set and ITT set to be displayed.	Source: Listing 16.2.3.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.2	Demographic and Baseline Characteristics (Intention-To-Treat Set)	DMT001	- Overall column should be displayed. - Variables to be summarized: Age, Age Category, Gender, Childbearing Potential (only for females) (yes/no), Race (categories as per CRF to be displayed), Height, Weight and BMI at baseline. - All categories should be displayed even if empty.	Source: Listing 16.2.4.1
Table 14.1.3	Other Baseline and Disease Characteristics (Intention-To-Treat Set)	BLT001	- Overall column should be displayed. - Variables to display: – SBP (mmHg) – DBP (mmHg) – Pulse Rate (bpm) – PaO2/FiO2 ratio – FiO2 (%) – SOFA Score	Source: Listing 16.2.4.3
Table 14.1.4	SAS COVID-19 ARDS History (Safety Set)	BLT001	- Overall column should be displayed. - Variables to be summarized: – Days Between Screening Positive SARS-COV-19 rt-PCR Test and Start of Intubation – Days Between ICU Admission Date and Start of Intubation – SARS-COV-19 ARDS Medication Category (categories as per CRF to be displayed)	Source: Listing 16.2.4.2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.5.1	Medical and Surgical History (Safety Set)	MHT001	- Overall column should be displayed. - Replace <Condition/Procedure> by 'Medical History'.	Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.4.4
Table 14.1.5.2	Concomitant Diseases (Safety Set)	MHT001	- Overall column should be displayed. - Replace <Condition/Procedure> by 'Concomitant Disease'	Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.4.5
Table 14.1.5.3	Prior Procedures (Safety Set)	MHT001	- Overall column should be displayed. - Replace <Condition/Procedure> by 'Prior Procedure'	Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.4.6
Table 14.1.5.4	Maintained Procedures (Safety Set)	MHT002		Same as Table 14.1.5.3
Table 14.1.5.5	Concomitant Procedures (Safety Set)	MHT002		Same as Table 14.1.5.3
Table 14.1.6.1	Prior Medications (Safety Set)	CMT001	Overall column should be displayed.	Add the footnote: [1] ATCs and Preferred Name are coded using WHO-DD March 2020. Source: Listing 16.2.4.7
Table 14.1.6.2	Maintained Medications (Safety Set)	CMT002	Overall column should be displayed	Same as Table 14.1.6.1
Table 14.1.6.3	Concomitant Medications (Safety Set)	CMT002	Overall column should be displayed	Same as Table 14.1.6.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1	Summary of Number of Days Alive and Ventilator-free at Day 21 (Intention-To-Treat)	TPT002	- Display the number of days alive and Ventilator-free at Day 21 - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories.	Add the footnote: [1] Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days. Source: Listing 16.2.6.2-b
Table 14.2.2	Summary of Proportion of Subjects Alive and Free of Respiratory Failure at Day 28 (Intention-To-Treat)	TPT006	- There is only one timepoint to display: Day28. - Do not present 'At Any timepoint' line. - Do not display 'Visit' on the title line.	Source: Listing 16.2.6.2-b
Table 14.2.3	Summary of Number of Days Alive and Ventilator-free at Day 28 (Intention-To-Treat)	TPT002	- Display the number of days alive and Ventilator-free at Day 28. - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories.	Add the footnote: [1] Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days. Source: Listing 16.2.6.2-b
Table 14.2.4	Summary of Mortality at Day 21 and Day 28 (Intention-To-Treat)	TPT006	- Display the number of death at Day 21 and Day 28. - Do not present 'At Any timepoint' line.	Source: Listing 16.2.6.2-b

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.5	Summary of Number of Days Alive and Free from Invasive Ventilation at Day 21 and Day 28 (Intention-To-Treat)	TPT002	- Display the number of days alive and free from invasive ventilation at Day 21 and Day 28 - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories.	Add the footnote: [1] Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days. Source: Listing 16.2.6.2-b
Table 14.2.6	Summary of Number of Days Alive and Free from Non-Invasive Ventilation at Day 21 and Day 28 (Intention-To-Treat)	TPT002	- Display the number of days alive and free from non-invasive ventilation at Day 21 and Day 28 - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories.	Add the footnote: [1] Subjects who die or are mechanically ventilated longer than this period are assessed as zero ventilator-free days. Source: Listing 16.2.6.2-b

