Clinical Study Protocol

EudraCT Number: 2020-002213-18

A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFECTS OF EDP-938 IN HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS WITH ACUTE RESPIRATORY SYNCYTIAL VIRUS INFECTION OF THE UPPER RESPIRATORY TRACT

Protocol Number: EDP 938-103

IND number	135874
[redacted]	
Date:	07 March 2023
Study Sponsor:	Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472
Sponsor Medical Officer:	[redacted]

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Effects of EDP-938 in Hematopoietic Cell Transplant Recipients With Acute Respiratory Syncytial Virus Infection of the Upper Respiratory Tract

Protocol Number EDP 938-103

Protocol Date 07 March 2023, [redacted]

Protocol accepted and approved by:

[redacted]

Enanta Pharmaceuticals, Inc.
500 Arsenal St.
Watertown, MA 02472

[redacted]

Signature Date

Protocol Approval – Lead Statistician

Study Title	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Effects of EDP-938 in Hematopoietic Cell Transplant Recipients With Acute Respiratory Syncytial Virus Infection of the Upper Respiratory Tract
Protocol Number	EDP 938-103
Protocol Date [redacted]	07 March 2023, [redacted]

Protocol accepted and approved by:

[redacted]

Enanta Pharmaceuticals, Inc.
500 Arsenal St.
Watertown, MA 02472

[redacted]

Signature Date

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines.

Principal Investigator:

Signature: _____ Date: _____

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LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{0-24}	area under the curve from 0 to 24 hours
AUC_{0-inf}	area under the curve from 0 to infinity
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CNI	calcineurin inhibitor
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
EC	ethics committee
EC_{50}	half-maximal effective concentration
EC_{90}	90% maximal effective concentration
ECG	Electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EOS	End-of-Study
EOT	End-of-Treatment
FDA	United States Food and Drug Administration
FIH	first-in-human
[redacted]	
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCT	hematopoietic cell transplant
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IRB	institutional review board

IRT	interactive response technology
ITT	intent-to-treat
IWRS	Interactive Web Response System
LD	loading dose
LLN	lower limit of normal
LRTC	lower respiratory tract complication
LRTI	lower respiratory tract infection
MAARI	medically attended acute respiratory infection
MDRD	Modification of Diet in Renal Disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic(s)
PND	postnatal day
QD	once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RAV	resistance-associated variant
RSV	respiratory syncytial virus
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	safety (for the analysis population)
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Assessments
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	time to elimination half-life
TEAE	treatment-emergent adverse event
TSS	total symptom score
ULN	upper limit of normal
URTI	upper respiratory tract infection
WHO	World Health Organization

PROTOCOL SUMMARY

Name of Sponsor/Company: Enanta Pharmaceuticals, Inc.
Name of Investigational Product: EDP-938
Study Title: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Effects of EDP-938 in Hematopoietic Cell Transplant Recipients With Acute Respiratory Syncytial Virus Infection of the Upper Respiratory Tract
Protocol Number: EDP 938-103
Phase of Development: 2b
Study Centers: This will be a multicenter global study and may include sites in North America, South America, Europe, and Asia-Pacific
Number of Subjects Planned: Approximately 200 subjects will be enrolled.
Planned Study Population: Male and female subjects aged between 16 and 75 years, inclusive, who have had a hematopoietic cell transplant (HCT) and have an acute respiratory syncytial virus (RSV) infection of the upper respiratory tract (URTI).
Investigational Product, Dosage, and Mode of Administration: EDP-938 will be supplied as [redacted] tablets for oral administration. The total dose administered (once daily [QD]) will be either: • [redacted] EDP-938 or placebo (for subjects not taking azole antifungals that are moderate or strong cytochrome P450 [CYP] CYP3A4 inhibitors) • [redacted] EDP-938 or placebo (for subjects taking azole antifungals that are moderate CYP3A4 inhibitors) • [redacted] EDP-938 or placebo (for subjects taking azole antifungals that are strong CYP3A4 inhibitors)
Duration of Treatment: 21 days
Study Objectives: **Primary Objective** • To evaluate the effect of EDP-938 on the development of lower respiratory tract complication (LRTC) in HCT subjects with an acute RSV URTI

