Official Title:	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
NCT Number:	NCT04488575
Document date:	05 August 2020

Clinical Study Protocol

Protocol Title: 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

Sponsor Protocol Number: EDP1815-205

Protocol Amendment Number: 03 (protocol version 4.0)

Sponsor Compound Number: EDP1815

Short Title: Safety and efficacy of EDP1815 in the treatment of patients hospitalised with SARS-CoV-2 Infection

Sponsor: Evelo Biosciences Inc. 620 Memorial Drive, Suite 500, Cambridge MA 02139, USA

IND Number: 22047

EudraCT Number: Not applicable

Sponsor Approval Date: 05 August 2020

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Clinical Project Manager	[redacted]
Principal (Chief) Investigator	[redacted]

Approvals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical protocol in addition to the following:

- Ethical principles originating from the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 and Good Clinical Practice (GCP).
- All applicable laws and regulations including data privacy laws and regulations.

Sponsor Signatories:

[redacted]

Date

Chief Medical Officer

[redacted]

Statistician

Investigator Agreement

I confirm that I have read and that I understand this clinical protocol, the Investigator's Brochure, and other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this clinical protocol and also protect the rights, safety, privacy, and wellbeing of study participants in accordance with the following:

- Ethical principles originating from the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 and Good Clinical Practice (GCP).
- All applicable laws and regulations including data privacy laws and regulations.

Signature of Investigator **Date**

Investigator Name

Investigator Title

Name of Facility

Location of Facility (City)

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ABBREVIATIONS

AE	Adverse Event
ACE2	Angiotensin-converting Enzyme 2
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory
AST	Aspartate Aminotransferase
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRP	C-reactive Protein
CRC	Covid Related Complications
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
DAD	Diffuse Alveolar Damage
eGFR	Estimated Glomerular Filtration Rate
Evelo	Evelo Biosciences Inc. (the Sponsor company)
FDA	Food and Drug Administration
FiO2	Fraction of Inspired Oxygen
FoxP3	Forkhead Box P3
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
iDMC	Independent Data Monitoring Committee
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LFT	Liver Function Test
LPS	Lipopolysaccharide
KLH	Keyhole limpet haemocyanin
OSCI	WHO Ordinal Scale for Clinical Improvement
MedDRA	Medical Dictionary for Regulatory Activities
O2	Oxygen
OTC	Over-The-Counter
PBMC	Peripheral Blood Mononuclear Cell

PIS	Patient Information Sheet
PCR	Polymerase Chain Reaction
QC	Quality Control
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SaO2	Oxygen Saturations
SAP	Statistical Analysis Plan
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SF	SaO2 / FiO2 ratio
SINTAX	Small Intestinal Axis
SoA	Schedule of Activities
SpO2	Saturation of Oxygen
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Woman of Child-Bearing Potential

1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Short Title: Safety and efficacy of EDP1815 in the treatment of patients hospitalized with SARS-CoV-2 Infection.

Rationale: EDP1815 is a single strain of a small-intestine targeted, systemically immune-modulating, monoclonally-expanded commensal gut bacteria. Preclinical and clinical data have demonstrated that EDP1815 reduces levels of IL-6, TNFα and IL-8, while elevating epithelial expression of IL-10 and FoxP3. At the same time, EDP1815 is well tolerated with no overall difference from placebo in human trials to date. This profile could be highly relevant with respect to treating COVID-Related Complications (CRC).

An exaggerated host immune response leads to the life-threatening complications of COVID-19 infection. The cytokine IL-6 and chemokine IL-8 have been shown to be increased in subjects hospitalized with coronaviral infections, infections with influenza A, and in secondary HLH, and their exaggerated levels are pathogenic in the development of complications such as ARDS. The host immune response is clearly important in the initial anti-viral response of the host and IL-6 in particular has been shown to be important in the early phase of the infection. A prolonged and exaggerated immune response is however associated with pulmonary complications, hospitalization and ultimately death. A therapeutic agent that does not abrogate the host immune response entirely, but instead modulates multiple pathways and returns it back to a state of immune homeostasis, could offer significant clinical benefit to subjects with coronaviral infections.

The profile of EDP1815 as an oral agent with good tolerability modulating multiple key immune pathways without blocking them completely – that is, immune normalization rather than immune suppression – could offer significant clinical benefit to patients at risk of developing serious complications secondary to COVID-19.

Table 1: Clinical Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of EDP1815 on pulmonary function as measured by the change in Oxygen Saturation (SpO2) / Fraction of Inspired Oxygen (FiO2) [S/F ratio]	• Change from baseline to the lowest S/F ratio measured in days 1-14

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 $\geq 38^{o}C$. • 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.

• To evaluate the safety and tolerability of EDP1815 in participants with COVID-19	• Incidence and severity of treatment emergent adverse events and serious adverse events. • Incidence of clinically significant abnormal changes in safety laboratory parameters.
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, and to confirm lack of systemic absorption.	• 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

Overall Design:
This is a randomized, placebo-controlled clinical study to assess the safety and efficacy of EDP1815 in patients hospitalized with COVID-19 infection. The study is designed to evaluate the efficacy of EDP1815 at reducing time to resolution of symptoms, preventing progression of COVID-19 symptoms and preventing COVID-Related Complications (CRC). The study will be fully blinded to the participants, investigator, and sponsor. This is a pilot study with a primary objective of investigating the potential of EDP1815 in the prevention of COVID-19 disease progression. The secondary objective is to evaluate multiple endpoints for clinical relevance and sensitivity, while informing the sample size for future studies. Where possible, data will be taken from assessments performed as part of the participant's routine clinical care in this pragmatic study.

Participants who are hospitalized with confirmed COVID-19 disease and are confirmed to be eligible for the study will be randomized to either the active (EDP1815) or placebo group (1:1 randomization), in addition to standard of care. Dosing will be initiated on a twice daily regime for the first 3 days (6 doses) and then once daily for the remaining 11 days (14 days total treatment course). The trial hypothesis is that treatment with EDP1815 in hospitalized patients reduces oxygen requirements by normalizing the exaggerated host immune response to COVID-19. This will be measured by assessing the ratio of the Oxygen Saturation (SpO2) / Fraction of Inspired Oxygen (FiO2), which is a validated measure of severity of ARDS.

Dosing will be stopped if participants are admitted to ICU, efficacy and safety data will continue to be collected according to the schedule of activities, where practical. However, if the participant is eligible for another interventional trial at this point, they may be enrolled into it, and withdrawn

from this study, after discussion with the chief investigator. Inclusion in concurrent interventional studies will not be permitted. Inclusion in observational studies in parallel to this study is allowed.

Number of Participants:
Sixty subjects will be enrolled into the study and randomized in a 1:1 ratio. A further 40 subjects may be enrolled on the request of the DMC if it was felt likely to provide further beneficial information to take forward into planning future studies.

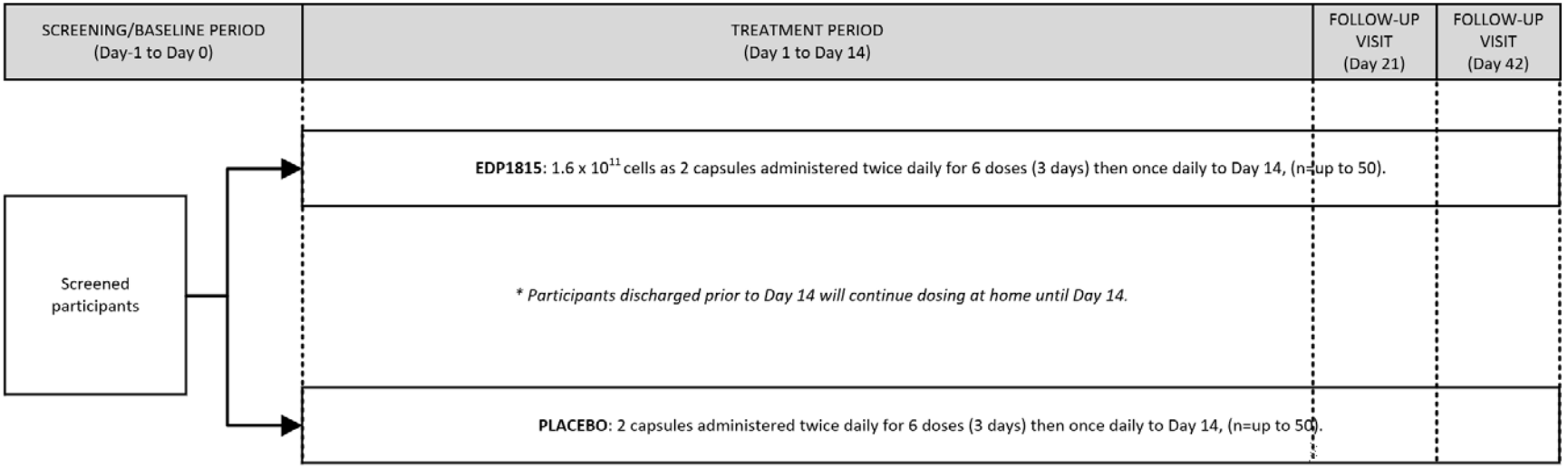
Participant Trial Duration:
This study will consist of a 14-day treatment period followed by a 28-day post-treatment follow-up visit, as described below:

- Up to 2 days for Screening and Baseline assessment period. ***Note:*** *Due to the urgent nature of the study, screening, baseline and Day 1 assessments can occur on the same day. Eligible patients will be randomized and dosed as soon as possible after eligibility is confirmed.*
- A 14-day treatment period (treatment will be stopped if the participant is admitted to ICU).
- A 28-day post-treatment period, with final follow-up via telephone assessment at Day 42.

Number of Centers:
The study will be run at multiple centers in the United States.

1.2. Schema

Figure 1: Clinical Trial Design



1.3. Schedule of Activities (SoA)

Figure 2: Schedule of Activities

Data	Screening^ (Day -1 to Day 0)	Baseline^ (Day -1 to Day 0)	D 1^	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D14 or day of discharge&	D21 ~ (Follow-up Telephone Visit)	D42 (Final Follow-Up Telephone Visit)
Informed consent	x																	
Inclusion and exclusion criteria	x																	
Demographics and anthropomorphic data (e.g. age, height, weight)	x																	
Smoking status [9]	x																	
Medical history	x																	
Significant Covid-19 Comorbidities	x																	
Physical examination	x																	
Pregnancy test (blood/urine) [1]	x																	
Vital signs#*		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant Medications#	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Oxygen therapy status#		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SaO2/FiO2 status#2*		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Blood tests (FBC, CRP, LFT, Creatinine, Urea and Electrolytes, Ferritin, D-		x				x[3]			x[3]									

Data	Screening^ (Day -1 to Day 0)	Baseline^ (Day -1 to Day 0)	D 1^	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D 11	D 12	D 13	D14 or day of discharge[&]	D21 ~ (Follow-up Telephone Visit)	D42 (Final Follow-Up Telephone Visit)
dimer, Troponin) [#*]																		
HIV test	x																	
Cytokine Panel, Paxgene sample, and Biobanking sample*		x				x[3]			x[3]									
Plasma PCR for EDP1815									x[3]									
Day since onset of symptoms[#]		x																
8-point ordinal scale[#]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
COVID-19 RTPCR[#]	x																	
Review of adverse events[#*@]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Retrieval of relevant clinical data[4]																		x
Outpatient questionnaire[5]				x	x	x	x	x	x	x	x	x	x	x	x	x[6]	x[6]	x[6]
Telephone call[5]									x							x	x	x
Discharge status[#]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mortality status[#]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Faecal sample for microbiome analysis		x[7]							x[7]									
EDP1815 or Placebo administration[8]			x[8]	x[8]	x[8]	x	x	x	x	x	x	x	x	x	x	x		

^ Due to the urgent nature of the study, screening, baseline and Day 1 assessments can occur on the same day. Eligible patients will be randomized and dosed as soon as possible after eligibility is confirmed.
~ This assessment can be performed between days 20-22.

[#]Results will be extracted from the patient record where available – no research specific test may be required.
*If a patient is discharged then these assessments may not be performed.
@Whilst an inpatient, participants should have a daily assessment for evidence of nausea, vomiting, diarrhoea, bloating and abdominal pain. This information will be collected for outpatients in the patient questionnaire.
& If a participant is not discharged at Day 14 and remains in hospital, Day 14 assessments will be performed until a participant is discharged from hospital or they reach the final follow-up visit (Day 42).
[1] Pregnancy test will only be performed in women of child-bearing potential (Appendix 2).
[2] If the patient is on 3L/min oxygen flow or less, this assessment should be performed after the patient is at rest on room air for 10 minutes, as detailed in section 8.1.1.
[3] If the patient is discharged prior to these blood tests, where possible outpatient blood testing will be organised.
[4] Extraction of relevant clinical data from the patient's medical record (such as but not limited to symptoms, concomitant medications, other relevant blood tests, and radiology reports such as chest radiograph or CT scan).
[5] If the patient is discharged, they will be given a daily questionnaire to complete; a telephone call will be made on day 7, 14, 21 and 42 (telephone call has a window of +/- 1 day).
[6] The patient will be asked to continue to fill the questionnaire daily until their symptoms have fully resolved for 48 hours or until the day 42 telephone visit (whichever is earlier).
[7] This is an optional sample for research purposes but will be collected whenever possible once at the Baseline visit and then again once between Days 5-14. If the patient is discharged prior to this faecal test, where possible, an outpatient sample will be collected.
[8] Administered twice daily for six doses) and then once daily for the remaining days (17 doses total). Treatment will be stopped if the participant is admitted to ICU, meets individual stopping criteria, or is withdrawn from the study.
[9] Smoking status to include whether current-smoker, ex-smoker, or never-smoker; and to quantify current usage and total pack-year history.

2. Introduction

2.1. Background

The COVID-19 pandemic, as declared on 11th March 2020 by World Health Organization (WHO), is caused by a novel coronavirus (SARS-Cov-2). It is estimated to result in ~50,000 – 160,000 deaths in the USA, if optimal healthcare can be delivered, and up to in excess of 2.2 million deaths if healthcare resources such as ventilated beds are exhausted (Cookson 2020). It is the pulmonary complications of the viral infection that results in the majority of hospitalizations, admissions to ICU and ultimately death (Guan 2020; Huang 2020; Liu 2020; Wang 2020). The COVID-Related Complications (CRC) include acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute kidney injury, acute cardiac injury, liver dysfunction and secondary infection (Huang 2020; Maharaj 2020). There are no vaccines, prophylactic or therapeutic agents of proven efficacy. Significant symptoms that do not result in hospitalization are also common and result in significant illness even short of hospitalization.

Study of coronavirus infections in tissue culture and animal models and of historical, SARS-coronavirus outbreaks, provide insights into the likely pathophysiology of infection with COVID-19 (Guan 2020; Gralinski 2015). The majority of tissue damage following infection with SARS-Cov1 appears to be due to a later, exaggerated, host immune response (Gralinski 2015). The host anti-viral response is driven by the induction of type I interferons which inhibit transcription and translation of the viral genome and reduce the threshold for activation of natural killer cells. Type I interferons also decrease expression of Serping1, a regulator of the complement system and coagulation proteases; this may lead to complement-mediated tissue damage and a prothrombotic tendency. In airway epithelial cells, type I IFNs upregulate expression of ACE2 in airway epithelial cells. Whereas ACE2 has been shown to be protective in models of acute lung injury, it is also the receptor for the spike protein of COVID-19 and is used by the virus for binding to its target cells.

While SARS-CoV-2 infection evades detection by the immune system in the first 24h of infection, after 7-14 days following symptom onset an exaggerated response from the host immune system occurs in a subgroup of people. This leads to progressive lung damage leading to the need for hospitalization and oxygen therapy that can progress to severe pulmonary complications requiring ventilation and even death. It is important to note that the development of Diffuse Alveolar Damage (DAD) is often independent of high-titer viral replication (Peiris 2003). Other end organ damage can also occur secondary to the host immune response. This abnormal immune and inflammatory response in affected lungs includes production of high levels of IL-6, IL-8, TNFα, IL-1β, influx of neutrophils and cytotoxic T cells. A Th_2 (IL4, IL13) response from alternatively-activated macrophages, and an associated profibrotic phenotype (including increased TGF β and PDGFα production) can lead to lung fibrosis and chronic sequelae (Ruan 2020). Activation of the coagulation cascade is associated with development of fibrin clots in the alveoli. IL- 6 and IL-8 are increased in subjects hospitalized with coronaviral infections (Mehta 2020). A therapeutic agent with anti-inflammatory effects across IL-6, IL-8 and TNFα could prevent this host immune mediated organ damage. The host immune response is clearly important in the initial anti-viral response of the host. A prolonged and exaggerated immune response as measured by these cytokines / chemokines is however associated with pulmonary complications, hospitalization and ultimately death. A therapeutic agent that does not abrogate the initial host anti-viral immune

response but modulates the delayed excess immune response via multiple pathways, restoring a state of immune homeostasis, could offer significant clinical benefit to subjects with COVID-19 infections.