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.7.1	Summary of Proportion of Subjects with Improvement in Severity Status at Day 28/Discharge (Intention-To-Treat)	TPT006	- Summarize the Severity Status (Mild -1, Moderate -2, Severe -3 and Death - 4) at Baseline and Day 28/Discharge and then the Proportion of Subjects with an Improvement in Severity Status at Day 28/Discharge. - Do not present 'At Any timepoint' line.	Add the footnotes: [1] Mild : 200 mmHg<PaO2/FiO2<=300 mmg Moderate: 100 mmHg<PaO2/FiO2<=200 mmg Severe: Ratio PaO2/FiO2<=100 mmHg [2] An improvement is defined by a decrease of at least one point between baseline and Day 28/Discharge Source: Listing 16.2.6.2-b
Table 14.2.7.2	Severity Status: Shift from Baseline to Day 28/Discharge (Intention-To-Treat)	EGT005	- Do not present the 'Visit' line. - Display the following categories at Baseline and at Day 28/Discharge :Mild - 1, Moderate - 2, Severe - 3, Death - 4	Add the footnotes [1] Mild : 200 mmHg<PaO2/FiO2<=300 mmg Moderate: 100 mmHg<PaO2/FiO2<=200 mmg Severe: Ratio PaO2/FiO2<=100 mmHg Source: Listing 16.2.6.2-b

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.8	Summary of Actual Values and Change from Baseline in PaO2/FiO2 Ratio at Each Timepoint (Intention-To-Treat Set)	TPT001	- Overall column should not be displayed. - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories.	Add the footnote: [1] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation. Source: Listing 16.2.6.2-a
Table 14.2.9	Summary of Proportion of Subjects with PaO2/FiO2 Ratio Improvement >20% Compared to Baseline at Each Timepoint (Intention-To-Treat Set)	TPT006	- Do not present 'At Any timepoint' line.	Add the footnote: [1] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation. Source: Listing 16.2.6.2-a

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.10	Summary of Actual Values and Change from Baseline in FiO2 at Each Timepoint (Intention-To-Treat Set)	TPT001	- Overall column should not be displayed. - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories.	Add the footnote: [1] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation. Source: Listing 16.2.6.2-a
Table 14.2.11	Summary of Length of ICU Stay (Days) at Day 28 (Intention-To-Treat Set)	TPT001	- Overall column should not be displayed. - ICU stays (days) have to be display by stay and in total (see SAP section 9.3.8) - one row by stay and total for each considered subject. For example : First Stay: Duration (Days), Second Stay: Duration (Days), Total: Duration (Days) - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories.	Add the footnotes: [1] The length of ICU stay (days) is calculated as MIN (date of ICU discharge, date of Day 28) – date of ICU entrance + 1. [2] Subjects who die or are mechanically ventilated longer than this period are assigned with 28 days. Source: Listing 16.2.6.2-b

