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STATISTICAL ANALYSIS PLAN

Protocol: EDP1815-205
Protocol version: V4.0 05AUG2020

A Phase 2 double-blind placebo-controlled study investigating the safety and efficacy of EDP1815 in the treatment of patients hospitalized with SARS-CoV-2 Infection

SAP/Amendment Number	**Date**
Final SAP v1.0	30 July 2020
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1 Table of Contents

Table of Tables

Table of Figures

2 Abbreviations and Definitions

AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
CI	Confidence interval
CRC	Covid related complications
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
dp	Decimal place
eCRF	Electronic case report form
FiO2	Fraction of inspired oxygen
GI	Gastrointestinal
iDMC	Independent data monitoring committee
ICU	Intensive care unit
IMP	Investigational medical product
ITT	Intention to treat
LDH	Lactate dehydrogenase
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
O2	Oxygen
OSCI	Ordinal scale for clinical improvement
PCI	Potentially clinically important
RTPCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
S/F Ratio	SpO2/FiO2 ratio
SOC	System organ class
SpO2	Oxygen saturation by pulse oximetry
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
ULN	Upper limit of normal
WHO	World Health Organization

3 Introduction

The purpose of this SAP is to provide all information that is necessary to perform the required statistical analyses of study EDP1815-205. It also defines the summary TFLs to be included in the final clinical study report according to the protocol. The SAP is based upon, and assumes familiarity, with the study protocol, version 4.0, dated 05-Aug-2020.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. The content of this SAP is compatible with the ICH E9 Guidance document.

4 Study Objectives and Endpoints

4.1 Study Objectives

The primary objective of the study is

- To evaluate the effect of EDP1815 on pulmonary function as measured by the change in Oxygen Saturation by Pulse Oximetry (SpO2) / Fraction of Inspired Oxygen (FiO2) [S/F ratio]

Secondary objectives of the study are:

- To evaluate the effect of EDP1815 on the development and severity of complications of COVID-19 infection
- To evaluate the effect of EDP1815 on length of hospitalization and recovery in participants with COVID-19
- To evaluate the safety and tolerability of EDP1815 in participants with COVID-19

Exploratory objectives of the study are:

- To evaluate the effect of EDP1815 on the exaggerated host cytokine response to COVID-19 infection
- To identify clinical or biochemical predictors of response to EDP1815

4.2 Endpoints

Table 1 List of endpoints associated with each study objective

Objectives	Endpoints
Primary	
• To evaluate the effect of EDP1815 on pulmonary function as measured by the change in S/F Ratio	• Change from baseline to the lowest S/F ratio measured in days 1-14

Objectives	Endpoints
Secondary	
• To evaluate the effect of EDP1815 on the development and severity of complications of COVID-19 infection	• Change in S/F ratio at days 4, 7, 10 and 14/discharge day. • Percentage change in S/F ratio at days 4, 7, 10 and 14/discharge day. • Percentage of participants at each level on the WHO OSCI score at days 4, 7, 14, 21 and 42. • Percentage of participants with shifts from each level of the WHO OSCI score at baseline at days 4, 7, 14, 21 and 42. • Percentage of participants remaining at their baseline score on the WHO OSCI (or lower) at days 4, 7, 14, 21 and 42. • Percentage of participants reporting each level of the WHO OSCI score at their worst post-baseline day. • The time in days spent at each participant's worst reported WHO OSCI score (excluding death). • Intubation and mechanical-ventilation free survival, defined as the time in days from start of treatment to first occurrence of a WHO OSCI score of 6 or more. • Overall survival, defined as the time in days from start of treatment to death by any cause • Number of days requiring oxygen therapy. • Number of days with pyrexia ≥ 38°C. • Maximum daily temperature. • Minimum SpO2 level. • Maximum SpO2 level.
• To evaluate the effect of EDP1815 on length of hospitalization and recovery in participants with COVID-19	• Time to discharge, defined as the time in days from start of treatment to first occurrence of a WHO OSCI score of 2 or less. • Time to oxygen saturation (SpO2) ≥94% on room air without further requirement for oxygen therapy. • Time to recovery, defined as the time in days from symptom onset to alleviation of all COVID-19 symptoms.

Objectives	Endpoints
Exploratory	
• To evaluate the effect of EDP1815 on the exaggerated host cytokine response to COVID-19 infection	• Change from baseline in cytokine levels (including IL-6) at day 4 and day 7 (and/or at additional timepoints if samples are available). • Change from baseline in inflammatory response at day 4 and day 7 (and/or at additional timepoints if samples are available).
• To identify clinical or biochemical predictors of response to EDP1815.	• Statistical significance of each potential predictor-treatment interaction in exploratory models based on the final selected model for the primary efficacy analysis. • To identify the presence of EDP1815 in stool and/or blood using PCR primers

5 Study Methods

5.1 General Study Design and Plan

This is a double-blind, placebo-controlled parallel group study to assess the efficacy and safety of EDP1815 in the treatment of patients hospitalized by SARS-CoV-2 infection.

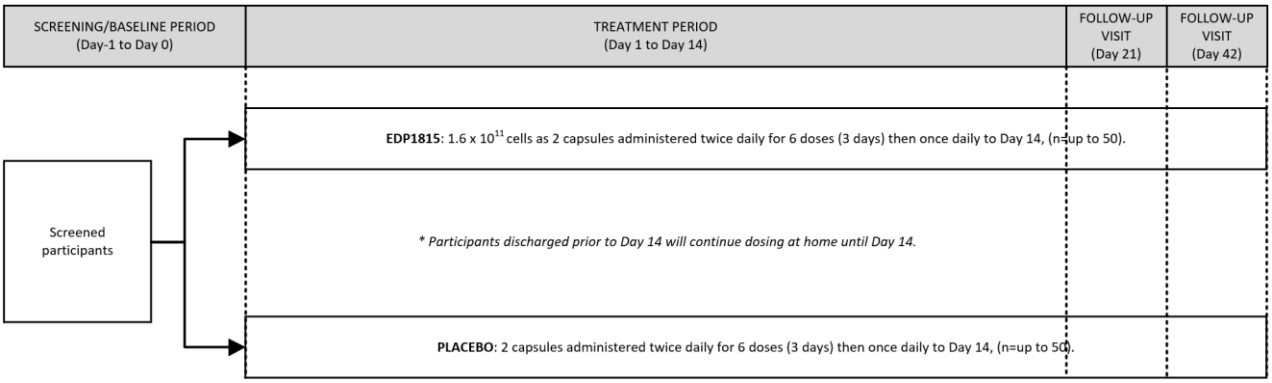
This is a pilot study designed to investigate the potential of EDP1815 in the prevention of COVID-19 disease progression.

60 participants who are hospitalized with confirmed COVID-19 disease will be randomized in a 1:1 ratio to EDP1815 and matching placebo, in addition to standard of care. The study may be extended to an additional 40 subjects, based on recommendations from an independent data monitoring committee (iDMC).

The study will comprise of a Screening Phase, a 14-day Treatment Phase and a 28-day Follow-up Phase as shown in Figure 1.

- Due to the urgent nature of the study, the screening phase may occur on the same day as the start of the treatment phase with eligible participants dosed as soon as possible after eligibility is confirmed.
- The treatment course is 14 days with twice daily dosing for the first 3 days followed by once daily dosing for the remainder of the treatment period.
- Participants who are discharged prior to the end of the follow-up period will remain in the study and complete a daily questionnaire on until their symptoms have resolved or the end of the follow-up period (whichever occurs first)
- Participants who are discharged prior to the end of the 14-day treatment period, will have medication dispensed to take at home.

Figure 1 Study Schema



5.2 Randomization and Blinding

Participants will be randomly allocated, in a 1:1 ratio, to EDP1815 or matched placebo using a pre-prepared, blocked randomization list. Randomization numbers will be allocated sequentially. If more than one site is used in this study each site will be given complete blocks of randomization numbers.

The study will be fully blinded to the participants, site staff and sponsor. An independent statistics and programming group will be used to prepare all unblinded outputs for the iDMC which will be held in a secure area until the study has completed.

The Sponsor must be notified immediately (within 24 hours) if the investigational drug blind is broken. The date, time, and reason the blind was broken must be recorded on the appropriate Case Report Form (CRF).

5.3 Derived variables

5.3.1 General

5.3.1.1 Relative Day and Time

The relative day of an assessment will be calculated as:

- For measurement performed on or after the date of first dose:
  Date of assessment – date of start of treatment +1

- For measurements performed before the date of first dose:
  Date of assessment – date of study treatment

5.3.1.2 Baseline

The last non-missing value collected before first study dose will be taken as the baseline measurement for all parameters. If data is collected on Day 1 without an associated time being provided, it will be assumed to be pre-dose.

5.3.1.3 Change and Percentage Change from Baseline

Change from baseline will be calculated as:

change from baseline = value at timepoint – baseline value

Change from baseline will be presented to the same level of precision as the original value in the listings.

Percentage change from baseline will be calculated as:

percentage change from baseline = 100*(change from baseline / baseline value)

Percentage change from baseline will be presented to 1 decimal place (dp) in the listings.

5.3.2 Demographic and Background Data

5.3.2.1 Age

Age (years) will not be recalculated using year of birth but will be taken directly from the CRF.

If participants aged >65 years are allowed to be entered into the study, then age (years) will be categorized as follows:

- 18-65 years
- 66-75 years
- >75 years

In addition, for age as a prognostic marker for COVID-19, a further categorization will be performed as follows:

- 18-59 years
- ≥ 60 years

5.3.2.2 Race and Ethnicity

Participants who select multiple races on the CRF will be coded as ‘Mixed race’.

Race and ethnicity will also be combined in the ‘Non-white or Hispanic/Latino’ covariate as follows:

- ‘Non-Hispanic/Latino white’ – participants who select only race=’White’ and no other race and who select ethnicity =’Not Hispanic/Latino’
- ‘Non-white or Hispanic/Latino’ – all other participants

5.3.2.3 Height, Weight and Body Mass Index

Height may be recorded in cm or inches. Height in inches will be converted to height in cm as follows:

Height (cm) = Height (inches)*0.3937

Height (cm) will be presented to 1 dp in the listings.

Weight may be recorded in kg or pounds. Weight in pounds will be converted to weight in kg as follows:

Weight (kg) = Weight (pounds) * 0.4536

Weight (kg) will be presented to 1 dp in the listings.

Body mass index (BMI) will be calculated as:

BMI (kg/m^2) = Weight (kg) / [height (cm)/100]^2

BMI (kg/m^2) will be presented to 1 dp in the listings.

BMI will also be categorized as:

- <30 kg/m^2
- ≥30 kg/m^2

5.3.2.4 Smoking Pack Years

Smoking pack years will be calculated using the type of tobacco product, amount used, frequency (daily or weekly) and duration of use.

Tobacco products other than cigarettes will be converted to cigarette equivalent using the rules in Table 2.

Table 2 Conversion to Cigarette-equivalent use for Other Tobacco Products

Tobacco Product	Amount	Cigarette equivalent
Pipe	1 bowl	2.5 cigarettes
Cigarillos	1 Cigarillo	2 cigarettes
Cigars	1 Cigar	4 cigarettes
Rolling tobacco	25g (1 ounce)	50 cigarettes

If frequency is reported as a weekly amount, then the daily amount smoked will be converted from weekly amount by dividing by 7.

Pack years will be calculated after all tobacco products have been converted to provide a total daily cigarette-use equivalent as:

Pack Years = Total daily cigarette-equivalent use/20 * Years smoked

If a participant reports more than one type of tobacco product or multiple periods of use, the pack years will be calculated separately for each type/period and then added together for total pack years.