Secondary Objectives

- To evaluate the effect of EDP-938 on RSV viral load as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) of nasopharyngeal swab samples
- To evaluate the effect of EDP-938 on progression to respiratory failure or all-cause mortality
- To evaluate the progression of RSV infection using the InFLUenza Patient-Reported Outcome (FLU-PRO) questionnaire
- To evaluate the pharmacokinetics (PK) of EDP-938 [redacted]
- To evaluate the safety and tolerability of EDP-938

[redacted]

Criteria for Evaluation:

Primary Endpoint

- Incidence of LRTC through Day 28 defined as at least one of the following as determined by the Endpoint Adjudication Committee
  - Lower respiratory tract infection (LRTI) by RSV
  - LRTI as secondary bacterial pneumonia
  - LRTI by unusual pathogens
  - LRTC of unknown etiology

Secondary Endpoints

- Change in RSV RNA viral load from Baseline through Day 49 in nasopharyngeal swab samples by RT-qPCR
- Incidence of subjects who develop respiratory failure of any cause requiring mechanical ventilation (invasive or noninvasive) or all-cause mortality through Day 49
- Incidence of subjects with RSV RNA viral load below the limit of detection in subjects receiving EDP-938 through Day 49
- Time to RSV RNA viral load below the limit of detection
- FLU-PRO questionnaire scores through Day 49
- Plasma PK concentrations of EDP-938 and [redacted]
- Safety endpoints include, but are not limited to, adverse events (AEs), serious adverse events (SAEs), vital sign measurements, pulse oximetry measurements, and clinical laboratory test results (including chemistry, hematology, and urinalysis)

[redacted]

Study Design:

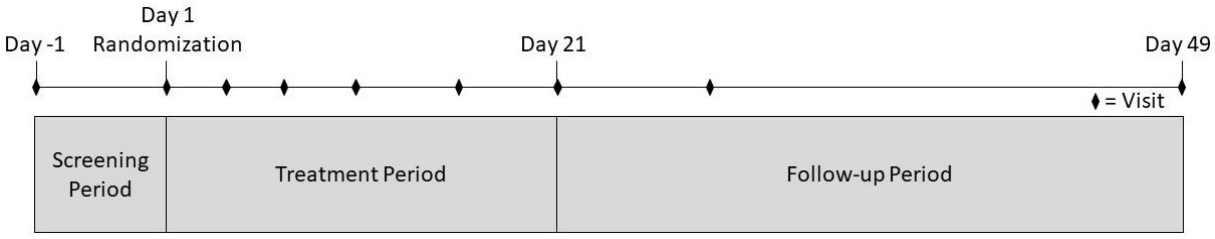
This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of EDP-938 in HCT recipients with acute RSV infection and symptoms of URTI.

For each subject, the duration of study participation will be approximately 7 weeks and will consist of Screening, Treatment, and Follow-up Periods, as follows:

Study Period	Duration
Screening	1 day
Treatment	21 days
Follow-up	28 days
Approximate total duration of participation	Up to 50 days

The design of the study is shown in Figure 1. All study procedures are detailed in the Schedule of Assessments (SoA; Appendix 1).

Figure 1: Study Design



Screening Period (Day -1 to Day 1): At Screening (Day -1 to Day 1), subjects must review and sign the informed consent form (ICF) before completing any study-specific procedures. After signing the ICF, screening assessments will be performed as soon as possible; the subject will be randomized and administered the first dose of study drug within 24 hours of signing the ICF. Subjects will be considered enrolled at the time of randomization. Some procedures performed as part of standard of care before Screening may be used in determining study eligibility, such as RSV diagnostic test or safety laboratory tests performed up to 3 days before informed consent and chest imaging performed up to 2 days before informed consent. As required, screening safety laboratory test samples will be sent to the local laboratory for expedited testing.