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.12	Summary of Proportion of Subjects Alive and Out of ICU at Day 28 (Intention-To-Treat Set)	TPT006	- There is only one timepoint to display: Day28. - Do not present 'At Any timepoint' line. - Do not display 'Visit'' on the title line.	Source: Listing 16.2.6.2-b
Table 14.2.13	Summary of Actual Values and Delta SOFA Score and Sub-Score from Baseline (Intention-To-Treat Set)	TPT001	- Replace 'Visit' by 'Timepoint' with categories: Day 3, ICU Discharge, Day 28. - Remove '95% CI for Mean', 'n geometric', 'Geometric mean' categories. - Overall column should not be displayed.	Source: Listing 16.2.6.3
Table 14.2.14	Summary of Proportion of Subjects Alive and Organ Failure Free at Day 28/Discharge (Intention-To-Treat Set)	TPT006	- There is only one timepoint to be display: Day28/Discharge. - Do not present 'At Any timepoint' line. - Do not display 'Visit' on the title line.	Add the footnote: [1] Organ Failure Free is defined as a SOFA score =0 Source: Listing 16.2.6.3
Table 14.2.15	Summary of Actual Values and Change from Baseline in Ventilatory Parameters (Intention-To-Treat Set)	LBT001	- See Section 13.2.1 for the list of timepoints to display. - Repeat summaries for each Ventilatory parameter (TV, RR, Cdyn, Cstat, PEEP, PIP, and Pplat). - Overall column should not be displayed.	Add the footnote: [1] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation. Source: Listing 16.2.6.2-a

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.16	Summary of Actual Values and Change from Baseline in Blood Gas Analysis Parameters: (Intention-To-Treat Set)	LBT001	- See Section 13.2.1 for the list of timepoints to display. - Repeat summaries for each Blood Gas Analysis parameter (pH, pCO2, pO2, HCO3, lactate). - Overall column should not be displayed.	Add the footnote: [1] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation. Source: Listing 16.2.6.4

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.17	Summary of Actual Values and Change from Baseline in Tracheal Aspirates and Blood Samples: (Intention-To-Treat Set)	LBT001	- See Section 13.2.1 for the list of timepoints to display. - Repeat summaries for each TA and blood samples parameters: As specified in section 9.4: - Surfactant Function measuring surface tension (mN/m) from TA samples. - Mass spec lipid analysis (%) from TA samples. - Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from TA samples. - Surfactant Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from Blood samples. - Add a subtitle to differentiate Blood and TA samples with LBSPEC 'Sample from' with Blood or Tracheal Aspirates as values - Overall column should not be displayed.	Source: Listing 16.2.6.6 Add the footnotes: [1] Sample not done (ND) or below the lower limit of quantitation (BLOQ) are not displayed.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.1	Summary of Extent of Exposure (Safety Set)	EXT001	- Display both treatment columns but only poractant alfa group can have data. Display a '-' in the n row for control group. Data to display: - Dose Administrations (1, 2 or 3) - Actual Diluted Volume Administered (ml)	Source: Listing 16.2.5
Table 14.3.2.1	Summary of Treatment Emergent Adverse Events (Safety Set)	AET001	Data to display: - Number of Subjects with at Least One TEAE - Number of Subjects with at Least One Serious TEAE - Number of Subjects with at Least One Non-Serious TEAE - Number of Subjects with at Least One ADR - Number of Subjects with at Least One Serious ADR - Number of Subjects with at Least One Severe TEAE - Number of Subjects with at Least One TEAE Leading to Study Drug Discontinuation - Number of Subjects with at Least One TEAE Leading to Death - Display '-' in the control group column when the selection is not applicable.	Source: Listing 16.2.7.2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.2
Table 14.3.2.3	Treatment Emergent Adverse Events by Preferred Term (Safety Set)	AET006		Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. [2] TEAEs sorted by decreasing overall frequency. Source: Listing 16.2.7.2
Table 14.3.2.4	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.3
Table 14.3.2.5	Non-Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.4
Table 14.3.2.6	Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003	Display '-' in the first row for control group as this is not applicable.	Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.5