5.3.2.5 Time Since Symptom Onset

Time since symptom onset at first dose will be calculated as:

Time since symptom onset (days) = Date of first dose – Date of symptom onset + 1

5.3.2.6 Presence of Co-morbidities at Baseline

A targeted medical history will be collected at the Screening visit. Participants will be considered to have each relevant co-morbidity if it is marked as 'ongoing'.

5.3.2.7 Treatment Compliance

Participants will be expected to dose twice daily with two capsules for 6 doses and then once daily with two capsules to Day 14 for a total of 17 doses.

Unless a participant enters the study too late on Day 1 to have at least a 2-hour gap between doses, they will receive two doses on Days 1-3 and one dose on Days 4-14. Participants who do not enter the study in time to receive 2 doses with at least a 2-hour gap between doses will only receive one dose on Day 1, two doses on Days 2-4 and one dose on Days 5-14.

The expected number of capsules will be calculated as per Table 3.

Table 3 Calculation of Expected Dose

Subject Status	Doses received on Day 1	Number of capsules expected
Completed treatment to Day 14	Any	34
Discontinued treatment on or after Day 4	Any	=2*(Relative Study Day+3)
Discontinued treatment on Day 3	2 doses	12
	1 dose	10
Discontinued treatment on Day 2	2 doses	8
	1 dose	6
Discontinued treatment on Day 1	2 doses	4
	1 dose	2

Number of capsules taken will be calculated as:

Number of capsules taken = Number of capsules dispensed – Number of capsules returned

Treatment compliance will be taken from the dosing log.

5.3.2.8 Daily Diary Compliance

The daily diary should be completed on every day following discharge from hospital until the participant has reported at least two consecutive days with no symptoms (Q1) and a return to their usual activities (Q3).

The last day on which a daily diary is expected is defined as the earliest of the second consecutive day on which the participant reported no symptoms and a return to their usual activities and Day 42/Study day of early withdrawal from the study.

The number of days on which a daily diary is expected will be defined as:

Number of diary days expected = Date of last expected diary day – Date of discharge

The number of diary days completed will include all days on which at least questions 1-3 of the diary were answered up to and including the date of the last expected diary day. Diary days completed after Day 42 or after the second consecutive day with no symptoms and a return to their usual activities will not be included.

Daily diary compliance will be calculated as:

Daily diary compliance (%) = 100 x Number of diary days completed / Number of diary days expected

Daily diary compliance will be presented to 1 dp in the listings.

5.3.3 Efficacy

5.3.3.1 SpO2

The endpoints for maximum SpO2 and minimum SpO2 will be calculated from available data only.

Maximum and minimum SpO2 will be calculated for each of the following periods:

- Days 1-7
- Days 1-14
- Days 1-28
- Days 1-42

5.3.3.2 FiO2

FiO2 will be derived from the device used to deliver oxygen according to the rules shown in Table 4. FiO2 will be expressed to 2 dp.

Table 4 Derivation of FiO2 values

Oxygen Delivery Method	Data collected		Derived FiO2 (fraction of 1)
None (room air)	N/A		0.21
Nasal cannula	Oxygen flow rate in L/min	1	0.24
		2	0.27
		3	0.30
		4	0.33
		5	0.36
		6	0.39
		7	0.42
Venturi mask or similar device	FiO2 recorded directly from notes as percentage (e.g. 60%) to be converted to fraction (e.g. 0.60)		
Non-invasive ventilation	FiO2 recorded directly from notes as percentage (e.g. 60%) to be converted to fraction (e.g. 0.60)		

Oxygen Delivery Method	Data collected		Derived FiO2 (fraction of 1)
Non-rebreathe mask	Oxygen flow rate in L/min	15	1.00
Invasive ventilation	FiO2 recorded directly from notes as percentage (e.g. 60%) to be converted to fraction (e.g. 0.60)		
High flow nasal cannula	FiO2 recorded directly from notes as percentage (e.g. 60%) to be converted to fraction (e.g. 0.60)		

5.3.3.3 S/F Ratio

The S/F ratio will be calculated as:

S/F ratio = SpO2 (%) / FiO2 (fraction of 1).

The S/F ratio will be expressed to 0 dp.

Missing S/F ratios will be imputed using the rules in Table 5.

Table 5 Rules for Imputation of Missing S/F Ratios on Individual Study Days 1-14

Reason for Missingness	Data Availability	Value to be Imputed
Participant died	N/A	0
Participant was discharged	N/A	Last S/F ratio recorded prior to discharge
Participant withdrawn from the study	N/A	Not imputed, value will remain as missing.
Other reason	S/F ratio available within window of +/- 1 day	Average of non-missing S/F ratios reported on the day before and day after the study day with missing data
Other reason	No S/F ratio available within window of +/- 1 day	Not imputed, value will remain as missing.

Trough S/F ratio is defined as the lowest S/F ratio reported in Days 1-14. Participants who die on or before Day 14 will have their trough S/F ratio imputed to 0.

If more than one S/F ratio is provided for a relevant study day, the lowest S/F ratio reported for that study day will be used in all summaries and analyses.

5.3.3.4 WHO OSCI

The WHO OSCI has values ranging from 0 to 8 as shown in Table 6.

Table 6 WHO Ordinal Scale for clinical Improvement

Participant State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2

Participant State	Descriptor	Score
Hospitalized – Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized – Severe Disease	Non-invasive ventilation or high flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support	7
Dead	Death	8

The WHO OSCI will be recorded daily in the eCRF while participants remain in hospital. Once discharged, the WHO OSCI will be derived from questions 1 and 2 of the daily COVID-19 diary using the rules defined in Table 7.

Table 7 Derivation of WHO OSCI using the Outpatient Daily Covid-19 diary

Question 1: Overall, how severe were your COVID-19 symptoms today?	Question 2: How much did your COVID-19 symptoms interfere with your usual activities today?	WHO OSCI Score
No COVID-19 symptoms today	Any response	0
Mild, moderate, severe or very severe	Not at all	1
Mild, moderate, severe or very severe	Somewhat or Very much	2

For participants who report question 1 as "No COVID-19 symptoms today" and a return to their usual activities (Q3) for 2 days in a row do not need to complete the COVID-19 diary on subsequent days. If this condition is met, the missing WHO OSCI score will be imputed as 0 for any remaining study days up to and including Day 42.

Note that participants who are discharged on home oxygen will still be considered as having WHO OSCI score =2 as the participant state is considered before the descriptor in Table 6.

For participants who die, the WHO OSCI score will be imputed to 8 for all remaining study days after death.

WHO OSCI scores that are missing for reasons other than death or full recovery of symptoms will not be imputed.

For the secondary endpoint looking at whether participants remained at or below their baseline WHO OSCI score at Days 4, 7, 10, 14, 21 and 42, participants who show an increased score and then return to their baseline score (or lower) will not be considered as having met the criterion for this endpoint. Only participants who have not reported a score above their baseline score on any day prior to the endpoint day will be considered as having met the endpoint for that day.

5.3.3.5 Overall Survival and Intubation and Mechanical Ventilation Free Survival

Overall survival (OS) is defined as the time in days from randomization until death by any cause.

Intubation and mechanical ventilation free survival (IMVFS) is defined as the time in days from randomization until the earliest event of death by any cause or requirement for intubation and/or mechanical ventilation as indicated by the first occurrence of a WHO OSCI score of 6 or above.

Participants who complete the 42-day study period or prematurely withdraw from the study without experiencing the relevant event will be censored on the date of study completion/withdrawal.

Participants who prematurely withdraw from treatment but remain in the study will not be censored and will continue to be followed up until the first occurrence of the relevant event, study completion or withdrawal from the study.

Time to the relevant event will be calculated as:

Time to event (days) = Date of event/censoring – date of randomization +1

5.3.3.6 Time to Discharge, Time to SpO2 ≥94% on Room Air and Time to Recovery

Time to discharge is defined as the time in days from randomization until the date of discharge.

Time to SpO2 ≥94% on room air is defined as the time in days from randomization to the first day at which an SpO2 measurement ≥94% on room air is reported after which there were no further requirements for oxygen therapy during the study.

Time to recovery is defined as the time in days from the date of symptom onset until the first day on which a WHO OSCI score of 0 is reported with no further increase above 0 during the study.

Participants who die during the study before the relevant event occurring will be given a status of 'death' which will be considered as a competing risk rather than an event or a censored observation in the analysis.

Participants who are still alive at the end of the 42-day study period or who withdraw prematurely from the study for reasons other than death without experiencing the relevant event will be censored on the date of study completion/withdrawal.

As the endpoint of SpO2 ≥94% on room air without further requirement for oxygen therapy cannot be measured after discharge (as SpO2 is not measured after discharge), any participants who have not achieved this before discharge will be considered as having met the endpoint criterion at the discharge date if they are discharged without oxygen for home use and will be censored at the discharge date if they are discharged with oxygen for home use. Note that these rules only apply for participants who are discharged before study completion/withdrawal.

Time to discharge and time to SpO2 will be calculated as:

Time to event (days) = Date of event/censoring/death – date of randomization +1

Time to recovery will be calculated as:

Time to event (days) = Date of event/censoring/death – date of symptom onset +1

5.3.3.7 Number of Days Requiring Oxygen Therapy

For participants who are discharged with ongoing oxygen therapy, any changes to their oxygen therapy are to be reported in the participant diary they complete daily. This data will be transcribed to the oxygen therapy page of the main CRF.

Each study day will be flagged as with or without oxygen therapy based on the start and stop dates for relevant records in oxygen therapy page. For example, if a record for oxygen therapy is shown as starting on Day 2 and ending on Day 6 then Days 2-6 inclusive will all be flagged as with oxygen therapy.

Number of days with oxygen therapy will be reported for the following intervals:

- Days 1-14
- Days 1-28
- Days 1-42

For each interval, the percentage of days with oxygen therapy will be calculated, using the number of days in the interval prior to death or premature withdrawal as the denominator.

For participants who die or withdraw prematurely from the study, a sensitivity variable will be created which counts study days after death/early withdrawal as 'with oxygen therapy' up to Day 42.

5.3.3.8 Temperature and Number of Days with Pyrexia ≥ 38°C

Temperature will be reported daily for participants prior to discharge. The daily temperature reported on the CRF should be the highest recorded in the participant notes for that day.

After discharge, participants are asked to report their temperature daily while they are still experiencing symptoms if they have a thermometer at home. If they do not have a thermometer at home, they should answer a question on the daily diary to say if they feel like they have a fever.

In the event that a subject reports data in both the patient diary and on the vital signs CRF for a single study day, both measurements will be listed but the temperature collected on the CRF vital signs page will be used in the tables and figures.

Temperature may be recorded in °C or °F. Temperature recorded in °F will be converted to temperature in °C as follows:

Temperature (°C) = (Temperature (°F) – 32)*(5/9)

Temperature (°C) will be presented to 1 dp in the listings.

Each study day will be flagged as with or without pyrexia ≥ 38°C based on the actual data reported.

Number of days with pyrexia ≥ 38°C will be reported for the following intervals:

- Days 1-14
- Days 1-28
- Days 1-42

For each interval, the percentage of days with pyrexia ≥ 38°C reported will be calculated, using the number of days with a temperature measurement recorded as the denominator.
As temperature data is expected to be missing not at random (MNAR), i.e. that the reason for missingness may be dependent on the missing value (were it to have been observed), an alternative method for counting days with pyrexia will be used for sensitivity analyses as detailed below:

- Missing temperature measurements because a participant has died or withdrawn from the study
  - Days after death/withdrawal will be counted as having pyrexia ≥ 38°C

- Missing temperature measurements while participant is still in hospital
  - If there exists at least one temperature measurement within 1 day of the missing measurement, it will be imputed with the average of the measurements reported within the window of +/- 1 day
  - If there is no recorded temperature on the day before or after the missing measurement, then carry forward the response from the last day on which temperature was measured.