2.2. Mechanism of Action

EDP1815 is an orally administered pharmaceutical preparation of a single strain of *Prevotella histicola* isolated from the duodenum of a human donor. *Prevotella* is the genus of human commensal organisms commonly found on oral, nasopharyngeal, gastrointestinal, and genito-urinary mucosal surfaces. It has been found in all human population groups studied so far. EDP1815 is currently in phase 2 clinical development and has European and US approval to initiate a multinational psoriasis study, scheduled for 2Q2020.

Preclinical and clinical data have demonstrated that EDP1815 can systemically suppress IL-6, TNFα and IL-8, while elevating epithelial expression of IL-10 and FoxP3. At the same time, EDP1815 is well tolerated with no overall difference from placebo in human trials to date. This profile could be highly relevant with respect to treating CRC.

EDP1815 works via the small intestinal axis (SINTAX): a network of anatomical and functional connections between the small intestine and the rest of the body. SINTAX links small intestinal mucosal immunology with systemic inflammation, accessible with oral medicines. EDP1815 is non-pathogenic, not genetically modified, does not colonize or persist in the gut, and does not modify the colonic microbiome. It acts locally in the gut - which is, in effect, on the outside of the body - but has pharmacodynamic activity throughout the inside of the body modulating the immune system without any systemic exposure.

EDP1815 is not systemically absorbed and there are no expected ADRs. Safety and tolerability have been indistinguishable from placebo, with no SAEs or AEs of severe intensity reported. The nature of the pharmaceutical preparation of EDP1815 ensures that there is no unwanted persistence of the drug after administration. It does not modify the colonic microbiome as assessed by 16S ribosomal RNA sequencing of stool samples from patients, and the drug is undetectable in stool samples once dosing has ceased. Importantly, there has been no increased risk of infections observed in the phase 1 program.

The therapeutic effects of these orally delivered medicines come from their interaction with pattern recognition receptors on immune cells in the lining of the small intestine. These cells, in turn, modulate immune cells circulating throughout the body. Preclinical and clinical data provide evidence that EDP1815 is capable of modulating multiple immune pathways in humans, and therefore has the potential to become an attractive therapeutic strategy in patients with inflammatory diseases: including the abnormal host immune responses to acute viral infections.

Preclinical studies using EDP1815 have been carried out across a range of human and mouse cell *in vitro* assays, as well as in 5 key in vivo models, which all support the use of this agent in the treatment of immunoinflammatory diseases. *In vitro*, EDP1815 has been found to stimulate secretion of anti-inflammatory cytokines such as interleukin (IL)-10, IL-27, and IL-1RA, from human macrophages and dendritic cells. Furthermore, pre-clinical results have also shown that there is no effect on type 1 interferons, an important interferon for antiviral response.

In human testing EDP1815 improves psoriasis lesions (a condition due to abnormal Th_{17} activity) and reduces the inflammatory response to keyhole limpet hemocyanin (KLH) challenge (a Th_1 driven healthy volunteer model). In addition, in ex-vivo testing EDP1815 has been shown to reduce, or normalize, the secretion of both IL-6 and IL-8, which are 2 of the key cytokines / chemokines involved in exaggerated host responses to viral infections. This confirmed the preclinical findings that EDP1815, despite being gut restricted, can modulate systemic immune biology along multiple pathways, and this unique profile and mechanism makes EDP1815 an ideal candidate for this trial.

2.3. Rationale for Use

As has been discussed above, exaggerated host immune responses lead to the life-threatening complications of COVID-19 infection.

Systemic cytokine interleukin (IL)-6 and chemokine IL-8 levels have been shown to be elevated in subjects hospitalised with coronaviral infections, infections with influenza A (de Jong 2006; Hagau 2010) and in secondary haemophagocytic lymphohistiocytosis (Wong 2004; Ruan 2020). These exaggerated levels are pathogenic in the development of complications such as acute respiratory distress syndrome (ARDS). Although host immune response is important in the initial anti-viral response, prolonged and exaggerated immune response is associated with pulmonary complications, hospitalisation and death. A therapeutic agent that modulates multiple pathways back to a state of immune homeostasis without frank immunosuppression could offer significant clinical benefit to subjects with SARS-CoV-2 infection.

The profile of EDP1815 as an oral agent with good tolerability modulating multiple key immune pathways without abrogating them completely – that is, immune normalization rather than immune suppression – could offer significant clinical benefit to patients at risk of developing serious complications secondary to COVID-19. Its safety profile positions it as an appropriate treatment to use early in the disease course, prior to the onset of these significant symptoms or complications.

2.4. Benefit/Risk Assessment

EDP1815 is a specific pharmaceutical preparation of *Prevotella histicola*, a natural human commensal organism, commonly found on oral, nasopharyngeal, GI, and genito-urinary mucosal surfaces.

EDP1815 is being investigated for its potential benefit in immunoinflammatory disorders, including the cytokine storm associated with COVID-19. There is significant morbidity and mortality benefit to be derived from reducing COVID-Related Complications.

The safety profile of EDP1815 has been indistinguishable from placebo in both the EDP1815-101 and EDP1815-102 studies, with no serious adverse events (SAEs) or adverse events (AEs) of severe intensity reported in either study. Mild and transient AEs have included headache and diarrhoea.

3. Objectives and Endpoints

Table 2: Clinical Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of EDP1815 on pulmonary function as measured by the change in Oxygen Saturation (SpO2) / Fraction of Inspired Oxygen (FiO2) [S/F ratio]	• Change from baseline to the lowest S/F ratio measured in days 1-14
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 $\geq 38^{o}C$. • 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.
• To evaluate the safety and tolerability of EDP1815 in participants with COVID-19	• Incidence and severity of treatment emergent adverse events and serious adverse events. • Incidence of clinically significant abnormal changes in safety laboratory parameters.
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, and to confirm lack of systemic absorption.	• 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

4. Study Design

4.1. Overall Design

This is a randomized placebo-controlled clinical study to assess the safety and efficacy of EDP1815 in patients hospitalized with COVID-19 infection, to determine the efficacy of EDP1815 at reducing time to resolution of symptoms, preventing progression of COVID-19 symptoms and preventing COVID-Related Complications (CRC). The study will be fully blinded to the participants, investigator, and sponsor. This is a pilot study with a primary objective of investigating the potential of EDP1815 in the prevention of COVID-19 disease progression. The secondary objective is to evaluate multiple endpoints for clinical relevance and sensitivity, while informing the sample size for future studies. Where possible, all assessments will be taken from those performed as part of the participant's routine clinical care in this pragmatic study.

Participants who have been recently hospitalized for confirmed COVID-19 disease and are confirmed to be eligible for the study will be randomised to either the active (EDP1815) or placebo group, in addition to standard of care, and dosing will be initiated on a twice daily regime for the first 6 doses, then once daily for the remaining days. The treatment course is 14 days. The trial hypothesis is that treatment with EDP1815 in hospitalized patients reduces oxygen requirements by normalizing the exaggerated host immune response to COVID-19. This will be measured by assessing the Oxygen Saturation (SpO2) / Fraction of Inspired Oxygen (FiO2) [S/F] ratio.

Dosing will be stopped if participants are admitted to ICU. Efficacy and safety data will continue to be collected according to the schedule of activities, where possible. However, if the participant is eligible for another interventional trial at this point, they may be enrolled into it and withdrawn from this study, after discussion with the chief investigator. Inclusion in concurrent interventional studies will not be permitted. Inclusion in observational studies in parallel to this study is allowed.