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.7	Serious Treatment Emergent Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003	Display '-' in the first row for control group as this is not applicable.	Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.6
Table 14.3.2.8	Severe Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003		Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.7
Table 14.3.2.9	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term (Safety Set)	AET003	Display '-' in the first row for control group as this is not applicable.	Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.8
Table 14.3.2.10	Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Set)	AET003		Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0. Source: Listing 16.2.7.9
Table 14.3.4.1	Vital Signs: Summary of Actual Values and Change from Baseline (Safety Set)	VST001	- Replace 'Visit' by 'Timepoint'. See Section 13.2.1 for the list of timepoints to display. - Repeat summaries for each parameter (Pulse Rate, Systolic Blood Pressure, and Diastolic Blood Pressure). - Remove '95% CI for mean' category.	Add the footnote: [1] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation. Source: Listing 16.2.8.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.4.2	Haematology: Summary of Actual Values and Change from Baseline (Safety Set)	LBT001	- Replace 'Visit' by 'Timepoint'. See Section 13.2.1 for the list of timepoints to display. - Repeat summaries for each parameter on the 'Haematology' CRF page. - Remove '95% CI for mean' category. In case of original unit missing, do not display the value in the table.	Source: Listing 16.2.8.2 Add the footnote: [1] Value with original unit missing are not displayed.
Table 14.3.4.3	Chemistry: Summary of Actual Values and Change from Baseline (Safety Set)	LBT001	Same as Table 14.3.6.1	Source: Listing 16.2.8.3 Add the footnote: [1] Value with original unit missing are not displayed.

16.2 Listings

Listings will include data at observed Timepoints only, without imputation for missing data.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.1.7	Randomisation Schedule (Enrolled Set)	DSL001		
Listing 16.2.1.1	Subjects Disposition (Enrolled Set)	DSL004	- 'Period of last intake of study treatment' and 'Last treatment received' columns not to be displayed. - Date of first and last doses are fulfilled only for poractant alfa group.	Add the following footnotes: [1] [Day 1] is the study Day at Date of Study Discontinuation calculated with reference to the Informed Consent Date [2] [Day 2] is the study Day at Date of Study Discontinuation calculated with reference to the First Dose [3] [Day 3] is the study Day at Date of Study Discontinuation calculated with reference to the Last Dose Date

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.1.2	Study Visits (Intention-To-Treat Set)	SVL001	- Remove the word 'Retest' in header.	Ass the footnote: [1] [Study Day] is the study Day at Visit calculated with reference to the randomization Date
Listing 16.2.2.1	Violation of Eligibility Criteria (Enrolled Set)	DVL001	- Only deviations from DV in relation to inclusion/exclusion criteria. - Change 'Visit' to 'Timepoint'. - Remove 'Reference analysis set' column.	
Listing 16.2.2.2	Protocol Deviation (Enrolled Set)	DVL002	- Include all deviations from DV. - Remove 'Randomised sequence', 'Period', and 'Reference analysis set' columns.	
Listing 16.2.3.1	Analysis Sets Disposition (Enrolled Set)	DSL006	- Remove 'Period' and 'Randomised sequence' - Include Safety Set and ITT Set	
Listing 16.2.3.2	Exclusion from Safety and Intention-To-Treat Sets (Enrolled set)	DSL007	- Remove 'Period' and 'Randomised sequence' - Include reason for exclusion from safety set and form ITT sets	
Listing 16.2.4.1	Demographic Characteristics (Intention-To-Treat Set)	DML001	- Remove Ethnicity' column.	
Listing 16.2.4.2	SARS-COV-19 ARDS History (Intention-To-Treat Set)	SCL001	The following columns will be presented: - Subject ID - Treatment Group - Date of Positive SARS-COV-19 rt-PCR - ICU Admission Date - Intubation Date/Time - Medication Category	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.3	Other Baseline and Disease Characteristics (Intention-To-Treat Set)	DML001	The following columns will be presented: - Subject ID - Treatment Group - SBP (mmHg) - DBP (mmHg) - Pulse Rate (bpm) - PaO_2/FiO_2 ratio (mmHg) - FiO_2 (%) - SOFA Score	
Listing 16.2.4.4	Medical and Surgical History (Intention-To-Treat Set)	MHL001		Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0.
Listing 16.2.4.5	Concomitant Diseases (Intention-To-Treat Set)	MHL002		Same as Listing 16.2.4.4
Listing 16.2.4.6	Procedures (Intention-To-Treat Set)	PRL001	- Remove 'Analysis Period' in the header - [CAT]: Prior, Maintained, And Concomitant. - Drop the last column 'Indication'	Add the footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version 23.0.
Listing 16.2.4.7	Medications (Intention-To-Treat Set)	CML001	- Remove 'Analysis Period' In the header - [CAT]: Prior, Maintained And Concomitant.	Add the footnote: [1] ATCs and Preferred Name are coded using WHO-DD March 2020. [2] [Day] is the study Day at Start Date calculated with reference to the First Dose Date