- Missing temperature after participant was discharged
  - If the participant has answered the question 'Do you feel like you have a fever?' as 'Yes' then count the day as with pyrexia ≥ 38°C
  - If the participant has answered the question 'Do you feel like you have a fever?' as 'No' then count the day as without pyrexia ≥ 38°C
  - If the participant had stopped completing the daily diary as they had already reported no after 2 consecutive days of no symptoms and a return to their usual activities, then count the day as without pyrexia ≥ 38°C
  - Otherwise carry forward the response from the last day on which either temperature was measured or the daily diary question about fever was answered

5.3.3.9 Cytokines

Any values expressed as <x or >x will be imputed as a value of x for the summary tables and for calculating changes from baseline. The actual value will be displayed in the listings.

5.3.4 Safety

5.3.4.1 Duration of Exposure

The duration of exposure will be calculated as

Duration of exposure (days) = Treatment stop date – treatment start date + 1

5.3.4.2 Treatment-Emergent Adverse Events

An adverse event (AE) will be classified as 'treatment-emergent' if the onset date/time was on or after the start date/time of study treatment. Where dates or times are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates/times, see Section 7.3.2) to suggest that the AE started prior to dosing.

AEs will be classified into the following study phases based on the onset date/time of the AE after any imputations:

- Pre-Treatment Phase: All AEs with onset date/time prior to the first dose of randomized study treatment
- Treatment Phase: All AEs with onset date/time at the time of or after the first dose of randomized study treatment (Day 1) up to and including the date of the last dose of treatment received.
- Follow-up Phase: All AEs with onset date after the date of the last dose of treatment received.

For participants who complete 14 days of dosing per protocol the Treatment Phase will be from Day 1 to Day 14 and the Follow-up Phase will be from Day 15 to Day 42. In all cases the day will be assumed to start at 00:00 hours and end at 23:59 hours. Adverse events occurring in both the Treatment Phase and Follow-up Phase are classified as treatment emergent.

The onset phase of all AEs will be included in the relevant data listings.

5.3.4.3 Hematology Differentials

The database allows the white blood cell differential results (neutrophils, lymphocytes, monocytes, eosinophils and basophils) to be entered on to the CRF as either absolute values or relative values (percentage of white blood cells). If both absolute and relative values are provided in the lab report then the expectation is that the absolute values will be entered, and the relative values marked as 'Not done'.

In order to summarize all differential values together, all relative values will be converted to absolute values as follows:

Absolute value = (Relative value (%) /100) x White Blood Cell Count

The units for the absolute value will be the same as for the white blood cell count (x10^/uL).

6 Sample Size

This is a pilot study designed to give an initial evaluation of the efficacy and safety of EDP1815 in treating Covid-19 and in evaluating multiple endpoints for clinical relevance and sensitivity, while informing the sample size for future studies. A formal power calculation was not performed, and the number of participants was selected based on feasibility.

Based on this sample size, Table 8 below indicates the expected size of a 95% confidence interval for the difference between the treatments based on possible observed sample variation and drop-out rates, both for the initial recruitment of 60 participants and the possible extended recruitment to 100 participants.

Table 8 Estimated Size of Confidence Intervals for the Primary Endpoint

Participants providing at least one post-baseline S/F ratio	SD of Change from Baseline in S/F ratio	95% Confidence Interval Half-width for Treatment Difference
60 (0% drop-out)	50	25.8
	100	51.7
	150	77.5
56 (7% drop out)	50	26.8
	100	53.6
	150	80.4
52 (13% drop out)	50	27.9
	100	55.7
	150	83.6
100 (extended recruitment, 0% drop-out)	50	19.8
	100	39.7
	150	59.5
92 (extended recruitment, 8% drop out)	50	20.7
	100	41.4
	150	62.1
84 (extended recruitment, 16% drop out)	50	21.7
	100	43.4
	150	65.1

Confidence interval calculated based on the assumption that the mean change from baseline in trough S/F ratio follows a t-distribution and the two treatment groups having a common standard deviation.
Example: If all participants provided at least one valid post-baseline S/F measurement (0% drop out), the difference between the treatments was found to be 50 and the common standard deviation was 100 then the 95% confidence interval for treatment difference would be 50 ± 51.7 = (-1.17, 101.7) with 60 participants or 50 ± 39.7 = (10.3, 89.7) with 100 participants.

7 General Considerations

7.1 Analysis Populations

7.1.1 Enrolled Population

All participants who sign the informed consent form (ICF) will be included in the enrolled population.

7.1.2 Intention to Treat (ITT) Population

All participants randomly assigned to a study treatment group will be included in the ITT population.

Participants will be analyzed according to the study treatment group to which they were randomized.

7.1.3 Safety Population

All participants randomly assigned to a study treatment group who take at least one dose of study medication will be included in the Safety population.

Participants will be analyzed according to the intervention they received.
If a participant takes both placebo and EDP1815, due to an error in dosing, they will be assigned to the EDP1815 treatment group for all analyses using the Safety population.

7.2 Covariates and Subgroups

The following covariates will be considered as possible prognostic factors for inclusion in the analysis models described in Section 7.2:

- Age ≥60 years (yes, no)
- Gender (male, female)
- Race (Non-Hispanic/Latino white, non-white or Hispanic/Latino)
- Baseline WHO OSCI score (4, 5)
- Time since onset of symptom at Baseline (days)
- Presence of obesity: BMI ≥30 kg/m^2 (yes, no)
- Current type 1 diabetes (yes, no)
- Current type 2 diabetes (yes, no)
- Current hypertension (yes, no)
- Other current chronic cardiovascular disease (yes, no)
- Current chronic respiratory disease (yes, no)
- Active cancer, excluding skin basal cell carcinoma or localized squamous cell carcinoma (yes, no)
- Smoking status (current smoker, not current smoker)
- Neutrophils > 8.0 $x10^3/uL$
- C-Reactive protein (CRP) > 40 mg/dL

Other covariates may also be considered if emerging research into COVID-19 suggests other possible prognostic factors for outcome that can be determined from the data captured on the CRF.

Prior to database lock, the inferential primary analysis model described in Section 9.2.2 will be examined on the blinded data in order to determine which baseline factors may have a prognostic effect on the efficacy endpoints. Covariates will be selected for inclusion in the model using forward stepwise selection procedure with a 5% level of significance applied for both the selection and deselection of variables from the model.

Where applicable, the baseline value of the endpoint will be automatically fitted first, regardless of significance before additional covariates are considered. A maximum of 3 covariates, in addition to the

baseline value where applicable, may be selected for each model in order to avoid over-parameterization and a reduction in the efficiency of treatment estimates.
If, during the study, a new treatment is approved for use in COVID-19 and becomes part of the standard of care for hospitalized participants at the study site(s), additional sensitivity analyses will be performed using covariates defined by use of this treatment.

- For ANCOVA analyses of trough S/F ratio
  - New SOC covariate: 'yes' if taken at any time before Day 14, 'no' otherwise
- For ANOVA analyses of S/F ratio at Day X
  - New SOC covariate: 'yes' if taken prior to Day X, 'no' otherwise
- For time-to-event analyses
  - New SOC covariate will be fitted as a time-dependent covariate with value 'yes' at time t if taken prior to time t, 'no' otherwise.

Note that the purpose of this sensitivity analysis is to account for any biases to the endpoints caused by a standard of care treatment that was available to later participants but not to those first entered. Any new medication that becomes standard of care and is available for use by all participants before Day 14 will not meet the criteria for performing this sensitivity analysis.

Subgroup analyses based on use of any new SOC medication may also be performed, depending on results seen from the sensitivity analyses using this covariate.

In addition to the covariates mentioned above, other baseline biomarkers will be examined for a prognostic effect on treatment response as part of the exploratory analysis. These will be fitted as continuous variables in the model and include the following:

- CRP (mg/dL)
- Neutrophils (10^3/uL)
- IL-6 (pg/mL)
- Ferritin (ng/mL)
- D-dimer (ng/mL)
- Neutrophil/Lymphocyte ratio (fraction of 1)
- Lactate Dehydrogenase (LDH) (IU/L)
- Troponin I (ng/mL)

7.3 Missing Data

7.3.1 General

Participants who discontinue treatment before the end of the scheduled 14 days treatment period will remain in the study and complete assessments as scheduled unless they die, start an alternate experimental treatment, or withdraw consent. Data collected at scheduled visits following discontinuation of study treatment will be included in all analyses.

Participants who are discharged from hospital before the end of the 42-day study period will be asked to complete a participant diary everyday with details of their symptoms, any AEs experienced and any changes to their concomitant medications.

Imputation rules for individual variables with missing data have been provided in Section 5.3.

7.3.2 Partial Dates/Times

Partial dates and times for AEs, medical conditions and concomitant medications will be imputed for the purpose of assigning study phases and calculating duration. Listings will always include the reported date/time information rather than any imputations.

Partial AE onset and concomitant medication start dates will be imputed as follows:

- If only the month and year are specified, and the month and year of the start of treatment are not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified, and the month and year of the start of treatment are the same as the month and year of the start date, then use the date of start of treatment. If this results in a start date after a known or partial end date, then use the 1st of the month.
- If only the year is specified, and the year of the start of treatment is not the same as the year of the start date, then use January 1 of the year of the start date.
- If only the year is specified, and the year of the start of treatment is the same as the year of the start date, then use the date of the start of treatment. If this results in a start date after a known or partial end date, then use January 1 of the year of the start date.
- If the start date is completely unknown, then use the date of the start of treatment. If this results in a start date after a known or partial end date, do not impute the start date.

Partial AE onset and concomitant medication start times will be imputed as follows:

- If the actual or imputed start date is the same as the treatment start date, and the start time is completely missing, then use the time of start of treatment.
- If the actual or imputed start date is not the same as the treatment start date, and the start time is completely missing, then use 00:00 h.
- If the actual or imputed start date is the same as the treatment start date, and the start time is partially missing then use the following:
    - If the hour is missing (XX:mm) then use the complete time of the start of treatment (i.e., both hours and minutes)
    - If the minutes are missing (hh:XX), use hh:59 h.
- If the actual or imputed start date is not the same as the treatment start date, and the start time is partially missing then use the following:
    - If the hour is missing (XX:mm) then use the 00:mm h
    - If the minutes are missing (hh:XX), use hh:00 h

Partial medical conditions start dates will be imputed as follows:

- If only the month and year are specified, then use the 1st day of the month.

- If only the year is specified, then use January 1st of that year.
- If the start date is completely unknown, do not impute the stop date.

Partial AE resolution, medical condition stop dates and concomitant medication stop dates and date last smoked will be imputed as follows:

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date.

Partial AE resolution and concomitant medication stop times will be imputed as follows:

- If the actual or imputed stop date is non-missing, and the stop time is completely missing, then use 23:59h on that date.
- If the actual or imputed stop date is non-missing, and the stop time is partially missing, then use 23:mm h for missing hours and hh:59 h for missing minutes.
- If the actual or imputed stop date is missing, do not impute the stop time.

7.3.3 Adverse Event Information

AEs with missing severity will be considered as 'Severe' for summary purposes but recorded as missing in the listings.

AEs with missing relationship will be considered 'Related' for summary purposes but recorded as missing in the listings.

7.4 Interim Analyses and Data Monitoring

An independent data monitoring committee (DMC), consisting of at least a chairperson, two physicians independent of the study team and an unblinded statistician will monitor the safety for the study in an ongoing fashion. DMC support staff for blinded sessions will include the Principal Investigator, the Evelo medical monitor, a blinded statistician, the Evelo Chief Medical Officer and an Evelo clinical operations representative.

7.4.1 Purpose of Interim Analyses

The purpose of the planned interim analyses will be to:

- Allow for the ongoing safety monitoring of the study.
- Provide information for the DMC recommendation on whether recruitment can be open to participants aged >65.
- Provide information for the DMC recommendation on whether recruitment should be increased to a further 40 participants.