4.2. Scientific Rationale for Study Design

The exaggerated immune response to COVID-19 infection can affect multiple organs, causing pulmonary, renal and cardiac complications. Pulmonary complications are the most common CRC and progression to ARDS is the most common cause of death. The study therefore focusses on pulmonary function as the primary endpoint and the ratio of the Oxygen Saturation (SpO2) / Fraction of Inspired Oxygen (FiO2) is a validated measure of severity of ARDS (Villar 2013). Due to the lack of established literature on the progression of COVID-19 infection, a large number of secondary endpoints are being collected to understand the potential of EDP1815 in the treatment of this disease. As this is a pilot study an initial sample size of 60 subjects has been used with the potential to expand this to a maximum of a 100 should that be required to understand the effects of EDP1815 and inform future larger-scale studies.

There is no approved treatment for the immunological response to COVID-19 infection and so a placebo-controlled study in addition to best standard of care is the optimal design.

4.3. Dose Justification

EDP1815 will be administered in the EDP1815-205 study as an enteric coated powder in capsule formulation; this formulation has already been dosed in humans in EDP1815-101 (EudraCT Number: 2018-002807-32), a study currently ongoing in the UK with data from completed cohorts reported in the Investigator's Brochure.

The treatment regimen for this study will be $1.6x10^{11}$ cells of EDP1815 (2 capsules) given twice a day for 3 days (6 doses) then once a day for 11 days (14-day total course).

The doses of EDP1815 tested in humans to date ($1.6x10^{11}$ cells to $8.0x10^{11}$ cells in EDP1815-101) were based on allometric scaling from the preclinical in vivo experimental data. Both doses had clear effects on IL-6 and IL-8 based on lipopolysaccharide (LPS) stimulation of whole blood samples taken at baseline and after a course of daily administration of EDP1815. The study included patients with mild to moderate psoriasis, and improvements in their skin condition were also demonstrated. There was no clear difference between the 2 dose levels tested on IL-6 and IL-8 and so the lower dose has been selected for this study. These data are presented in the Investigator's Brochure.

An initial twice daily (bd) dosing regimen has been selected to maximise the speed of response. EDP1815 works via direct interaction with immune cells in the epithelium of the upper small intestine. A twice a day regimen doubles the duration of exposure of the microbes to the immune cells in the upper small intestine per 24 hours and will increase the speed of response. The total daily dose is less than half the maximum daily dose tested for 28 days in EDP1815-101.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the treatment period and completed their final safety follow-up visit 28 days after their last dose. A participant is also considered to have completed the study if they are withdrawn from the study. If a participant is admitted to ICU and is enrolled in a subsequent study then they are deemed to have completed this study at the point of signing the informed consent.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA).

5. Study Population

This protocol contains participants with a confirmed diagnosis of COVID-19 viral infection.

Potential participants will be identified by reviewing hospital admissions, as well as reviewing the positive results from COVID-19 testing. Potential participants will be referred to the research team if they are interested in participating in this clinical trial. Once contact has been made with the patient, the research team will outline and explain the aims of the trial. An electronic or paper copy of the Patient Information Sheet (PIS) will then be given to the patient who will have the opportunity to consider the information and discuss the trial with the trial staff, and raise any queries before consenting to participate in the trial.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Each participant must meet **all** of the following study criteria to be enrolled in this study:

1. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Informed consent will be obtained prior to any Screening procedures and in accordance with national, local, institutional guidelines.
2. Hospitalized within the last 36 hours.
3. Receiving any form of supplementary oxygen therapy at baseline.
4. Confirmed COVID-19 viral infection by RTPCR at screening.
5. Age:
    a. 18-65 years old, OR
    b. >65 year-olds can be included after DMC approval (see section 10.1.5)
6. Contraception:

    Male participants:
    A male participant must agree to use contraception as detailed in **Appendix 2** of this protocol during their participation in this study and for a period of 90 days after the last dose; and also refrain from donating sperm during this period.

    Female participants:
    A female participant is eligible to participate if she is not pregnant, and at least one of the following conditions applies:

    a. Not a woman of child-bearing potential (WOCBP) as defined in **Appendix 2.**

    OR

    b. A WOCBP who agrees to follow the contraceptive guidance in **Appendix 2** during their participation in this study for at least 1 complete menstrual cycle (≥30 days) after last dose.

5.2. Exclusion Criteria

Participants meeting **any** of the following criteria will be excluded from the study:

1. Contraindications/hypersensitivity to *P histicola* or any of the capsule excipients
2. Patients with chronic hypoxia or underlying significant chronic respiratory disease (such as COPD, Pulmonary Fibrosis, or Bronchiectasis).
3. Admission to ICU at time of screening.
4. Mechanically ventilated, on CPAP, or on non-invasive ventilation at the time of screening.
5. Patient is taking a systemic immunosuppressive agent such as, but not limited to, oral steroids, methotrexate, azathioprine, ciclosporin, or tacrolimus, unless these are given as part of COVID standard of care treatment.
6. Patient has a diagnosed primary immunodeficiency.
7. Patient has a diagnosis of HIV/AIDS
8. Patient has pre-existing known chronic kidney disease stage 4 or 5 or requiring renal replacement therapy (i.e. estimated glomerular filtration rate (eGFR) <30ml/min/1.73m^2); [Laboratory results within the last 48 hours may be used].
9. Patient has pre-existing known significant liver disease with Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5.0 x upper limit of normal (ULN); [Laboratory results within the last 48 hours may be used].
10. Patient has pre-existing known significant gastrointestinal tract disease expected to affect absorption within the small intestine (e.g. short bowel syndrome, inflammatory bowel disease affecting the small intestine, gastroparesis); or prior malabsorptive bariatric surgery that could interfere with GI delivery and transit time.
11. GI signs or symptoms equivalent to CTCAE v5.0, gastrointestinal disorders, grade 3 or 4 event.
12. Patient has pre-existing known substantially impaired cardiac function or pre-existing clinically significant cardiac diseases, including unstable angina or acute myocardial infarction ≤ 6 weeks prior to Screening.
13. Currently participating in an interventional clinical trial (observational studies allowed).
14. Moribund at time of screening
15. Female participant who is currently pregnant at time of screening
16. Female participant who is unwilling to stop breastfeeding during treatment period
17. Any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to make the patient ineligible for inclusion because of a safety concern.
18. Unwilling to comply with study procedures, including follow-up, as specified by this protocol; or unwillingness to cooperate fully with the investigator.

5.3. Lifestyle Restrictions

Participants must refrain from consuming acidic drinks for 1 hour either side of dosing and from eating 2 hours before dosing and 1 hour after dosing.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

If subjects fail the screening procedures then they will not be allowed to be re-screened.

6. Study Interventions

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

All study interventions in this study will be administered orally. EDP1815 will be supplied as capsules that are enteric coated to release the contents in the duodenum and jejunum. The drug product is manufactured by [redacted].

The EDP1815 drug product is available as enteric coated hydroxylpropyl methylcellulose (HPMC) hard capsules in white to off-white color. The formulation of EDP1815 consist of freeze-dried powder of *P histicola* and excipients. The excipients include mannitol, magnesium stearate and colloidal silicon dioxide. Each EDP1815 PIC contains 8.0x 10^{10} cells of *P histicola*.

The matching placebo are identical in appearance but do not contain *P histicola* or any other bacteria. Matching placebo is supplied by [redacted]. The placebo excipients include microcrystalline cellulose and magnesium stearate.

Treatment with EDP1815 or placebo will be twice daily for 6 doses and then once daily for 11 doses (14-day total course). There should be a minimum of two hours between the twice daily doses. For subjects who are discharged within the 14-day period, medication will be dispensed to take at home.

Table 3: Treatment Arms

Arm	Dosage
EDP1815	1.6 x 10^{11} cells as 2 capsules twice daily for 6 doses, then once daily to 14 days
Placebo	2 capsules twice daily for 6 doses, then once daily to 14 days

Participants must refrain from consuming acidic drinks 1 hour either side of dosing and from eating 2 hours before dosing and 1 hour after dosing. Refer to the Pharmacy Manual for further details.

6.2. Preparation/Handling/Storage/Accountability

All capsules will be supplied in blister packs and must be kept in controlled conditions of 2-8°C while at the study site.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during storage and transit for all study interventions received and any excursions are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive the study intervention and only authorised site staff may supply the study intervention. While at the study site, all study intervention must be stored in a secure, environmentally controlled, and monitored area

(manual or automated with the ability to show minimum and maximum temperatures daily), in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3. If the study intervention is given to participants to take at home, the participants should be instructed to take it straight home from the hospital, and then to store it at home in the refrigerator and out of reach of children.
4. The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a randomized controlled study and therefore, the treatment allocation is random. Randomized treatment ensures minimisation of selection bias, so that the individuals in the two treatment groups are not systematically different, other than the treatment that they receive. A paper randomisation will be used to assign participants to study interventions.