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.8	Thoracic CT or Chest X-Ray (Intention-To-Treat Set)	PEL001	- Remove Analysis Period column - Display 'Assessment date/Time [Study Day]' instead of 'Assessment date/time [study day / study day in period]' - Display 'Procedure' instead of Body System'	
Listing 16.2.5	Study Drug Administration (Intention-To-Treat Set)		The following columns will be presented: - Subject ID - Randomized Treatment - Actual Treatment - Kit Number - Timepoint - Date/Time of Administration [Day] - Planned Vol. to be Admin. (ml) - Planned Vol. to be Admin. after Dilution (ml) - Actual Diluted Vol. Admin. (ml) - Administration Interrupted Only poractant alfa group should have data listed.	
Listing 16.2.6.1	Ventilatory Support (Intention-To-Treat Set)		The following columns will be presented: - Subject ID - Randomized Treatment - Actual Treatment - Ventilator Type - Start Date/Time [Day] - Stop Date/Time [Day] or Ongoing - Duration of Ventilatory Support (Days) – displayed by Type of Support (Invasive or Not Invasive) - Overall Duration of Ventilator Support	Add the footnotes: [1]: Duration of ventilatory support have been calculated as the difference between end date and start date +1. [2]: Overall duration of ventilatory support has been calculated as the difference between the maximum end date (between invasive and non-invasive ventilation) and start date +1.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.2-a	Ventilatory Parameters by Timepoint (Intention-To-Treat Set)	VSL002	- Remove 'Analysis Period' - Display 'Assessment date/Time [Study Day]' instead of 'Assessment date/time [study day / study day in period]' - Do not display [H] flag in Change from baseline column - Skip the last column (Change from pre-dose) - In Test <Unit> column, display: - FiO2 (%) - Mean Arterial Pressure (mmHg) - Dynamic Compliance (ml/cmH2O) - Static Compliance (ml/cmH2O) - PaO2/FiO2 Ratio - Tidal Volume (ml/kg BW) - Respiratory Rate (/min) - Peak Inspiratory Pressure - PIP (cmH2O) - Plateau Pressure (cmH2O) - Positive End-Expiratory Pressure - PEEP (cmH2O) - Blood Flows (L/min) - Sweep Gas Flows (L/min) - Add a last column displaying PaO2/FiO2 Ratio Improvement (<20%, >=20% or death)	Add the footnotes: [1]: Baseline=Y flags baseline value [2]: Use=Y: included in the analysis [3] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation.

Listing Number	Listing Title	Template Code	Notes	Footnotes

Listing 16.2.6.2-b	Ventilatory Derived Parameters by Timepoint (Intention-To-Treat Set)	-	- Display:
			- Subject ID
			- Randomized Treatment
			- Actual Treatment
			- Parameter <Unit>
			  - Number of Days Free From Invasive Ventilation
			  - Number of Days Free From Non-invasive Ventilation
			  - Mortality
			  - Number of Days Alive and Ventilator-free
			  - Alive and Free of Respiratory Failure
			  - Alive and Out of ICU
			  - Length of Primary ICU Stay (Days)
			  - Length of Secondary ICU Stay (Days)
			  - Length of Total ICU Stay (Days)
			  - Alive and Organ Failure Free
			  - Severity PaO2/FiO2 ratio
			  - Improvement in Severity PaO2/FiO2 ratio
			
			- Values (*display one column for Baseline, one for D21 and one for D28 results*)
			