7.4.2 Planned Schedule of Interim Analyses

Interim analyses are planned after 10, 20, 30, 40 and 60 participants have completed 7 days follow-up after their last dose (Day 21 for participants who complete dosing as scheduled).

At all interim analyses, the DMC will review safety and study disposition data to assess the safety of the interventions and to monitor the overall conduct of the study. Safety review will focus on the number and details of severe and serious adverse events, gastrointestinal (GI) events of any grade and laboratory data which meets the criteria for potentially clinically important (PCI).

At the second interim, after 20 participants have completed 7 days of follow-up after their last dose, the DMC will also specifically address the question of recruitment can be opened to participants aged >65 years.

At the final interim, after 60 participants have completed 7 days of follow-up after their last dose, the DMC will also review the efficacy data in order to make a recommendation on whether recruitment should be extended to a further 40 participants.

7.4.3 Scope of Adaptations

At all DMC meetings, the iDMC can recommend one of the following options for the study:

- The study may continue
- The study may continue with modifications (to be provided in the minutes)
- Temporary suspension of the study
- Termination of the study

Their recommendation will be based on a review of relevant unblinded safety data and where appropriate unblinded efficacy data for them to review the risk/benefit profile of EDP1815 in comparison with placebo.

At the second DMC (20 participants at Day 21) meeting, the DMC members will be asked to make additional recommendations, based on safety data, on whether the eligibility criteria should be extended to allow adults aged >65 years to enter the study.

At the final DMC (60 participants at Day 21) meeting, the DMC members will be asked to make a recommendation as to whether an additional 40 participants should be recruited into the study. There are no precise or pre-defined rules for this recommendation and DMC members will be asked to use their clinical expertise and experience. The option to extend to 100 participants should be strongly considered where there appears to be an emerging clinically meaningful treatment difference, but where the size of variation means that no significant conclusions can be drawn on efficacy. If there is clear efficacy shown, no evidence of efficacy shown or a concern regarding safety then no further recruitment should be recommended. Guidance on this decision, including some hypothetical scenarios provided for illustrative guidance to the DMC are provided in the DMC Charter.

7.4.4 Stopping Rules

The study stopping criteria, in Section 6.6.1 of the protocol, specify that the study should be terminated if either of the following conditions are met:

- One (or more) participants on treatment with EDP1815 has symptoms of a clinically significant bacteremia and has a positive blood culture for the EDP1815 strain of *P. histicola*.
- The iDMC believes that EDP1815 is potentially detrimental to participant outcomes.

In addition, the DMC may recommend stopping the study for the following reasons:

- The data show a distinct increased risk of serious adverse effects in the active treatment group.
- It becomes clear that successful completion of the study is not feasible (e.g. there is an excess of participant dropout, missing data, lack of recruitment, etc.)
- Other important safety finding(s) as identified by the Sponsor or iDMC.
- The risk/benefit profile for the product is deemed to have changed and is considered unacceptable for the study to continue.

7.4.5 Practical Measures to Minimize Bias

The unblinded interim summaries and analyses will be performed by an unblinded team led by the unblinded statistician who sits on the iDMC as a non-voting member. The members of the unblinded team will not be involved in any aspects of study trial conduct, including the development of the final summaries and analyses for the study.

No unblinded data, either as individual participant results or as aggregated summaries will be shared by with any study personnel involved in the conduct or final reporting of the study.

Interim results of the analysis, beyond the recommendations to continue, modify, suspend or stop the study, will not be shared with the sponsor prior to the end of the study in order to avoid any bias or potential alpha-spending issues as per the FDA guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics.

The expected summaries and listings which will be provided to the iDMC, both in blinded and unblinded form will be a subset of those expected for the final analysis and will be flagged as such in the list of tables, figures and listings in Appendix 1: List of Tables, Figures and Listings.

7.4.6 Documentation of Interim Analyses

All unblinded data and summaries together with minutes from the closed sessions will be held in a restricted file structure by the unblinded statistician until after the study has finished and the data has been unblinded after database lock.

A DMC charter is available to provide further details of the required documentation, content and structure of the iDMC meetings.

7.5 Multiple Testing

No adjustments for alpha spending will be performed.

8 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, SD, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

In general, all data will be listed, sorted by randomized treatment (Placebo, EDP1815) and participant number. If additional sites are added, then data will be sorted by participant number within site. Relevant listings will include whether the assessment was performed and the date, study day/visit and time of the assessment as applicable.

Unless otherwise specified below, all summary tables will be structured with a column for each treatment (placebo, EDP1815) and, for data collected prior to dosing, will include an overall total column where appropriate.

Columns will be ordered and labelled as follows:

- Placebo
- EDP1815
- Total

Except for disposition tables in which it is appropriate to include screened subjects, the enrolled population will be used, otherwise the ITT population will be used for all summaries of disposition, demographic and baseline data and efficacy.

The safety population will be used for all summaries of safety.

Unless otherwise specified, all listings will be produced using the ITT population.

8.1 Subject Disposition

All subject disposition summaries will be presented by treatment group and overall. The ITT population will be used unless otherwise specified.

Completion/withdrawal from the study and completion/discontinuation from treatment, together with reasons for withdrawal from the study or discontinuation from treatment will be listed and the following will also be tabulated

- Number and percentage of participants who completed the study
- Number and percentage of participants withdrawn from the study and the reported reason for withdrawal

- For the interim analyses, the number and percentage of participants still ongoing in the study will also be presented
- Number and percentage of participants who completed the 14-day treatment period
- Number and percentage of participants who discontinued treatment early and reason for discontinuation
- For the interim analyses, the number and percentage of participants who have treatment ongoing will also be presented

For subjects who fail screening, the reasons for screen failure including details on which inclusion/ exclusion criteria were not met will be summarized and listed.

For the enrolled population, the number and percentage of participants in each analysis population will be presented. Inclusion/exclusion in each study population will also be listed, together with reasons for exclusion.

The number and percentage of participants with data available for each study day, broken down by inpatient or outpatient status will be summarized.

8.2 Protocol Deviations

The number and percentage of participants in the ITT population with at least one major protocol deviation will be summarized by treatment group and overall, together with the number and percentage of participants reporting at least one major protocol deviation within each category.
All protocol deviations will also be listed.

8.3 Demographic and Baseline Variables

All summaries of demographic and baseline variables will be presented by treatment group and overall using the ITT population.

The following summaries will be produced, using appropriate summary statistics as specified in Section 8:

- Demographic variables: age, sex, race, ethnicity, height weight and BMI
- Smoking status (never, former, current), type of smoking product used, years since last smoked and pack-years.
- Baseline disease characteristics: time since start of symptoms, time since first positive RTPCR test, SpO2, S/F ratio, WHO OSCI score and temperature

8.4 Concurrent Illnesses and Medical Conditions

All summaries of concurrent illnesses and medical conditions will be presented by treatment group and overall using the ITT population.

Concurrent illnesses and medical conditions will be classified as 'current' if the end date is on or after the date of first dose of study drug, or the condition has been marked as ongoing. Otherwise they will be classified as 'past'.

Targeted questions will be used to report the following known comorbidities for COVID-19 as part of the medical history CRF page:

- Type 1 diabetes
- Type 2 diabetes
- Hypertension
- Other chronic cardiovascular disease
- Chronic respiratory disease
- Ongoing diagnosis of cancer

In addition, other medical history and concurrent illnesses will be captured and coded using the v23.0 of the Medical Dictionary for Regulatory Activities (MedDRA®).

The number and percentage of participants reporting each relevant medical condition will be summarized together with the following potential risk factors for severe illness with COVID-19 which will be assessed from the demographic and baseline data:

- Age ≥60 years
- Male
- Non-white or Hispanic/Latino
- Obesity (BMI ≥30 kg/m^2)
- Current smoker
- Baseline WHO OSCI score of 5
- Baseline neutrophils > 8.0 x10^3/uL
- Baseline CRP >40 mg/dL

In addition, the number and percentage of participants reporting 0, 1, 2, 3, 4, ≥5 potential risk factors will be summarized.

All medical history will be summarized, individually for past and current conditions. All medical history will be listed.

8.5 Prior and Concomitant Therapy

Medications will be coded according to the World Health Organization Drug Dictionary (WHODD) Version dated 01Mar2020. Medical procedures will not be coded.

Oxygen therapy will be collected on a separate CRF page and will be considered part of the efficacy data with the reporting described in Section 9.3.6.

Concomitant medications are defined as any medications taken during the treatment period or follow-up period after treatment. This includes any medications started before the first dose and ongoing after the first dose. Prior medications are defined as any medication taken before or during the screening period which were stopped before the first dose of study medication.

Missing and partial start and stop dates will be imputed using the rules specified in Section 7.3.2 before classifying therapies as prior or concomitant. If the classification is still ambiguous after missing and partial dates have been imputed, then the medication will be considered concomitant.

Medications will be summarized using the ITT population, by treatment group and overall and the WHODD Anatomical Main Group (Level 1), Therapeutic Subgroup (Level 2) and preferred term. The summaries will report incidence within each relevant level so that a participant taking multiple medications coded to the same relevant Level 1, Level 2 or preferred term would only be counted once within the incidence count for that level or term.

Concomitant medications taken for COVID-19 will be defined using the indication field on the CRF.

Separate summaries will be produced for each of the following:

- Prior medications
- Concomitant medications taken for COVID-19
- Concomitant medications taken for COVID-19 started pre-treatment
- Concomitant medications taken for COVID-19 during the treatment period (including any which started pre-treatment)
- Concomitant medications taken for COVID-19 started during the follow-up period
- Concomitant medications not taken for COVID-19
- Concomitant medications not taken for COVID-19 started pre-treatment
- Concomitant medications not taken for COVID-19 during the treatment period (including any which started pre-treatment)
- Concomitant medications not taken for COVID-19 started during the follow-up period

All prior and concomitant medications will be listed. Concomitant medical procedures carried out during the study will be listed separately.

8.6 Compliance

Treatment compliance will be summarized for the safety population and daily diary compliance will be summarized for the ITT population, by treatment group and overall.

Treatment and daily diary compliance data will also be listed.

9 Efficacy Analyses

Unless otherwise specified, all efficacy summaries and analyses will be presented by treatment group and overall. The ITT population will be used for all summaries and analyses of efficacy.

In addition to the inferential analyses described below, descriptive statistics will be provided to summarize all efficacy endpoints by treatment group.

For categorical variables, summary tabulations of frequency and percentage of participants within each category will be presented.

For continuous variables, the number of participants, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

For time to event endpoints, the number of participants with the event, the number of participants censored will be presented together with Kaplan-Meier estimates of median time to event and the predicted proportion of subjects with the event at Days 4, 7, 14, 21 and 42 as appropriate to the endpoint. Kaplan-Meier curves of time to event will also be presented.

All analyses will be considered as descriptive only and no adjustment for multiple testing will be performed.

9.1.1.1 Early Stopping

In the case of stopping the study early due to low recruitment, no inferential efficacy analysis will be carried out. Figures will not be presented. Only summaries and listings of the study population, primary and secondary efficacy endpoints, and safety data will be produced.

The list of outputs produced in case of early stopping of the study is provided in Appendix 1: List of Tables, Figures and Listings.

9.1.1.2 Blinded Model Fitting

Prior to database lock the models to be used in the primary analysis will be examined on the blinded data in order to determine which baseline factors may have a prognostic effect and should be included in the models. The covariates defined in Section 7.2 will be examined in a model of trough S/F ratio and selected as covariates for the relevant model at a 5% level of significance using forward stepwise selection.

Baseline S/F ratio will be the first fitted term in the model regardless of significance. A maximum of 3 further covariates may be included in the model in order to avoid over-parameterization and a reduction in the efficiency of the treatment estimates.