Blind Break (Scratch-off code breaks)	A scratch-off code break that contains the study intervention assignment for each participant will be provided to each site investigator. The scratch-off code breaks will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. Once the study is complete, all scratch-off code breaks (revealed and non-revealed) must be inventoried and returned to the Sponsor.

The investigational drug blind shall not be broken by the investigator unless information concerning the study intervention is necessary for the medical treatment of the participant.

For unblinding a participant, the investigational drug blind can be obtained by scratching off the blinded area to reveal the treatment information.

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).

6.4. Study Intervention Compliance

Drug supplies will be counted and reconciled at the study site before being returned.

The investigator must maintain 100% accountability for all study intervention received and dispensed during the entire duration of the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date or retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers and/or packs used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

The investigator must maintain a current inventory (Drug Accountability Log) of all study intervention delivered to the site, inventory at the site, dispensing log, and participants' use records. This log must accurately reflect the drug accountability of the study intervention at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of study intervention, kit numbers, expiry or retest date (if applicable) and amount dispensed, and the date and amount returned to the site by the participant, including the initials of the person dispensing and receiving the study intervention. The log should include all required information as a separate entry for each participant to whom study intervention is dispensed.

Prior to site closure or at appropriate intervals, a representative from the Sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the Sponsor or its designee for destruction. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the Sponsor.

The investigator will be notified of any change in expiry date or retest date of clinical study material during the study conduct. On expiry date notification from the Sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the Sponsor or its designee for destruction. In the event of expiry date extension of supplies already at the study site, supplies may be relabeled with the new expiry date at that site. In such cases, the Sponsor or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

6.5. Concomitant Therapy

All standard of care therapy is permitted for use any time during the study.

There are no contraindications to treatment. There are no prohibited concomitant medications and no anticipated drug-drug interactions. Of note, no significant inhibition or induction of any of the CYP450 enzymes were observed *in vitro* after EDP1815 treatment.

Any medication or vaccine (including OTC or prescription medicines, probiotics, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Study stopping criteria

6.6.1. Safety

Safety data will be evaluated on an ongoing basis by a Data Monitoring Committee (DMC) which will consist of at least; a chairperson, 2 physicians independent of the study team, and an unblinded statistician. The DMC support staff for the blinded sessions will include the Principal Investigator, the Evelo medical monitor, a blinded statistician, and an Evelo clinical operations representative. The DMC will review the data in a blinded manner but can request unblinded data if required. Any unblinded data will be reviewed only by the chairperson, 2 independent clinicians, and the unblinded statistician. The DMC can halt the study at any point for safety concerns. Further details can be found in the DMC charter.

The study should be terminated if either of the following conditions are met:

1. One (or more) subjects on treatment with EDP1815 has symptoms of a clinically significant bacteremia and has a positive blood culture for the EDP1815 strain of *P. histicola*.(Note: the study will be paused and dosing held in all participants while identifying the specific strain of *P.histicola*).
2. The DMC believe that EDP1815 is potentially detrimental to patient outcomes.

6.7. Intervention after the End of the Study

No specific interventions are planned after the end of the study, which is the visit 28 days after the last dose of the study drug (Day 42).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation from Study Treatment and/or Withdrawal from the Study

Participants may discontinue from study treatment or withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep participants in the study. The reasons for participants discontinuing treatment and/or withdrawing from the study will be recorded in the CRF. A participant may discontinue from the study drug or withdraw for the following reasons:

1. The participant does not meet the protocol inclusion or exclusion criteria.
2. The participant is non-compliant with the protocol.
3. The participant is admitted to ICU. At this point, dosing for this individual subject will be stopped, but they will remain in the study until Day 42 for data collection where practical. However, if the subject is eligible for another interventional trial, they may be enrolled into this trial after discussion with the chief investigators. The participant is deemed to have completed this study at the point of signing the informed consent of this other study.
4. The participant has a serious or intolerable AE that in the investigator's opinion requires discontinuation from study treatment or withdrawal from the study (see section 7.2).
5. The participant has laboratory safety results that reveal clinically significant changes from the baseline values that are not, in the opinion of the investigator, explained by COVID-19 infection or CRCs.
6. The participant is lost to follow-up.
7. Other reasons (e.g. pregnancy).
8. The participant withdraws consent, or the investigator or sponsor decides to discontinue the participant's participation in the study.

7.2 Discontinuation from Study Treatment

7.2.1 Temporary Cessation of Dosing in an Individual Participant:

- Subjects with grade 3 GI-related AEs will pause dosing for up to 72 hours. Dosing may be restarted when/if symptoms improve, after discussion with the sponsor medical monitor. If symptoms do not improve within 72 hours then the subject will be withdrawn from the study.
- Subjects with non GI-related grade 3 adverse events, not attributed to Covid-19 infection, will pause dosing for up to 72 hours, unless the baseline value was grade 2. Dosing may be restarted when/if symptoms improve, on discussion with the sponsor medical monitor. If symptoms do not improve within 72 hours then the subject will be withdrawn from the study.

The participant should discontinue treatment permanently if the AE occurs a second time on restarting treatment.

7.2.2 Permanent Cessation of Dosing in an Individual Participant

It may be necessary for a participant to permanently discontinue study treatment. If study drug is definitively discontinued, the participant will be encouraged by the investigator to continue to participate in all scheduled study visits and assessments, so that study data will be collected for the participant per protocol. Every effort should be made to keep participants in the study. Individual treatment stopping rules are:

- "Any CTCAE grade 4 gastrointestinal-related adverse event."
- "Any non GI-related CTCAE grade 4 adverse event, not attributed to Covid-19 infection."
- "A new diagnosis of HIV / AIDS"

7.3 Withdrawal from the Study

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The investigator will also withdraw participant(s) if Evelo terminates the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the CRF.

Participants who withdraw from the study should complete the assessments for the follow-up visit.

7.4 Lost to Follow Up

A participant will be considered lost to follow-up if he or she has been discharged or transferred to another hospital, and the study site is unable to contact the participant for their telephone visit.

Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant by telephone. These contact attempts should be documented in the CRF.

If the participant continues to be unreachable after 3 attempts, he/she will be considered to have withdrawn from the study.

7.5 Replacements

Participants who withdraw or are withdrawn from the study within 1 week of randomisation may be replaced in order to have approximately 60 participants provide at least 7 days of post baseline data.

8. Study Assessments and Procedures

- Study procedures and their timing are summarised in the SoA (section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA. Likewise, procedures conducted as part of the participant's routine clinical management may be utilised for any of the study data provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, for the purposes of the study, including any extra assessments that may be required, will not exceed 140mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Repeat or unscheduled visits may be conducted at the investigator's discretion but all details must be recorded in the CRF.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA. This data can be collected from the patient's medical records if performed at the same time-point, and need not be repeated for research purposes. Where possible, all assessments will be taken from those performed as part of the participant's routine clinical care.

8.1.1. Oxygen Saturation

Oxygen saturation will be measured using a peripheral pulse oximeter and will also be analysed as a ratio with the oxygen flow (SpO_2 /FiO_2). The measurement will ideally be performed with the subject sitting and having been rested for at least 10 minutes.

If the subject is on 3litres/min oxygen flow or less, and the investigator feels it is safe to do so, the investigator will remove the subject's supplemental oxygen for 10 minutes while they remain seated, and while continuously monitoring the oxygen saturation. After 10 minutes the oxygen saturation reading will be taken to calculate the S/F ratio on room air. If, during this process, the saturations drop by greater than 4%, the oxygen will be immediately replaced and the ratio measured on oxygen.

8.1.2. WHO Ordinal Scale

The WHO ordinal scale will be collected throughout the study. This is an accepted instrument which has been developed specifically for trials in patients with COVID-19.

Figure 3: WHO ordinal scale for clinical improvement (OSCI) of COVID-19

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
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 – pressors, RRT, ECMO	7
Dead	Death	8

8.1.3 Participant Questionnaire and Diary

When participants are discharged, they will be given a daily questionnaire and diary to complete. The purpose is to record if the participant changes their current medications, starts taking any new medication, whether they are on home oxygen therapy, whether they continue to have COVID-19 symptoms, and whether these symptoms interfere with their usual activities (to enable calculation of the OSCI score) and to record any adverse events.