			Add the following Flags as relevant at D21 and/or D28 results:
			  - Min 12H Ventil. Free
			  - Min 12H Inv. Ventil. Free
			  - Min 12H NInv. Ventil. Free
				Add the footnotes:
				[1] * Flag subject with minimum 12H of ventilation free
				[2] ^ Flag subject with min 12H of NIV free
				[3]# Flag subject with minimum 12H of IV free

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.3	SOFA Score (Intention-To-Treat Set)	VSL002	- Remove 'Analysis Period' - Display 'Assessment date [Study Day]' instead of 'Assessment date/time [study day / study day in period]' - Do not display [H] flag in Change from baseline column - Skip the last column (Change from pre-dose) - Do not display the unit in column 'Test'(no unit for SOFA score) - In Test column, display: - Respiratory system Score - Nervous system Score - Cardiovascular system Score - Liver Score - Coagulation Score - Kidney Score - SOFA Score (derived)	Add the footnotes: [1]: Baseline: Y flags baseline value [2]: Use=Y: included in the analysis
Listing 16.2.6.4	Blood Gas Analysis (Intention-To-Treat Set)	VSL002	- Remove 'Analysis Period' - Display 'Assessment date/Time [Study Day]' instead of 'Assessment date/time [study day / study day in period]' - Do not display [H] flag in Change from baseline column - Skip the last column (Change from pre-dose) - In Test <Unit> column, display: - pH - pCO2 (mmHg) - paO2 (mmHg) - HCO3 (mmol/L) - Lactate (mmol/L)	Add the footnotes: [1]: Baseline: Y flags baseline value [2]: Use=Y: included in the analysis [3] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.5	Hospitalization (Intention-To-Treat Set)		Variables to be listed: - Subject ID - Randomized Treatment - Hospitalization Type - Admission Date/Time [Day] - Discharge Date/Time [Day] - Hospital Stay (days) - Hospital Transfer (Date [Day]/Destination)	Add the footnote: [1] Hospital Stay has been calculated as the difference between discharge date and admission date +1.
Listing 16.2.6.6	Tracheal Aspirate and Blood Samples (Intention-To-Treat Set)	LBL001	- Remove 'Analysis Period' - Display 'Assessment date/Time [Study Day]' instead of 'Assessment date/time [study day / study day in period]' - Do not display CSA [4] column - Add a column with LBSPEC 'Sample from' with Tracheal Aspirate and blood as value - In Test <Unit> column, display: Surfactant Function measuring surface tension (mN/m) from TA samples. - Mass spec lipid analysis (%) from TA samples. - Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from TA samples. - Surfactant Protein D Enzyme Linked Immunosorbent Assay (ng/mL) from Blood samples. - Cytospin from TA samples - There is no normal range for TA aspirates samples, Normal range and ABN column will remain empty.	Add the footnotes: [1] Baseline=Y flags baseline value [2] USE=Y: included in the analysis [3] H = Abnormally High Value / L = Abnormally Low Value, compared to the Normal Range. [4] No Normal range for tracheal aspirate samples [5] ND: Not Done, BLOQ: Below the lower limit of quantitation

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.7.1	Pre-treatment Adverse Events (Intention-To-Treat Set)	AEL001	- Remove 'Ethnicity', 'Pattern'. - Replace 'Concomitant Therapy' 'Concomitant Procedure' by 'Concomitant Therapy / Concomitant Procedure' - Concatenate AEACN with AEACNOTH (Action taken : <specify>	Add the footnotes: [1] CA = Is a congenital anomaly or birth defect; DI = Results in persistent or significant disability or incapacity; DTH = Results in death; HSP = Requires hospitalization or prolongation of existing hospitalization; LTH = Is life-threatening; SIG = Is a medically significant adverse event. [2] System Organ Class and Preferred Term are coded using MedDRA Version 23.0.
Listing 16.2.7.2	Treatment Emergent Adverse Events (Intention-To-Treat Set)	AEL002	- Remove 'Ethnicity', 'Period/Actual Treatment', 'Starting dose/dose at onset/weight' and 'Pattern'. - Replace 'Concomitant Therapy' 'Concomitant Procedure' by 'Concomitant Therapy / Concomitant Procedure' - Concatenate AEACN with AEACNOTH (Action taken : <specify>	Same as Listing 16.2.7.1
Listing 16.2.7.3	Serious Treatment Emergent Adverse Events (Intention-To-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.1
Listing 16.2.7.4	Non-Serious Treatment Emergent Adverse (Intention-To-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.1