Treatment Period (Day 1 to 21): Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized 2:1 to receive [redacted] EDP-938 or placebo administered orally for 21 days (see Section 4.1) . Subject randomization will be stratified by ribavirin treatment (presence or absence) and absolute lymphocyte count (ALC, <200 or ≥200 cells/µL). The treatment duration is 21 days, during which 6 study visits will be performed.

Randomized subjects will be assigned to an electronic device [redacted].

Following randomization on Day 1, subjects must complete baseline assessments before receiving the first dose of EDP-938 or placebo. Although prior local safety laboratory test results may have been used to determine eligibility, separate safety laboratory samples must be collected and sent to the central laboratory for baseline assessment. If Screening and randomization/first dose occur on the same day, then screening assessments for vital signs and pulse oximetry will be used as baseline values. If Screening and randomization/first dose occur on different calendar days within a 24-hour period, vital signs and pulse oximetry will be performed again on Day 1 (predose).

Subjects will receive the first dose of study drug while at the study site. After the first dose, subjects will be instructed to take EDP-938 or placebo QD at approximately the same time every day (±1 hour) on each of the 20 subsequent days. The subject will also receive instructions on the appropriate storage and transport of study drug. At each study visit, subjects should bring their study drug with them as part of their study site visit for drug accountability and for dosing of study drug. If a subject is unable to attend a study site visit, a home visit by study site personnel may be arranged, if feasible.

Safety evaluations will include assessment of clinical laboratory findings, physical examination findings (as applicable), vital sign measurements, pulse oximetry measurements, AEs, concomitant medications, hospitalizations, ICU admissions or utilization of ICU care for >24 hours, standard of care test results, and supplemental oxygen use (≥2 L/min for >24 hours). Except for Screening and Day 1, assessments may be completed at the study site or by study site personnel via a home visit, if feasible.

Follow-up Period (Day 22 to 49): Follow-up visits will occur 1 and 4 (End-of-Study [EOS] visit) weeks after the last dose of study drug for all subjects including those who discontinue treatment early (ie, before completing 21 days of dosing). Visit assessments may be completed at the study site or by study site personnel via a home visit, if feasible.

All study assessments during the Follow-up Period are detailed in the SoA (Appendix 1).

Early Termination: Subjects who discontinue treatment before completing 21 days of dosing should return to the study site within 24 hours from the last dose of study treatment to complete an End-of-Treatment (EOT) visit. They should then return to the clinic for the Follow-up Visit 1 (EOT +1 week) and the EOS visit 4 weeks following the last dose of study drug.

Subjects who discontinue the study before Day 28 should return to the site within 48 hours to complete Follow-up Visit 1 (EOT +1 week) procedures. Subjects who discontinue the study early between Day 28 and Day 49 should return to the study site within 48 hours to complete the EOS procedures.

Subject Eligibility Criteria: Males and females aged between 16 and 75 years, inclusive, who have received an autologous HCT (within 6 months of signing ICF) and have an ALC <300 cells/ µL OR received an allogeneic HCT (any time) and have an ALC <500 cells/µL,

and are diagnosed with RSV with new onset of respiratory symptom(s). This includes subjects who have oxygen saturation ≥95% on room air and body mass index (BMI) up to 40 kg/m^2.

Subjects with new abnormalities consistent with LRTI on chest imaging, hospital admission for a lower respiratory tract disease of any cause, positive for other respiratory viruses or having clinically significant viremia, bacteremia, or fungemia will be excluded from the study. Also excluded are subjects with known heart, liver, or kidney disease, or any historical or current medical condition that, in the opinion of the Investigator, deems the subject unsuitable for the study.

Statistical Methods: Detailed statistical analysis will be outlined in the statistical analysis plan, which will be developed and finalized before database lock.