These questionnaires and diary should be completed once daily, until the patient is symptom free and off oxygen therapy for at least 48 hours, or until Day 42 (whichever is sooner).

8.1.4 Telephone call

If patients are discharged, they will be contacted by telephone on days 7, 14, 21 and 42 (+/- 1 day). The purpose of this call is to seek reporting of AEs, remind the participant to continue to fill their daily questionnaire (until symptoms have resolved or Day 42, whichever is sooner), and to offer the opportunity for any study-related questions.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, and GI systems. Height and weight will also be measured and recorded. The physical examination data will be recorded from the admission record and medical notes where possible.

8.2.2. Vital Signs

- Blood pressure, pulse rate, respiratory rate, oxygen saturations and temperature will be assessed.

8.2.3. Strain-specific PCR for EDP1815

- Plasma samples will be taken from participants at day 7, to assess for the presence of EDP1815 levels by PCR with strain-specific primers that can detect EDP1815 specifically, even when other strains of *Prevotella Histicola* are present.
- If a participant has a positive blood culture for P. histicola identified as part of their clinical care, then isolates will be tested for the EDP1815 strain.

Note: the study will be paused, and dosing held in all participants while identifying the specific strain of P. histicola.

8.2.4. Gastrointestinal Assessment

- Inpatients will have a daily assessment for evidence of any severity of nausea, vomiting, diarrhoea, bloating and abdominal pain. This will be recorded as an adverse event and an assessment of causality will be made.
- Outpatients will complete the daily diary card (section 8.1.3), where they will be prompted to record GI side-effects such as nausea, vomiting, diarrhoea, bloating and abdominal pain as AEs.

8.2.5. Clinical Safety Laboratory Assessments

- An HIV test will be performed at screening. Subjects with a positive result will be excluded or withdrawn from the study.
- The safety laboratory assessments are Full blood count, Creatinine, Urea and Electrolytes and Liver function test, performed at baseline, Day 4 and Day 7.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal and which are not associated with the underlying disease during participation in the study or within 14 days after the last dose of study drug should be repeated until the values return to normal

or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA in addition to local procedures.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative). Due to the nature of the patient population and disease only SAEs and AEs of severe (CTCAE Grade 3) and potentially life threatening (CTCAE Grade 4) intensity will be documented in the CRF. AEs of mild (CTCAE Grade 1) or moderate (CTCAE Grade 2) intensity should be documented in the medical notes. However, adverse events relating to nausea, vomiting, diarrhoea, bloating and abdominal pain of any grade will be recorded and assessed as an adverse event.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF at Screening until the follow--up visit (28 days after last dose) at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. The Sponsor will inform all study sites of any SAEs as soon as possible after an SAE has been reported.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Death, progression to ICU, mechanical ventilation and organ failure can all result from COVID 19 infection and are endpoints within the study. These events will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE, unless deemed drug related by the PI or sponsor.

8.4. Treatment of Overdose

For this study, any dose of EDP1815 taken which is more than $8.0x10^{11}$ cells (10 capsules) within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose unless there is evidence of subsequent related infection and/or colitis. If the clinical situation warrants it, then the Sponsor

would recommend the use of a penicillin--based antibiotic (e.g. Penicillin V) which may be used in case of overdose. If the patient is allergic to penicillins, then alternatives including cephalosporins; macrolides (e.g. clarithromycin or erythromycin); or tetracyclines (eg. Doxycycline) may be used as an alternative.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately upon becoming aware of the overdose.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for 72 hours or until they have resolved, whichever is the longer.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Biomarkers

Biomarker samples will be collected at baseline, day 4 and day 7. A small panel of biomarkers will be conducted on all subjects at these time points. Additional biomarkers may be measured based on the results of the trial.

8.5.1. Biomarkers to be measured on all subjects

Specific biomarkers have been associated with progression and poor outcome following infection with COVID-19. These include differential white cell count, neutrophil to lymphocyte ratio, CRP, IL-6, IL-8, Ferritin, D-Dimer, and Troponin levels. These will be measured in all subjects at baseline, day 4 and day 7.

8.5.2. Additional plasma biomarkers

Additional plasma biomarkers may be analysed subject to the clinical data in the trial. These biomarkers may help understand the response to EDP1815 and / or the progression of COVID-19 disease. These markers could include Eotaxin, Eotaxin-3, GM-CSF, IFN-γ, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-7, IL-8 (HA), IL-10, IL-12/IL-23p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, IP-10, MCP-1, MCP-4, MDC, MIP-1α, MIP-1β, TARC, TNF-α, TNF-β, VEGF-A. Additional plasma biomarkers may be analysed if emerging data suggests they could be useful in understanding the drug response and / or disease progression.

8.5.3. Transcription analysis

RNA will be collected from PBMCs and may be analysed subject to the clinical data in the trial. The exact genes to be analysed will be defined by an expert sub-group of the study but will include genes related to host immune response as well as those related to the disease pathology.

8.5.4. Microbiome Research

The microbiome composition of stool samples will be assessed as an optional research test collected at baseline and once more between Days 5-14. EDP1815 is not expected to alter the composition of the microbiome, but the microbiome will be evaluated for separate research purposes. Microbiome analysis may be performed through 16s ribosomal RNA sequencing and/or whole genome microbial sequencing depending on the question being asked.

8.5.5. Biobanking Sample

Blood will be stored in a research tissue bank for up to [redacted] for future research of COVID-19. Samples will be labelled with a code and if shared with others, will be deidentified. The samples may be used by the Sponsor, the participating investigators or other IRB-approved investigators at the participating institutions.

8.6 Additional Baseline Information

8.6.1 Smoking Status

Data on whether the participant is a current-smoker, past-smoker, or never-smoker will be collected. For past- or current-smokers, a pack year history will be collected (packs of cigarettes smoked per day * years the patient has smoked).

8.6.2 Significant Covid-19 Co-morbidities

Information on the presence or absence of current comorbidities that are relevant as prognostic factors for Covid-19 will be collected. This includes the presence/absence of diabetes, hypertension, chronic other cardiovascular disease, chronic respiratory disease, and cancer.

9. Statistical Considerations

The SAP will be developed and finalised before database lock and will fully describe the participant populations to be included in the analyses, procedures for accounting for missing, unused, and spurious data and the statistical methods to be applied to the data.

All analyses will be performed using SAS® version 9.3 or later (SAS Institute, Cary, NC, USA).

9.1. Sample Size Determination

60 participants will be randomly assigned to EDP1815 or matching placebo in a 1:1 ratio.

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, the table 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.

Table 4: Estimated Size of Confidence Intervals of Treatment Difference in Change from Baseline in Trough S/F Ratio

Subjects 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

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 subjects 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 $50 \pm 51.7 = (-1.17, 101.7)$.

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 5: Description of Patient Populations

Population	Description
Enrolled	All participants who sign the ICF.
Intention to Treat (ITT)	All participants randomly assigned to study intervention. Participants will be analysed according to the intervention to which they were randomized.
Safety	All participants randomly assigned to study intervention who take at least 1 dose of study intervention. Participants will be analysed according to the intervention they actually received.

9.3. Estimands and Intercurrent Events

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

Intercurrent events will be accounted for in the following manner:

Table 6: 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.
Initiating other experimental treatment not considered standard of care before day 14	While-on-treatment Trough S/F ratio prior to starting non SOC treatment will be used

9.3.2. Secondary Efficacy Estimands

All secondary endpoints defined in Section 3 will be considered on the ITT population.