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.7.5	Treatment Emergent Adverse Drug Reactions (Intention-To-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.1
Listing 16.2.7.6	Serious Treatment Emergent Adverse Drug Reactions (Intention-To-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.1
Listing 16.2.7.7	Severe Treatment Emergent Adverse Events (Intention-To-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.1
Listing 16.2.7.8	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Intention-To-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.1
Listing 16.2.7.9	Treatment Emergent Adverse Events Leading to Death (Intention-To-Treat Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.1
Listing 16.2.8.1	Vital Signs (Intention-To-Treat Set)	VSL001	- Remove 'Analysis Period' column. - Remove 'Study day in Period'. - Change 'Analysis Timepoint' to 'Timepoint'. - Change 'Body Weight (kg)' to 'Pulse Rate' and put as last column. - Do not display 'CHG [3]' (Change from pre-dose)	Add the footnotes: [1] Use=Included in the Analysis; B: Flags Baseline value [2] CFB is Change from Baseline [3] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.8.2	Laboratory Results: Haematology (Intention-To-Treat Set)	LBL001	- Remove 'Analysis Period' column. - Remove 'Study day in Period'. - Change 'Analysis Timepoint' to 'Timepoint'. - Remove 'Fasted' column - Remove 'CSA' column. In case of original unit missing, do not display the value.	Add the footnote: [1] Value with original unit missing are not displayed.
Listing 16.2.8.3	Laboratory Results: Chemistry (Intention-To-Treat Set)	LBL001	Same as Listing 16.2.8.1	Add the footnote: [1] Value with original unit missing are not displayed.
Listing 16.2.8.4	Physical Examination (Intention-To-Treat Set)	PEL001	- Remove 'Analysis Period' column. - Remove 'Study day in Period'.	
Listing 16.2.9	Comments (Intention-To-Treat Set)	COL001	Variables to be listed: - Subject ID - Randomized Treatment - Assessment - Comment	

16.3 Figures

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Table Number
Figure 14.1.1	Disposition Flow Chart (Enrolled Set)	DSF001		Source: Tables 14.1.1.1 and 14.1.1.4
Figure 14.2.1	PaO2/FiO2 Ratio profile (Intention-To-Treat Set)	TPF002	- Treatment to be presented in legend - X-axis should be "Timepoint" including Baseline - Display below the X-axis, the number of subjects with available results. - Display the mean +/- SD	Source: Table 14.2.8 Footnote: [1] Data are displayed until the subject is discharged from ICU. [2] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation.
Figure 14.2.2	FiO2 Profile (Intention-To-Treat Set)	TPF002	Same as Figure 14.2.3	Source: Table 14.2.10 Footnote: [1] Data are displayed until the subject is discharged from ICU. [2] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation.

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Table Number
Figure 14.2.3	SOFA Score Profile (Intention-To-Treat Set)	TPF002	Same as Figure 14.2.3	Source :Table 14.2.13 Footnote: [1] Data are displayed until the subject is discharged from ICU.
Figure 14.2.4	Ventilatory Parameters Profiles (Intention-To-Treat Set) -	TPF002	- Y-axis should be “Mean values”. - X-axis should be “Timepoint”. - Display below the X-axis, the number of subjects with available results. - Display the mean values +/- SD. - Display one parameter per page (TV, respiratory Rate, Cdyn, Cstat, PEEP, PIP, and Pplat).	Source: Table 14.2.15 Footnote: [1] Data are displayed until the subject is discharged from ICU. [2] Duplicated data reported twice at 2 different timepoints are reported at the first occurrence for post dose/post randomisation and at the last occurrence for pre dose/pre randomisation.