Distributional assumptions underlying the models used for analysis will be also be examined during the blinded review by obtaining a normal probability plot of the residuals and a plot of the residuals versus the

fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If the distributional assumptions underlying the model are found not to be reasonable, a log-transformation of the response variable will first be considered. In this event, the LS mean treatment ratio will be presented instead of the LS mean treatment difference. If this model is also found to violate the distributional assumptions, then further models including other transformations or nonparametric alternatives will be explored. An addendum to the SAP will be produced prior to database lock and unblinding detailing the methods to be used will be produced detailing the model strategy to be used in this event.
This approach to the inclusion of baseline covariates which may have a prognostic effect on response will also be used for the Cox proportional hazards and Fine and Gray models to be used for the secondary analyses.

9.2 Primary Efficacy Analysis

9.2.1 Primary Efficacy Estimand

The primary estimand will be the effect of EDP1815 compared to placebo on the change from baseline to trough S/F ratio in Days 1-14.

The population summary measure of interest will be the difference in mean change from baseline in trough S/F between EDP1815 and placebo.

Intercurrent events will be accounted for in the following manner:

Table 9 Intercurrent Event Strategies for the Primary Estimand

Intercurrent event	Strategy to account for intercurrent event
Treatment discontinuation before the end of the 14-day treatment period	Treatment policy Trough S/F ratio will be taken as the lowest recorded value on or off treatment
Death prior to day 14	Composite Trough S/F ratio will be imputed as 0
Discharge prior to day 14	While-on-treatment Trough S/F ratio prior to discharge will be used. Participants will be assumed to remain above trough value after discharge.
Withdrawal from the study prior to day 14.	While-on-treatment Trough S/F ratio prior to starting study withdrawal will be used

9.2.2 Main Analytical Approach

Trough S/F ratio and change from baseline in trough S/F ratio will be summarized and listed.

Change from baseline in trough S/F ratio will be analyzed with an analysis of covariance (ANCOVA) model. The model will include fixed effect parameters for treatment and baseline S/F ratio together with the additional baseline covariates which were identified during the blinded review.

Least square (LS) estimates of the mean change from baseline trough S/F ratio together with the standard error and 95% confidence interval will be reported. The LS mean treatment difference and 95% confidence interval will also be presented.

The distributional assumptions for the final unblinded model will be checked in the same manner as described above in Section 9.1.1.2. If the inclusion of treatment effect causes the models to no longer be valid compared to the blinded data models, a Wilcoxon test will be used to compare the treatments instead and only a p-value will be produced for the comparison.

9.2.3 Sensitivity Analyses

A sensitivity analysis will be performed where no imputation of trough S/F ratio will be made for participants who die. Instead the lowest reading recorded prior to death will be used.

If a newly approved medication for COVID-19 becomes part of the standard of care treatment at the investigational site during the study an additional sensitivity analysis will be performed. A new medication covariate (yes, no for use before Day 14) will be fitted into the ANOCOVA model used for the main analytical approach together with its interaction with the EDP1815 treatment term.

In addition to the estimates of LS means for effect of each treatment group and their difference, the p-values for the significance of the new medication*treatment interaction will be provided.

9.2.4 Subgroup Analyses

If the sensitivity analysis for a newly approved COVID-19 medication described in Section 9.2.3 is performed and the p-value for the new medication*treatment interaction is found to be significant at the 5% level, the analysis described for the main analytical approach will be performed by use of the new medication prior to Day 14.

9.3 Secondary Efficacy Analyses

9.3.1 Change from Baseline in S/F Ratio

9.3.1.1 Estimands

The endpoints will be the change from baseline in S/F ratio as measured on Days 4, 7, 10 and 14. The population summary measure of interest will be the difference in mean change from baseline in S/F ratio between EDP1815 and placebo at the relevant study day.

The intercurrent event strategy for these estimands is described in Table 10.

Table 10 Intercurrent Event Strategies for the Change from Baseline in S/F Ratio Secondary Estimands

Intercurrent event	Strategy to account for intercurrent event
Death prior to the study day of interest	Composite S/F ratio will be imputed as 0
Discharge prior to the study day of interest	Composite Last S/F ratio prior to discharge will be used. Participants will be assumed to remain above this value after discharge.
Treatment discontinuation before the study day of interest without withdrawal from the study	Treatment policy The actual S/F ratio reported at the timepoint will be used regardless of treatment discontinuation
Withdrawal from the study prior to the study day of interest.	While-on-treatment Participants will be excluded from the analysis at that study day

Data missing for reasons other than an intercurrent event will be imputed as defined in Table 5.

9.3.1.2 Analytical Approach

Actual values and change from baseline in S/F ratio will be summarized at Days 4, 7, 10, and 14 and all daily S/F ratio data will be listed. This summary will be produced once showing only available data with no imputation and once after the rules specified in Table 5 have been applied.

Mean (+/- standard error (SE)) S/F ratio and change from baseline in S/F ratio will be plotted by study day for Days 1-14, once using only available data with no imputation and once after the rules specified in Table 5 have been applied.

As missing data due to the intercurrent events of death, discharge and initiation of another experimental treatment cannot be considered missing at random, a mixed model for repeated measures is not considered an appropriate analysis for this data. As such, the endpoint at each study day will be analyzed using separately using ANCOVA models.

Two models will be fitted at each study day, one with S/F ratio as the response variable and one with change from baseline in S/F ratio as the response variable. The models will include treatment and baseline S/F ratio together with the additional baseline covariates included in the primary analysis model for trough S/F ratio.

LS mean and LS mean change from baseline in S/F ratio will be reported with their corresponding standard error and 95% confidence interval. Estimated treatment difference for the mean change from baseline and corresponding 95% confidence interval will also be reported.

LS mean (95% CI) change from baseline in S/F ratio will be plotted against time for Days 4, 7, 10 and 14.

The distributional assumptions for the final unblinded model will be checked in the same manner as described above in Section 9.1.1.2.

A sensitivity analysis will be performed where no imputation will be used for participants who die. These participants will be excluded from the analysis at any timepoints after death has occurred.

If at least 10% of participants have withdrawn from the study before Day 14, a sensitivity analysis will be performed. Data for participants who have either been discharged or died will be imputed as per the rules in Table 5, but no other imputation will be performed. The change from baseline in S/F ratio will be analyzed in a mixed model for repeated measurements including treatment, baseline S/F ratio, study day, study day*treatment and study day*baseline S/F ratio and any additional covariates identified during the blinded modelling phase. Data from all study days between Day 1 and Day 14 would be included.

LS mean change from baseline in S/F ratio will be reported with their corresponding standard error and 95% confidence interval at Days 4, 7, 10 and 14. Estimated treatment difference for the mean change from baseline and corresponding 95% confidence interval will also be reported at these study days.

If a newly approved medication for COVID-19 becomes part of the standard of care treatment at the investigational site during the course of the study an additional sensitivity analysis will be performed at each visit in the same manner as described in Section 9.2.3. A new medication covariate (yes, no for use before the relevant study day) will be fitted into the ANOCOVA models at each visit together with its interaction with the EDP1815 treatment term.

In addition to the estimates of LS means for effect of each treatment group and their difference, the p-values for the significance of the new medication*treatment interaction will be provided at each visit. Mean (+/- standard deviation) S/F ratio at each study day will also be plotted once using only available data and once after the rules specified in Table 5 have been applied.

9.3.2 Percentage Change from Baseline in S/F Ratio

Percentage change from baseline in S/F ratio at Days 4, 7, 10 and 14 will be summarized and analyzed in the same manner as described for mean change from baseline in S/F ratio in Section 9.3.1.

9.3.3 WHO OSCI Score

9.3.3.1 Estimands

The endpoints will be recorded (inpatients) or derived (outpatients) WHO OSCI score at Days 4, 7, 14, 21 and 42. Population summary methods will be:

- Percentage of participants at each level of the WHO OSI score
- Percentage of participants with each possible shift from Baseline in WHO OSCI score
- Percentage of participants remaining at their baseline WHO OSCI score (or lower)

- Percentage of participants reporting each level of WHO OSCI score at their worst post-baseline day

The intercurrent event strategy for these estimands is described in Table 11.

Table 11 Intercurrent Event Strategies for the WHO OSCI Score Secondary Estimands

Intercurrent event	Strategy to account for intercurrent event
Death prior to the study day of interest	Composite WHO OSCI score of 8 will be carried forward to all further study days
Discharge prior to the study day of interest	Treatment policy The WHO OSCI score will be derived from the participant daily diary using the rules in Section 5.3.3.4
Treatment discontinuation before the study day of interest and no other experimental treatment not considered standard of care initiated	Treatment policy WHO OSCI score used as recorded for inpatients or derived for outpatients from the participant daily diary using the rules in Section 5.3.3.4
Withdrawal from the study due to initiating other experimental treatment not considered standard of care before the study day of interest	While-on-treatment Participants will be excluded from the analysis at that study day

Data missing for reasons other than an intercurrent event as detailed above will not be imputed.

9.3.3.2 Analytical Approach

WHO OSCI score at Baseline and Days 4, 7, 14, 21 and 42 will be summarized as a categorical variable. A Cochran-Mantel Haenszel (CMH) test for ordinal data will be used to compare the groups with respect to the percentage of participants reporting each category in the scale at each visit. Histograms of WHO OSCI scores at Days 4, 7, 14, 21 and 42 will also be produced.

Shift tables showing the changes from Baseline at each of Days 4, 7, 14, 21 and 42 in WHO OSCI score will also be provided.

The proportion of participants remaining at or below their baseline WHO OSCI score will be reported at Days 4, 7, 10, 14, 21 and 42 together with the corresponding 95% exact confidence interval. These proportions and confidence intervals will also be displayed graphically.

The maximum WHO OSCI score reported by each participant during the study will also be summarized and compared between the treatment groups with a CMH test for ordinal data. Within each maximum score, the number of days spent at that score will also be summarized. A histogram of maximum WHO OSCI score will also be produced.

WHO OSCI scores at all study days will also be listed.

9.3.4 Overall Survival and Intubation and Mechanical Ventilation Free Survival

9.3.4.1 Estimands

The endpoint will be time to event in days as defined in Section 5.3.3.5. The population summary measure of interest will be the hazard ratio for the EDP1815 group compared to the placebo group.

The intercurrent event strategy for these estimands is described in Table 12.

Table 12 Intercurrent Event Strategies for Overall Survival and Intubation and Mechanical Ventilation Free Survival Secondary Estimands

Intercurrent event	Strategy to account for intercurrent event
Discharge prior to Day 42	Treatment policy Participants actual status will be used
Treatment discontinuation before Day 14 without withdrawal from the study	Treatment policy Participants actual status will be used
Withdrawal from the study	While-on-treatment Participants will be censored at the time of withdrawal from the study.

For the interim analysis presented at the DMC meeting when 60 patients have completed 21 days in the study, subjects who are still ongoing and have not met the criteria for the relevant event will be censored at the date of the data cut.

9.3.4.2 Analytical Approach

The number of participants who died and the number of participants censored will be presented together with Kaplan-Meier estimates of median time to death (where calculable) and the predicted proportion of participants who died at Days 4, 7, 14, 21 and 42. Kaplan-Meier curves of overall survival will also be presented.

Overall survival will be analyzed using a Cox proportional hazards (Cox-PH) model. The model will include parameters for treatment together with the additional baseline covariates which were identified during the blinded review of the overall survival model. Participants who are still alive at the end of the 42-day study period or who withdraw prematurely from the study for reasons other than death will be censored on the day of their study completion/withdrawal. The hazard ratio for treatment difference with corresponding 95% confidence interval will be presented.