Intercurrent events strategies will be dependent on whether the endpoint is one evaluating the Objective 1 (to evaluate the effect of EDP1815 on the development and severity of complications of COVID-19 infection) or Objective 2 (To evaluate the effect of EDP1815 on length of hospitalization and recovery in participants with COVID-19) as follows:

Table 7: Intercurrent Event Strategies for the Secondary Estimands

Intercurrent event	Strategy for endpoints relating to Objective 1	Strategy for endpoints relating to Objective 2
Treatment discontinuation before the end of the 11 day treatment period	Treatment policy Actual values will be used regardless of treatment discontinuation	
Death prior to time of endpoint evaluation	Composite Subjects who die will be given a worst-case value from time of death	Competing risk Deaths will be accounted as a competing risk
Discharge prior to time of endpoint evaluation	While on treatment[1] Values up to the time of discharge will be used. Treatment policy[2] Actual values will be used regardless of inpatient/ outpatient status	Treatment policy Actual values will be used regardless of inpatient/ outpatient status
Initiating other experimental treatment not considered standard of care before endpoint evaluation	While-on-treatment Values prior to starting experimental treatment will be used	

[1] This will be used for all endpoints which are not recorded after discharge (e.g. S/F ratio).
[2] This will be used for all endpoints which are recorded after discharge (e.g. those relating to the WHO OSCI scale).

Population level summary measure will be assigned as appropriate to the type of endpoint as follows:

Table 8: Population Level Summary Measures for the Secondary Estimands

Type of endpoint	Population level summary measures
Categorical endpoint	Summary statistics, p-value for treatment difference (CMH test)
Binary endpoint	Risk difference between EDP1815 and placebo
Continuous endpoint	Mean difference between EDP1815 and placebo
Number of days with an event	Summary statistics
Time to event	Hazard ratio for EDP1815 vs. placebo

Full details of the individual secondary efficacy estimands will be provided in the SAP.

9.4. Statistical Analyses

In addition to the inferential analyses described in Sections 9.4.1 and 9.4.2 below, descriptive statistics will be provided to summarise all safety and 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.

9.4.1. Efficacy Analyses

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. Age, gender, race, baseline WHO OSCI score and other baseline covariates relating to underlying risk factors such as BMI and presence of co-morbidities 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 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-parameterisation and a reduction in the efficiency of the treatment estimates.

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.

9.4.1.1. Primary Efficacy Analysis

Change from baseline in trough S/F ratio will be analysed 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.

Distributional assumptions underlying the model used for analysis will be examined 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 during the course of 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 new-medication covariate (yes, no for use before Day 14) and an interaction for treatment*new medication will be included in the ANCOVA model described above.

9.4.1.2. Secondary Efficacy Analyses

Change from baseline in S/F ratio at Days 4, 7, 10 and 14 will be analysed separately ANCOVA models. The models will include treatment, baseline S/F ratio together with the additional baseline covariates included in the primary model for trough S/F ratio. Two models will be fitted, one with S/F ratio as the response variable and one with change from baseline in S/F ratio as the response variable.

If more than one S/F ratio measurement is provided at the relevant study day, the lowest S/F measurement within each study day will be used. Participants who are discharged from hospital will have their last observed S/F ratio prior to discharge carried forward to replace missing data at later timepoints. Data missing for reasons other than discharge will be imputed with the closest S/F ratio recorded within one day of the missing visit if such a value exists, otherwise the participant will be excluded from the analysis for that visit.

Other mechanisms for dealing with this missing not at random (MNAR) data may be further investigated for informing on the most credible methods to take forward into a future study. These methods will be further discussed in the SAP.

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.

If during the course of 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 new-medication covariate (yes, no for use prior to the relevant study day) and an interaction for treatment*new medication will be included in the ANCOVA models described above at timepoint.

Percentage change from baseline in S/F ratio will be analysed in the same manner as the change from baseline in S/F ratio described above.

A Cochran-Mantel Haenszel (CMH) test for ordinal data will be used to compare the treatment groups with respect the percentage of participants reporting each WHO OSCI score at Days 4, 7, 10, 14, 21 and 42.

Shift tables showing the shifts from Baseline to each of Days 4, 7, 10, 14, 21 and 42 in WHO OSCI score will be provided.

The difference in proportions between the treatment groups in the percentage of participants remaining at or below their baseline WHO OSCI score will be reported together with the corresponding 95% confidence interval at Days 4 7, 10, 14, 21 and 42.

A CMH test for ordinal data will be used to compare the treatment groups with respect to the maximum WHO OSCI score recorded by each participant. Within each maximum score, the time in days spent at that score will also be summarised.

Overall survival will be analysed 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 course of 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.

Intubation and mechanical ventilation free survival will be analysed in the same manner as described for overall survival above.

Number of days requiring oxygen therapy, number of days with pyrexia, maximum daily temperature, minimum and maximum SpO2 values will be summarised only.

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

Subjects who are not discharged and are still alive at the end of the 42-day study period or those who withdraw prematurely from the study without being discharged or dying will be censored on the day of study completion/withdrawal.

The number and percentage of participants who are discharged, who die and who are censored will be reported together with the estimated subdistributional hazard ratio (with 95% confidence interval) for treatment difference in risk of recovery and its p-value from the model. Cumulative incidence functions for time to full recovery will also be plotted by treatment group.

If during the course of 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.

Time to SpO2 ≥94% on room air without further requirement for oxygen therapy and time to recovery will be analysed in the same manner as described above for time to discharge.

9.4.1.3. Exploratory Efficacy Analysis

Exploratory endpoints will be summarized.

Exploratory modelling will be performed to look for potential predictors of response. This will use the model for change from baseline in trough S/F ratio from the primary analysis, including any baseline covariates found to be significant. For each potential predictor, the variable and its interaction with treatment will be added to the base model from the primary analysis and look for significant interactions. If during the course of the study, a newly approved medication for COVID-19 becomes part of the standard of care treatment at the investigational site, the interaction between treatment and the covariate defined by use of the new medication will also be investigated as part of this exploratory analysis.

Full details will be provided in the SAP.

9.4.2. Safety Analyses

All safety endpoints will be tabulated by treatment group and will be performed on the Safety Population. Further details will be described in the SAP.

9.5. Interim Analyses and Safety Monitoring

The independent Data Monitoring Committee (DMC) will consist of at least; a chairperson, 2 physicians independent of the study team, and an unblinded statistician. The DMC support staff for the blinded sessions will include the Principal Investigator, the Evelo medical monitor, a blinded statistician, and an Evelo clinical operations representative.

After 20 patients are enrolled, the DMC will review the safety data and decide whether to open recruitment to subjects aged >65 years.

The DMC can also recommend increasing the sample size of the study to a further 40 participants if their review of the data suggests that there would be substantial added benefit to the likelihood of meeting the trial objectives.

Interim results of the analysis, beyond the recommendations to continue 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.

Full details of the disposition and responsibilities of the DMC together with the frequency of reviews will be provided in the DMC charter.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants or changes considered non-substantial by the Sponsor.
- The investigator is responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.
- The investigator or designee will obtain electronic or paper written informed consent from each participant or the participant's legally acceptable representative before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the ethics

committee. The investigator will retain the original electronic or paper copy of each participant signed informed consent form.

- Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial, will be communicated to the participant and/or their legally accepted representative as soon as possible.
- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent and assent, where applicable, was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.
- Participants must be reconsented to the most current version of the informed consent form(s) during their participation in the study.
- A copy of the informed consent form(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

The only committee that will be set-up for this study is an independent Data Monitoring Committee (DMC). The DMC will consist of at least; a chairperson, 2 physicians independent of the study team, and an unblinded statistician. The DMC support staff for the blinded sessions will include the Principal Investigator, the Evelo medical monitor, a blinded statistician, and an Evelo clinical operations representative.

After 20 patients are enrolled, the DMC will review the safety data and decide whether to open recruitment to subjects aged >65 years.

Full details of the disposition and responsibilities of the DMC together with the frequency of reviews will be provided in the DMC charter.

10.1.6. Dissemination of Clinical Study Data

The Sponsor and the investigator are committed to publish data in accordance with applicable regulations and transparency guidance. Results will be published within 2 years of finalization of the CSR and will only be delayed to the second year if earlier publication may be detrimental to the financial position or intellectual property rights of the Sponsor.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF (eCRF) unless transmitted to the Sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at each investigator site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data agreement form for each site.

10.1.9. Study and Site Closure

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study

site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate enrolment of participants by the investigator
- Discontinuation of further study intervention development

10.1.10. Publication Policy

- Full details on the publication policy are provided in the contract between the Sponsor and the investigator. In summary: the results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor at least 30 days before submission. This allows the Sponsor to protect proprietary information, delay the publication if necessary to protect its patent rights, and to provide comments.
- The Sponsor will comply with the requirements for publication of study results as detailed in Section 10.1.6. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multisite studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Child-Bearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study.