If during the study, a newly approved medication for COVID-19 becomes part of the standard of care treatment at the investigational site, a further sensitivity analysis will be performed. A time-dependent

covariate for use of the new medication (yes, no) will be included in the model described above together with its interaction with treatment.

Overall survival information will be also be listed including survival status and time to death or censoring.

Intubation and mechanical ventilation free survival will be analyzed in the same manner as overall survival.

9.3.5 Time to Discharge, Time to SpO2 ≥94% on Room Air and Time to Recovery

9.3.5.1 Estimands

The endpoint will be time to event in days as defined in Section 5.3.3.6. The population summary measure of interest will be the hazard ratio for the EDP1815 group compared to the placebo group.

The intercurrent event strategy for these estimands is described in Table 13.

Table 13 Intercurrent Event Strategies for Time to Discharge, Time to SpO2 ≥94% on Room Air and Time to Recovery Secondary Estimands

	Strategy to account for intercurrent event		
Intercurrent event	Time to Discharge	Time to SpO2 ≥94% on Room Air	Time to Recovery
Death prior to the event	Competing Event Death will be considered as a competing event and accounted for as such in the analysis		
Discharge prior to the event with oxygen for home use	N/A	While-on-treatment Participant will be censored on the date of discharge	Treatment policy Actual values will be used regardless of inpatient/outpatient status
Discharged prior to the event without oxygen for home use	N/A	Composite Participant will be considered as having had the event on the date of discharge	Treatment policy Actual values will be used regardless of inpatient/outpatient status
Treatment discontinuation before the study day of interest without withdrawal from the study	Treatment policy Actual values will be used regardless of inpatient/outpatient status		
Withdrawal from the study for any reason	While-on-treatment Participant will be censored on the date of study withdrawal		

For the interim analysis presented at the DMC meeting when 60 patients have completed 21 days in the study, subjects who are still ongoing and have not met the criteria for the relevant event will be censored at the date of the data cut.

9.3.5.2 Analytical Approach

Time to discharge will be analyzed using a Fine and Gray subdistributional hazards model to allow for the competing risk of death (Fine, 1999). The model will include a parameter for treatment together with any additional baseline covariates identified during the blinded review of the time to discharge model.

The number and percentage of participants who are discharged, who die and who are censored will be reported together the estimate of median time to the event, and the predicted proportion of participants who were discharged at Days 4, 7, 14, 21 and 42. The estimated subdistributional hazard ratio (with 95% confidence interval) for treatment difference in risk of recovery and its p-value from the model will also be presented. Cumulative incidence functions for time to full recovery will also be plotted by treatment group.

Time to discharge information will be listed including event status and time to event/censoring or death.

Time to SpO2 ≥94% on room and time to recovery will be analyzed in the same manner as described above for time to discharge.

9.3.6 Other Secondary Endpoints

Number and percentage of days requiring oxygen therapy and the sensitivity variable described in Section 0 will be summarized for days 1-14, 1-28 and 1-42 and listed. Details of all oxygen therapy used will also be listed.

Number and percentage of days with pyrexia ≥ 38°C and the sensitivity variable described in Section 5.3.3.8 will be summarized for days 1-14, 1-28 and 1-42 and listed. Maximum temperature for each participant will also be summarized. Daily temperature data will also be listed.

Minimum and maximum SpO2 for each participant will be summarized and listed. Daily SpO2 values will be included in the listing of daily S/F ratio data.

9.4 Exploratory Efficacy Analyses

9.4.1 Biomarkers

Table 16 shows the parameters which will be collected and the units in which they will be supplied.

Actual values and change from baseline in cytokine levels will be summarized at Days 4 and 7. All cytokine level data will also be listed.

Actual values and change from baseline in inflammatory response markers will be summarized at Days 4 and 7. All inflammatory response marker data will also be listed.

9.4.2 Potential Predictors of Response to EDP1815

To identify clinical and biochemical predictors of response to EDP1815 exploratory modelling will be performed to identify potential interactions between treatment and each covariate defined in Section 7.2. The model fitted for the primary analysis of change from baseline in trough S/F ratio will be considered as the base model for this. For each potential predictor, the covariate (if not already fitted) and the treatment-covariate interaction will be added to the base model and the p-value for the treatment-covariate interaction will be reported. Each potential predictor will be considered in a separate model independently of other potential predictors.

In the event that a predictor is found to have a significant treatment interaction with EDP1815 on the primary endpoint, further exploratory analyses will be performed to find the extent and direction of the interaction as well as looking at the effect on other secondary endpoints. Any such analyses will be considered as adhoc and will not be further described here.

10 Safety Analyses

10.1 Extent of Exposure

The duration of exposure (days) and number of doses taken will be summarized by treatment for the Safety population using summary statistics for continuous data as well as the number and percentage of participants with:

- ≥ 7 days exposure
- 14 days exposure (completed treatment)

Treatment start and stop dates, exposure duration (days) and number of doses administered will be listed by participant.

10.2 Adverse Events

Due to the nature of the participant participation and disease, only serious AEs (SAEs), AEs of severe (Common Terminology Criteria for Adverse Events (CTCAE) Grade 3) and potentially life-threatening (CTCAE Grade 4) intensity, and AEs relating to nausea, vomiting, diarrhea, bloating and abdominal pain of any grade will be documented in the CRF. Other AEs of mild (CTCAE Grade 1) or moderate (CTCAE Grade 2) intensity are to be documented in the medical notes.

Only treatment emergent AEs and SAEs reported in the CRF will be included in the summaries, pre-treatment AEs and SAEs reported in the CRF will be included in the listings of all AEs.

All AEs will be coded using version 23.0 of MedDRA.

Treatment-emergent AEs will be summarized by treatment, system organ class (SOC) and preferred term. Summary tables will contain the number and percentage of participants and the number of events. A participant who has multiple events in the same SOC or the same preferred term will be counted only once in the participant counts but all events will be counted in the event counts. Adverse event

summaries will be sorted by the internationally agreed SOC order (Table 15) and decreasing incidence of preferred term within SOC in the EDP1815 column.

The above summary will be repeated for Treatment Phase AEs and for Follow-up Phase AEs.

AEs considered related to study treatment will also be summarized by treatment, SOC and preferred term in the same manner as described above.

All AEs, SAEs, fatal AEs, AEs leading to discontinuation of study treatment or withdrawal from the study will be listed separately by participant. Adverse events of special interest will be flagged in the listings.

10.3 Deaths, Serious Adverse Events and other Significant Adverse Events

Treatment emergent SAEs, TEAEs leading to discontinuation of study treatment or withdrawal from the study will be summarized separately by treatment, SOC and preferred term.

10.3.1 Adverse Events of Special Interest

TEAEs of nausea, vomiting, diarrhea, bloating and abdominal pain will be considered as adverse events of special interest (AESI).

AESI will be summarized by treatment, preferred term, and CTCAE grade. The summary will contain the number and percentage of participants and the number of events.

AESI will also be summarized by treatment, preferred term and relationship to study drug in the same manner.

10.4 Clinical Laboratory Evaluations

Local laboratory data will be used for all safety laboratory evaluations. Blood samples for safety laboratory evaluations will be collected at Baseline, Day 4 and Day 7. Table 17 shows the parameters which will be collected and the units in which they will be supplied.
Laboratory data (hematology and chemistry parameters) will be summarized by treatment and visit. Changes from baseline at Day 4 and Day 7 will also be summarized.

Relative differentials (neutrophils, lymphocytes, monocytes, eosinophils and basophils) will be converted to absolute values as described in Section 5.3.4.3.

The number and percentage of participants showing shifts from baseline to worst-case post-baseline with respect to the normal ranges will also be summarized for each parameter. Categories will be:

- Low
- Normal
- High

The determination of worst-case post-baseline will consider both scheduled (Day 4 and Day 7) and any unscheduled assessments which occur after the first dose of study treatment. Percentages will use the number of participants with at least one post-baseline assessment available. If the baseline value is missing it will be assumed to be normal for this summary. Worst-case can be either High or Low and if a participant has post-Baseline values both above and below the normal range then they will be counted in both relevant categories.

Safety laboratory values are also flagged for potentially clinically important (PCI) values if they meet any of the criteria for Grade 2 or higher events according to CTCAE V5.0 with the exception of lymphocytes where the lower limit for grade 3 is used as COVID-19 cases lymphopenia in most patients. The PCI criteria are listed in Table 17. The number and percentage of participants showing shifts from baseline to worst-case post-baseline with respect to PCI criteria will be summarized for all parameters where PCI criteria have been defined. Categories will be:

- Low
- Within range
- High

The determination of worst-case post-baseline will consider both scheduled (Day 4 and Day 7) and any unscheduled assessments which occur after the first dose of study treatment. Percentages will use the number of participants with at least one post-baseline assessment available. If the baseline value is missing it will be assumed to be within range for this summary. Worst-case can be either High or Low and if a participant has post-Baseline values both above and below the PCI criteria then they will be counted in both relevant categories.

Safety laboratory data will be listed by participant, including changes from baseline, normal ranges and flags for measurements outside the normal range and flags for meeting PCI criteria. In addition, for participants who meet at least one PCI criteria, all values within the laboratory type (hematology or clinical chemistry) will be listed separately.

10.5 Other Safety Measures

10.5.1 Vital Signs

Vitals signs (blood pressure, pulse rate and respiration rate) will be summarized by study day for Days 1-14, including change from baseline.

In addition, vital signs data will be flagged as potentially clinically important (PCI) if they meet the CTCAE (v5.0) criteria for a Grade 3 or above event as shown in
Table 14.

Table 14 PCI Criteria for Vital Signs

Parameter	Units	PCI Criteria
Systolic Blood Pressure	mmHg	≥ 160
Diastolic Blood Pressure	mmHg	≥ 100

The number and percentage of participants showing shifts from baseline to worst-case post-baseline with respect to the PCI criteria will also be summarized for each parameter. Categories will be:

- Within range
- High

The determination of worst-case post-baseline will consider both scheduled (Day 4 and Day 7) and any unscheduled assessments which occur after the first dose of study treatment. Percentages will use the number of participants with at least one post-baseline assessment available. If the baseline value is missing it will be assumed to be within range for this summary.

All vital signs data will be listed, including flags for values which meet the PCI criteria. In addition, a separate listing of all vital signs assessments for any participant who meet has at least one value meeting the PCI criteria will be produced.

10.5.2 Physical Examination

All data collected at the physical examination performed at the Screening visit will be listed.

10.5.3 Pregnancy Tests

Pregnancy test results will be listed together with female fertility status.

11 Pharmacokinetics

Analyses of the pharmacokinetics exploratory endpoints including the presence of EDP1815 in stool and/or blood using PCR primers will be addressed in a separate analysis plan and will not be further discussed in this document.

12 Reporting Conventions

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfil certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is 0, there will be no percentage presented at all
- All other percentage displays will use 1 decimal place

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean and median will use 1 decimal place more than the original data
- Standard deviation will use 2 decimal places more than then original data
- Minimum and maximum will be reported using the same number of decimal places as the original value

- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. However, if n<3, present the n, min and maximum only. If n=3, n, mean, median, minimum and maximum will be presented only. The other descriptive statistics will be left blank

Where reporting estimated statistics from inferential tests and models, the following rules will apply in general:

- P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001".
- Estimated parameters and 95% confidence intervals on the same scale as raw observations will be reported to 1 decimal place more than the original data, standard errors will be reported to decimal places more
- Estimated parameters and 95% confidence intervals of percentage change variables will be reported to 2 decimal places, standard errors will be reported to 3 decimal places
- Estimated parameters and 95% confidence intervals, not on the same scale as raw observations or for percentage change statistics (e.g. regression coefficients) will be reported to 3 significant figures, standard errors will be reported to one further decimal place.

13 Technical Details

Statistical evaluation will be performed by [redacted].

CDISC standards will not be used for this study. The analysis datasets will be produced using a similar structure to those described for the analysis dataset model (ADaM) but will be not be fully validated and will be programmed directly from the source CRF and external data rather than from SDTM datasets.

All analyses will be performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA).

14 Summary of Changes to the Protocol

Not applicable.

15 References

Fine, J. a. (1999). A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of American Statistics Association, 94*(446), 496-509.

16 Appendix 1: List of Tables, Figures and Listings

All outputs detailed in the following sections will be produced for the final analysis. Programming notes also indicate where tables will be produced for interims using the following abbreviations:
DMC-Blinded – produced as a blinded output with only the overall column shown - all DMC meetings
DMC-Unblinded – produced as an unblinded output – all DMC meetings
DMC-Safety – produced as an unblinded output – all DMC meetings after participants aged >65 years have been approved for inclusion
DMC-Efficacy – produced as an unblinded output – DMC meeting after 60 participants have completed 21 days treatment only

Note that some outputs will only be produced if the criterion specified in the programming notes is met.
Highlighted XXXXX text indicates that the full title is dependent on currently unknown factors (e.g. name of medications which becomes SOC during the study).

If the study is stopped early, outputs will be produced as specified in Early Stop column.

16.1 Study Population

16.1.1 Tables

Number	Title	Population	Early Stop	Programming notes[1]
14.1.1.1	Summary of Disposition	ITT	Yes	DMC-Blinded, DMC-Unblinded
14.1.1.2	Summary of Screening Status	Enrolled	Yes	DMC-Blinded
14.1.1.3	Summary of Participants by Site	ITT	Yes	
14.1.1.4	Summary of Data Availability at Each Study Day by Inpatient/Outpatient Status	ITT	Yes	
14.1.1.5	Summary of Important Protocol Deviations	ITT	Yes	
14.1.1.6	Summary of Populations	Enrolled	Yes	
14.1.2.1	Summary of Demographic Details	ITT	Yes	DMC-Unblinded
14.1.2.2	Summary of Smoking Status	ITT	Yes	
14.1.2.3	Summary of Baseline Disease Characteristics	ITT	Yes	

Number	Title	Population	Early Stop	Programming notes[1]
14.1.3.1	Summary of Potential Risk Factors for Severe Illness with COVID-19	ITT	Yes	DMC-Unblinded
14.1.3.2	Summary of Past Medical History	ITT	Yes	
14.1.3.3	Summary of Current Medical History	ITT	Yes	
14.1.4.1	Summary of Prior Medications	ITT	Yes	
14.1.4.2	Summary of All Concomitant Medications for COVID-19	ITT	Yes	DMC-Unblinded
14.1.4.3	Summary of Concomitant Medications for COVID-19 Started Pre-treatment	ITT	Yes	
14.1.4.4	Summary of Concomitant Medications for COVID-19 Started During the Treatment Phase	ITT	Yes	
14.1.4.5	Summary of Concomitant Medications for COVID-19 Started During the Follow-Up Phase	ITT	Yes	
14.1.4.6	Summary of All Concomitant Medications not for COVID-19	ITT	Yes	
14.1.4.7	Summary of Concomitant Medications not for COVID-19 Started Pre-treatment	ITT	Yes	
14.1.4.8	Summary of Concomitant Medications not for COVID-19 Started During the Treatment Phase	ITT	Yes	
14.1.4.9	Summary of Concomitant Medications not for COVID-19 Started During the Follow-Up Phase	ITT	Yes	
14.1.5.1	Summary of Treatment Compliance	Safety	Yes	DMC-Blinded, DMC-Unblinded
14.1.5.2	Summary of Daily Diary Compliance After Discharge	ITT	Yes	
14.1.6	Summary of Exposure to Study Medication	Safety	Yes	DMC-Unblinded

16.2 Efficacy

16.2.1 Tables

Number	Title	Population	Early Stop	Programming notes[1]
14.2.1.1	Summary of Change from Baseline in Trough S/F Ratio in Days 1-14	ITT	Yes	DMC-Efficacy
14.2.1.2.1	Analysis of Change from Baseline in Trough S/F ratio in Days 1-14	ITT		DMC-Efficacy

Number	Title	Population	Early Stop	Programming notes[1]
14.2.1.2.2	Analysis of Change from Baseline in Trough S/F ratio in Days 1-14, Sensitivity Analysis with No Imputation of Trough S/F Ratio for Participants Who Die	ITT		DMC-Efficacy
14.2.1.2.3	Analysis of Change from Baseline in Trough S/F Ratio in Days 1-14, Sensitivity Analysis Accounting for Use of New SOC Before Day 14	ITT		DMC - Efficacy Only produced if a on new SOC is introduced during the study
14.2.1.2.4	Analysis of Change from Baseline in Trough S/F Ratio in Days 1-14, by Use of Use of New SOC Before Day 14	ITT		DMC-Efficacy Only produced if a new SOC is introduced during the study and shows significant interaction with EDP1815
14.2.2.1.1	Summary of Change from Baseline in S/F Ratio at days 4, 7, 10 and 14, No Imputation	ITT	Yes	DMC-Efficacy
14.2.2.1.2	Summary of Change from Baseline in S/F ratio at days 4, 7, 10 and 14, With Imputation Applied	ITT		DMC-Efficacy
14.2.2.2.1	Analysis of Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14	ITT		DMC-Efficacy
14.2.2.2.2	Analysis of Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14, Sensitivity Analysis with No Imputation of S/F Ratio for Participants Who Die	ITT		DMC-Efficacy
14.2.2.2.3	Analysis of Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14, Sensitivity Analysis Using MMRM approach	ITT		Only produced if >10% drop-out before D14
14.2.2.2.4	Analysis of Change from Baseline in S/F ratio at Days 4, 7, 10 and 14, Sensitivity Analysis Accounting for Use of New SOC	ITT		Only produced if a on new SOC is introduced during the study
14.2.3.1.1	Summary of Percentage Change from Baseline in S/F ratio at days 4, 7, 10 and 14, No imputation	ITT	Yes	DMC-Efficacy
14.2.3.1.2	Summary of Percentage Change from Baseline in S/F ratio at days 4, 7, 10 and 14, With imputation applied	ITT		DMC-Efficacy

Number	Title	Population	Early Stop	Programming notes[1]
14.2.3.2.1	Analysis of Percentage Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14	ITT		DMC-Efficacy
14.2.3.2.2	Analysis of Percentage Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14, Sensitivity Analysis with No Imputation of S/F Ratio for Participants Who Die	ITT		DMC-Efficacy
14.2.3.2.3	Analysis of Percentage Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14, Sensitivity Analysis Using MMRM approach	ITT		Only produced if >10% drop-out before D14
14.2.3.2.4	Analysis of Percentage Change from Baseline in S/F ratio at Days 4, 7, 10 and 14, Sensitivity Analysis Accounting for Use of New SOC	ITT		Only produced if a on new SOC is introduced during the study
14.2.4.1	Summary and Analysis of WHO OSCI score at Days 4, 7, 14, 21 and 42	ITT	Yes, summary only	DMC-Unblinded
14.2.4.2	Shift Table of Changes from Baseline in WHO OSCI Score at Days 4, 7, 14, 21 and 42	ITT	Yes	DMC-Unblinded
14.2.4.3	Summary of Participants Remaining at or Below Their Baseline WHO OSCI Scale Score at Days 4, 7, 14, 21 and 42	ITT	Yes	DMC-Efficacy
14.2.4.4	Summary and Analysis of Maximum WHO OSCI Score Reported	ITT	Yes, exclude p-value	DMC-Efficacy
14.2.5.1	Summary and Analysis of Overall Survival	ITT	Yes, exclude Hazard ratio, CI and p-value	DMC-Efficacy
14.2.5.2	Summary and Analysis of Overall Survival, Sensitivity Analysis Accounting for Use of New SOC	ITT		
14.2.6.1	Summary and Analysis of Intubation and Mechanical Ventilation Free Survival	ITT	Yes, exclude Hazard ratio, CI and p-value	DMC-Efficacy

Number	Title	Population	Early Stop	Programming notes[1]
14.2.6.2	Summary and Analysis of Intubation and Mechanical Ventilation Free Survival, Sensitivity Analysis Accounting for Use of New SOC	ITT		
14.2.7	Summary and Analysis of Time to Discharge	ITT	Yes, exclude Hazard ratio, CI and p-value	DMC-Efficacy
14.2.8	Summary and Analysis of Time to SpO2 ≥94% on Room Air Without Further Requirement for Oxygen Therapy	ITT	Yes, exclude Hazard ratio, CI and p-value	DMC-Efficacy
14.2.9	Summary and Analysis of Time to Recovery from Onset of Symptoms	ITT	Yes, exclude Hazard ratio, CI and p-value	DMC-Efficacy
14.2.10	Summary of Number of Days Requiring Oxygen Therapy	ITT	Yes	DMC-Efficacy
14.2.11	Summary of Number of Days with Pyrexia	ITT	Yes	DMC-Efficacy
14.2.12	Summary of Maximum Daily Temperature	ITT	Yes	DMC-Efficacy
14.2.13	Summary of Maximum and Minimum Daily SpO2 values	ITT	Yes	DMC-Efficacy
14.2.14	Summary of Change from Baseline in Cytokine levels at Days 4 and 7	ITT		
14.2.15	Summary of Change from baseline in Inflammatory Response Markers at Days 4 and 7	ITT	Yes	
14.2.16	Exploratory Analysis of Potential Predictor-Treatment Interactions	ITT		

16.2.2 Figures

Figures will not be produced if the study is stopped early.

Number	Title	Population	Programming notes[1]
14.2.2.1.1	Mean (+/-SE) S/F Ratio by Day, No Imputation	ITT	DMC-Efficacy
14.2.2.1.2	Mean (+/-SE) S/F Ratio by Day, With Imputation Applied	ITT	DMC-Efficacy
14.2.2.2.1	Mean (+/-SE) Change from Baseline in S/F Ratio by Day, No Imputation	ITT	DMC-Efficacy
14.2.2.2.2	Mean (+/-SE) Change from Baseline in S/F Ratio by Day, With Imputation Applied	ITT	DMC-Efficacy
14.2.2.3.1	LS Mean (95% CI) Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14	ITT	DMC-Efficacy
14.2.2.3.2	LS Mean (95% CI) Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14, Sensitivity Analysis with No Imputation of S/F Ratio for Participants Who Die	ITT	DMC-Efficacy
14.2.2.3.3	LS Mean (95% CI) Change from Baseline in S/F Ratio at Days 4, 7, 10 and 14, Sensitivity Analysis Accounting for Use of New SOC	ITT	Only produced if a on new SOC is introduced during the study
14.2.3.1.1	Mean (+/-SE) Percentage Change from Baseline in S/F ratio by Day, No Imputation	ITT	DMC-Efficacy
14.2.3.1.2	Mean (+/-SE) Percentage Change from Baseline in S/F ratio by Day, With Imputation Applied	ITT	DMC-Efficacy
14.2.3.2.1	LS Mean (95% CI) Percentage Change from Baseline in S/F ratio at Days 4, 7, 10 and 14	ITT	DMC-Efficacy
14.2.3.2.2	LS Mean (95% CI) Percentage Change from Baseline in S/F ratio at Days 4, 7, 10 and 14, Sensitivity Analysis with No Imputation of S/F Ratio for Participants Who Die	ITT	DMC-Efficacy
14.2.3.2.3	LS Mean (95% CI) Percentage Change from Baseline in S/F ratio at Days 4, 7, 10 and 14, Sensitivity Analysis Accounting for Use of New SOC	ITT	Only produced if a on new SOC is introduced during the study
14.2.4.1	Histogram of WHO OSCI score at Days 4, 7, 14, 21 and 42	ITT	DMC-Efficacy
14.2.4.2	Proportion (95% CI) of Participants Remaining at or Below Their Baseline WHO OSCI Score at Days 4, 7, 14, 21 and 42	ITT	DMC-Efficacy
14.2.4.3	Histogram of Maximum WHO OSCI Score Reported	ITT	DMC-Efficacy
14.2.5	KM Curve of Overall Survival	ITT	DMC-Efficacy
14.2.6	KM Curve of Intubation and Mechanical Ventilation Free Survival	ITT	DMC-Efficacy
14.2.7	Cumulative Incidence Function of Time to Discharge	ITT	DMC-Efficacy