Contraception Guidance:

Male participants with a female partner of child-bearing potential must either

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom during each episode of penile penetration during their participation in the study and for 90 days after the last dose of study drug.
- Have a confirmed vasectomy.

In addition, all male participants must refrain from donating sperm for the duration of the study and for at least 90 days following their final visit.

Female participants

Female participants of child-bearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9.

Table 9: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomised partner A vasectomised partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, a highly effective method of contraception plus condoms should be utilised during their participation in the study up to and including at least 1 complete menstrual cycle (≥ 30 days) for women and 90 days for men post last dose.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative pregnancy test.
- Pregnancy testing is required at screening.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies to all male participants who receive EDP1815.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related- SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- Due to the nature of the patient population and disease only SAEs and CTCAE grade 3 and grade 4 AEs will be documented in the CRF. Grade 1 and 2 AEs should be documented in the medical notes. However, adverse events relating to nausea, vomiting, diarrhoea, bloating and abdominal pain of any grade will be recorded and assessed as an adverse event.
- When an AE of severe intensity / SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities or their health. The intensity of the AE will be rated in accordance with the CTCAE version 5.0.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each reported AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE of severe intensity, or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow--up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the Sponsor

Any AE that meets SAE criteria must be reported to [redacted] Clinical Safety immediately (i.e. within 24 hours) after the time site personnel first learn about the event.

To report the SAE, the investigator must record the SAE on the AE eCRF in the EDC system as well as any relevant eCRF forms (e.g. drug dispensation eCRF, applicable laboratory eCRF). When the AE eCRF is completed, [redacted] Safety personnel will be notified electronically automatically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, please complete the back-up paper SAE Form and send it by e-mail to [redacted] Safety at [redacted] or call the [redacted] SAE hotline and fax the completed paper SAE Form to [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: [redacted] Clinical Safety

Mode of Contact	[redacted] SAE Reporting Line – [redacted]
Telephone	[redacted]
Fax	
e-mail	

10.4. Appendix 4: Summary of Protocol Amendments

Protocol Amendment 1, Protocol version 2.0, dated 24 June 2020

The study protocol has been amended to address comments raised by the FDA and IRB following their review of the original protocol, Protocol version 1.0, dated 06 May 2020. Major changes are summarised below.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Section 1.1

- Secondary endpoints were revised to include data at Day 21 and Day 42, and not Day 28.
- Exploratory objective and endpoints revised to include detection of EDP1815 in stool and/or in blood.
- Participant Trial Duration revised to 42 days post first dose.

Section 1.2

- Schema revised to indicate longer study duration to 42 days post first dose.

Section 1.3

- Schedule of Assessments revised to indicate longer study duration to 42 days post first dose, including assessments to be performed.
- The following assessments were added to the Schedule of Assessments:
    - Smoking status.
    - Significant Covid-19 Comorbidities.
    - Plasma PCR for EDP1815.
- The timing of the following assessment was changed:
    - Faecal sample for microbiome analysis
- Schedule of Assessments footnotes revised:
    - to add surveillance for potential GI symptoms.
    - to clarify assessments to be collected in the event of remaining in hospital longer than 14 days.
    - to clarify faecal sample collection.
    - to add information on smoking status.

Section 3

- Secondary endpoints were revised to include data at Day 21 and Day 42, and not day 28.

- Exploratory objective and endpoints revised to include detection of EDP1815 in stool and/or in blood.
- Participant Trial Duration revised to 42 days post first dose.

Section 4.4

- End of Study Definition revised to indicate longer study duration to 42 days post first dose.

Section 5.1

- Inclusion criteria revised/clarified:
  - to include participants receiving any form of supplementary oxygen therapy at baseline.
  - to include participants with confirmed COVID-19 viral infection by RTPCR at screening.
  - Age:
    - 18-75 years old., OR
    - 15 - 17 year-olds can be included after DMC approval (see section 10.1.5), OR
    - .>75 year-olds can be included after DMC approval (see section 10.1.5).
- Removed the following inclusion criterion:
  - Are considered an appropriate subject for intervention with EDP1815 in the opinion of the investigator.

Section 5.2

- Exclusion criteria revised/clarified;
  - to exclude participants with a diagnosed primary immunodeficiency.
  - to allow the use of laboratory results reported in the last 48 hours.
  - to exclude participants with GI signs or symptoms equivalent to CTCAE v5.0, gastrointestinal disorders, grade 3 or 4 event.
  - clarified the exclusion if participants are currently participating in an interventional study.

Section 6.1

- Clarified the minimum time allowed between the twice daily doses.

Section 6.6.1

- Amended the study stopping criteria:
  - One (or more) subjects on treatment with EDP1815 has symptoms of a clinically significant bacteremia and has a positive blood culture for the EDP1815 strain of

P. histicola.(Note: the study will be paused and dosing held in all participants while identifying the specific strain of P.histicola).

Section 7.2

- Revised to include sub section 7.2.1, Temporary Cessation of Dosing in an Individual Participant and section 7.2.2, Permanent Cessation of Dosing in an Individual Participant.

Section 8.1.3

- Clarified that the dairy should be completed until the participant is asymptomatic and off oxygen for at least 48 hours or to Day 42, whichever is sooner.

Section 8.1.4

- Revised in line with longer duration of study.

Section 8.2

- Revised to include sub section 8.2.3: Strain-specific PCR for EDP1815 and section 8.2.4: Gastrointestinal Assessment.

Section 8.3

- Revised to include reference to the CTCAE grading of adverse events, including addition of wording related to collection of adverse events relating to GI adverse events.

Section 8.6

- Addition of section on Additional Baseline Information.

Section 9.4.1.1

- Addition of wording on handling newly approved medication for COVID-19 becoming a potential covariate.

Section 9.4.1.2

- Revised days in relation to the longer study duration.
- Addition of wording on handling newly approved medication for COVID-19 becoming a potential covariate.

Section 9.4.1.3

- Addition of wording on handling newly approved medication for COVID-19 becoming a potential covariate.

Section 9.5

- Revised wording to indicate the DMC involvement prior to enrolling participants aged 15-17, as well as participants aged >75 years.

Section 10.1.5

- Revised wording to clarify DMC membership and to indicate the DMC involvement prior to enrolling participants aged 15-17, as well as participants aged >75 years.

Section 10.3

- Revised classification of adverse events to use the CTCAE classification.
- Revised the SAE reporting wording with inclusion of contact telephone numbers and email address.

Protocol Amendment 2, Protocol version 3.0, dated 09 July 2020

The study protocol has been amended to address comments raised by the FDA following their review of Protocol version 2.0, dated 24 June 2020. Major changes are summarised below.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Section 1.3

- An HIV assessment at the time of screening was added to the Schedule of activities
- An 'x' was added to the screening visit for concomitant medications and adverse event checks.

Section 5.1

- The inclusion criteria were amended to an age range of 18-65 years old. Inclusion of subjects aged 15-17 years was removed; and text related to possible inclusion of subjects older than 65 after DMC review was added.

Section 5.2

- The exclusion criteria were amended to add individuals with HIV/AIDS.

Section 7.2.2

- Permanent cessation of dosing in an individual participant criteria were updated to include a diagnosis of HIV/AIDS.

Section 8.4

- Additional antibiotic options added in case of penicillin allergy.

Sections 9.5 and 10.1.5

- An update was made to the DMC review criteria, to include assessment after 20 subjects are enrolled for consideration of enrolling patients older than 65, and removal of consideration of enrolling adolescents aged 15-17.

Protocol Amendment 3, Protocol version 4.0, dated 03 August 2020

The study protocol has been amended to include biobanking language and to clarify the collection of the microbiome sample and what the site should do in the event of a positive blood culture during the study. Major changes are summarised below.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Page 13, Section Number of Centers

- Language changed to accommodate increase in number of potential sites to be utilized in the study to meet enrolment goals.

Section 1.3

- Biomarker sample added to the Schedule of Activities (SOA)
- SOA Footnote #7: language added to clarify when the Microbiome Sample should be collected.

Section 8.2.3

- Language added to clarify what should be done at the site level should there be a participant showing signs of bacteremia with a positive blood culture.

Section 8.5.4

- Language added to clarify when the Microbiome Sample should be collected.

Section 8.5.5

- New section added to describe the Biobanking samples, how long it will be retained, how the samples will be used, and who has access to these samples.

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