Number	Title	Population	Programming notes[1]
14.2.8	Cumulative Incidence Function of Time to SpO2 ≥94% Without Further Requirement for Oxygen Therapy	ITT	DMC-Efficacy
14.2.9	Cumulative Incidence Function of Time to Recovery from Onset of Symptoms	ITT	DMC-Efficacy
14.2.10	Mean (+/-SE) Maximum Temperature by Day	ITT	DMC-Efficacy
14.2.11	Mean (+/-SE) SpO2 by Day	ITT	DMC-Efficacy

16.3 Safety

16.3.1 Tables

Number	Title	Population	Early Stop	Programming notes[1]
14.3.1.1.1	Summary of All TEAEs by System Organ Class and Preferred Term	Safety	Yes	DMC-Unblinded
14.3.1.1.2	Summary of Treatment Phase TEAEs by System Organ Class and Preferred Term	Safety	Yes	DMC-Unblinded
14.3.1.1.3	Summary of Follow-up Phase TEAEs by System Organ Class and Preferred Term	Safety	Yes	DMC-Unblinded
14.3.1.1.4	Summary of All TEAEs by Age Group, System Organ Class and Preferred Term	Safety		DMC-Safety Only produced if participants aged >65 are permitted to enter the study
14.3.1.2	Summary of Treatment-Related TEAEs by System Organ Class and Preferred Term	Safety	Yes	
14.3.2.1	Summary of Serious TEAEs by System Organ Class and Preferred Term	Safety	Yes	DMC-Unblinded
14.3.2.2	Summary of TEAEs Leading to Permanent Discontinuation from Study Drug by System Organ Class and Preferred Term	Safety	Yes	
14.3.2.3	Summary of TEAEs Leading to Withdrawal from the Study by System Organ Class and Preferred Term	Safety	Yes	
14.3.2.4	Summary of Fatal TEAEs by System Organ Class and Preferred Term	Safety	Yes	

Number	Title	Population	Early Stop	Programming notes[1]
14.3.2.5.1	Summary of TEAEs of Special Interest by Preferred Term and CTCAE Grade	Safety	Yes	DMC-Unblinded
14.3.2.5.2	Summary of TEAEs of Special Interest by Preferred Term and Relationship to Study Drug	Safety	Yes	DMC-Unblinded
14.3.4.1.1	Summary of Change from Baseline in Hematology	Safety	Yes	
14.3.4.1.2	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the Normal Range in Hematology	Safety	Yes	DMC-Unblinded
14.3.4.1.3	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria in Hematology	Safety	Yes	DMC-Unblinded
14.3.4.1.4	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria in Hematology, by Age Group	Safety		DMC-Safety Only produced if participants aged >65 are permitted to enter the study
14.3.4.2.1	Summary of Change from Baseline in Clinical Chemistry	Safety	Yes	
14.3.4.2.2	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the Normal Range in Clinical Chemistry	Safety	Yes	DMC-Unblinded
14.3.4.2.3	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria in Clinical Chemistry	Safety	Yes	DMC-Unblinded
14.3.4.2.4	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria in Clinical Chemistry, by Age Group	Safety		DMC-Safety Only produced if participants aged >65 are permitted to enter the study
14.3.5.1	Summary of Change from Baseline in Vital Signs	Safety	Yes	
14.3.5.2	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria in Vital Signs	Safety	Yes	DMC-Unblinded

Number	Title	Population	Early Stop	Programming notes[1]
14.3.5.3	Summary of Shifts from Baseline to Worst-case Post-Baseline with Respect to the PCI Criteria in Vital Signs, by Age Group	Safety		DMC-Safety Only produced if participants aged >65 are permitted to enter the study

16.4 Listings

Number	Title	Population	Early Stop	Programming notes[1]
16.2.1.1	Reasons for Screen Failure	Enrolled	Yes	
16.2.1.2	Reasons for Discontinuation from Study Drug	ITT	Yes	
16.2.1.3	Reasons for Withdrawal from the Study	ITT	Yes	
16.2.1.4	Participants for Whom the Blind Was Broken	ITT	Yes	
16.2.1.5	Planned and Actual Treatments	ITT	Yes	
16.2.2	Protocol Deviations	ITT	Yes	
16.2.3	Participants Excluded from Any Population	Enrolled	Yes	
16.2.4.1	Demographics	ITT	Yes	DMC-Unblinded
16.2.4.2	Smoking Status	ITT	Yes	DMC-Unblinded
16.2.4.3	Baseline Disease Characteristics	ITT	Yes	DMC-Unblinded
16.2.4.4	COVID-19 Comorbidities	ITT	Yes	
16.2.4.5	Other Medical History	ITT	Yes	
16.2.4.6	Prior Medications	ITT	Yes	
16.2.4.7	Concomitant Medications	ITT	Yes	DMC-Unblinded
16.2.4.8	Concomitant Procedures	ITT	Yes	
16.2.4.9	Compliance with Study Treatment	Safety	Yes	
16.2.4.10	Compliance with Daily Diary Completion After Discharge	ITT	Yes	
16.2.5	Exposure to Study Treatment	Safety	Yes	DMC-Unblinded
16.2.6.1	Oxygen Saturation	ITT	Yes	

Number	Title	Population	Early Stop	Programming notes[1]
16.2.6.2	WHO OSCI Score	ITT	Yes	DMC-Unblinded
16.2.6.3	Overall Survival	ITT	Yes	
16.2.6.4	Intubation and Mechanical Ventilation Free Survival	ITT	Yes	
16.2.6.5	Time to Discharge	ITT	Yes	
16.2.6.6	Time to SpO2 ≥94% on Room Air Without Further Requirement for Oxygen Therapy	ITT	Yes	
16.2.6.7	Time to Recovery from Onset of Symptoms	ITT	Yes	
16.2.6.8	Temperature Data	ITT	Yes	
16.2.6.9	Oxygen Therapy	ITT	Yes	
16.2.6.10	Number of Days Requiring Oxygen Therapy and Number of Days with Pyrexia >=38 C	ITT	Yes	
16.2.6.11	Daily Diary	ITT	Yes	
16.2.6.12	Cytokine Levels	ITT		
16.2.6.13	Inflammatory Response Markers	ITT	Yes	
16.2.7.1	Adverse Events	Safety	Yes	DMC-Unblinded
16.2.7.2	Serious Adverse Events	Safety	Yes	DMC-Unblinded
16.2.7.3	Adverse Events Leading to Permanent Discontinuation from Study Drug or Withdrawal from the Study	Safety	Yes	DMC-Unblinded
16.2.7.4	Fatal Adverse Events	Safety	Yes	DMC-Unblinded
16.2.7.5	Adverse Events of Special Interest	Safety	Yes	DMC-Unblinded
16.2.8.1	Hematology Parameters	Safety	Yes	
16.2.8.2	Hematology Parameters for Participants with at Least One PCI Value	Safety	Yes	DMC-Unblinded
16.2.8.3	Clinical Chemistry Parameters	Safety	Yes	
16.2.8.4	Clinical Chemistry Parameters for Participants with at Least One PCI Value	Safety	Yes	DMC-Unblinded
16.2.9.1	Vitals Signs	Safety	Yes	
16.2.9.2	Vitals Signs for Participants with at Least One PCI Value	Safety	Yes	DMC-Unblinded
16.2.10	Physical Examination at Screening	Safety	Yes	
16.2.11	Female Fertility Status and Pregnancy Test Results	Safety	Yes	

Number	Title	Population	Early Stop	Programming notes[1]
16.2.12.1	Presence of EDP1815 in Plasma Samples	Safety		
16.2.12.2	Presence of EDP1815 in Stool Samples	Safety		

17 Appendix 2: MedDRA Internationally Agreed Order for System Organ Class

The internationally agreed SOC order to be used for medical history and AE summary tables is provided in Table 15.

Table 15 MedDRA Internationally Agreed SOC Order

Order Number	System Organ Class
1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

18 Cytokines and Inflammatory Response Markers

Table 16 Biomarker Parameters and Units

Category	Parameter	Unit
Cytokines	EGF	TBC
	Eotaxin/CCL11	TBC
	FGF-2	TBC
	Flt3 Ligand	TBC
	Fractalkine/CX3CL1	TBC
	G-CSF	TBC
	GM-CSF	TBC
	GROα	TBC
	IFNα2	TBC
	IFNγ	TBC
	IL-12 (p70)	TBC
	IL-13	TBC
	IL-15	TBC
	IL-17A/CTLA8	TBC
	IL-17E/IL-25	TBC
	IL-17F	TBC
	IL-18	TBC
	IL-1RA	TBC
	IL-1α	TBC
	IL-1β	TBC
	IL-27	TBC
	IL-3	TBC
	IL-4	TBC
	IL-5	TBC
	IL-6	TBC
	IL-7	TBC
	IL-8/CXCL8	TBC
	IL-9	TBC
	IP-10/CXCL10	TBC
	M-CSF	TBC
	MDC/CCL22	TBC
	MIG/CXCL9	TBC
	MIP-1α/CCL3	TBC
	MIP-1β/CCL4	TBC
	PDGF-AA	TBC
	PDGF-AB/BB	TBC
	RANTES/CCL5	TBC

Category	Parameter	Unit
	sCD40L	TBC
	TGFα	TBC
	TNFα	TBC
Inflammatory Markers	D-Dimer	ng/mL
	Ferritin	ng/mL
	Troponin I	ng/mL
	C-reactive protein	mg/dL
	Neutrophil/Lymphocyte Ratio	Fraction of 1

19 Appendix 3: Safety Laboratory Evaluations

Table 17 Safety Laboratory Parameters and Units

Category	Parameter	Unit	PCI Criteria	
			Low	High
Hematology	Hemoglobin	g/dL	<10 ≥2 decrease from BL	>2 increase from BL
	Hematocrit	%		
	Red blood cell count	10^6/uL		
	White blood cell count	10^3/uL	<3	
	Platelets	10^3/uL	<75	
	Mean Corpuscular Volume	fL		
	Mean Corpuscular Hemoglobin	pg		
	Mean Corpuscular Hemoglobin Concentration	g/dL		
	Absolute neutrophils	10^3/uL	<1.5	
	Absolute lymphocytes	10^3/uL	<0.5	>4
	Absolute monocytes	10^3/uL		
	Absolute eosinophils	10^3/uL		
	Absolute basophils	10^3/uL		
	Relative neutrophils	%		
	Relative lymphocytes	%		
	Relative monocytes	%		
	Relative eosinophils	%		
	Relative basophils	%		
Chemistry	Aspartate aminotransferase	IU/L		>3xULN if BL was normal, <3xBL if BL was above ULN
	Alanine aminotransferase	IU/L		>3xULN if BL was normal, <3xBL if BL was above ULN
	Lactate dehydrogenase	IU/L		
	Creatinine	mg/dL		>1.5xULN >1.5xBL
	Potassium	mmol/L		>5.5
	Sodium	mmol/L	<125	>150
	Urea	mg/dL		

Note: If local lab provides both absolute and relative differentials, only absolute differentials should be completed on the CRF and relative differentials should be marked as not done. If relative differentials only are provided these will be converted to absolute values in the analysis data sets as described in Section 5.3.4.3.