Sample Size Considerations: Assuming an LRTC rate of 30% for placebo, then a 20% reduction with 90% power and a two-sided alpha at 0.05 using a unpooled z-test, with a ratio of 2:1 would require approximately 160 subjects. Assuming a 15% dropout rate a total of 190 subjects will be randomized.

Statistical Analysis: The following analysis populations are planned:

Intent-to-Treat (ITT) Population: All subjects who receive at least one dose of study drug. Subjects will be analyzed as treated. The ITT Population is designated as the primary efficacy population.

Per Protocol Population: All subjects who are randomized and receive all planned doses of study drug and do not have major protocol deviations that may unduly influence outcome. Subjects will be analyzed in the treatment group that corresponds to the study drug received during the study.

Safety (SAF) Population: All subjects who receive at least one dose of study drug. Subjects will be analyzed in the treatment group that corresponds to the study drug received during the study.

Pharmacokinetic (PK) Population: All subjects receiving active study drug and having any measurable plasma concentration of study drug at any timepoint.

Subject Disposition and Demographic Data: The number of subjects screened, randomized, and in the SAF and PK Populations will be summarized using frequencies and percentages. Subject demographics will be summarized by treatment group for all subjects in the SAF Population. Appropriate baseline characteristics will be included in addition to demographic characteristics.

Efficacy Analyses: The proportion of LRTC between EDP-938 and placebo will be compared using a Cochran Mantel-Haenszel test with ribavirin use (presence or absence) and ALC (<200 or ≥200 cells/μL) as stratification factors. The primary analysis will be using the ITT Population based on the results of the Endpoint Adjudication Committee. A Fisher's exact test will be used to compare groups within each strata. The treatment difference in RSV RNA viral load area under the curve (AUC) will be analyzed using an analysis of covariance (ANCOVA) model with Baseline, treatment, and stratification factors in the model. FLU-PRO and TSS AUC overall score and individual components will be analyzed using an ANCOVA model with Baseline, treatment, and stratification factors in the model.

Safety Analyses: Statistical methods for the safety analyses will be primarily descriptive in nature. Safety data, including AEs, SAEs, vital sign measurements, concomitant medications, and laboratory values, will be summarized separately by treatment group. Change from Baseline will be included in summary tables for vital sign measurements and laboratory parameters. Shift tables will also be generated by laboratory analyte. All laboratory data will be included in the data listings, and all test values outside the normal range will be flagged.

Pharmacokinetic Analyses: Summary of plasma concentration data will be descriptive in nature. Mean plasma concentration-time figures may be created for EDP-938 [redacted], as allowed by the data.

Subgroup and Covariate Analyses: Subgroup analyses will be performed on the primary and secondary endpoints, primarily. A logistic regression model will be planned when categorical endpoints are analyzed. For continuous endpoints, an ANCOVA model will be planned with treatment group and stratification factors as fixed effects in the model, and with subgroup and subgroup-by-treatment interaction. Various study populations may be used. Forest plots will be provided to visually describe the association.

[redacted]

Data Monitoring Committee: The study data will be reviewed by a Data Monitoring Committee (DMC) throughout the study. The DMC will be headed by a DMC Chair and will include one or more physicians with expertise in transplant medicine. The DMC will consist of experts independent from the Sponsor. The DMC procedures will be governed by a separate DMC charter.

1. INTRODUCTION

1.1 Overview

EDP-938 is a novel orally administered nonfusion replication inhibitor of respiratory syncytial virus (RSV) that is being developed as a potential treatment for RSV infection. This Phase 2b study, EDP-938-103, is a randomized, double-blind, placebo-controlled, multicenter study designed to assess the efficacy, safety, and tolerability of EDP-938 compared with placebo in adult hematopoietic cell transplant (HCT) recipients with an acute RSV infection and symptoms of an upper respiratory tract infection (URTI).

1.2 Background

Respiratory syncytial virus is the leading cause of lower respiratory tract infection (LRTI) and presents a significant health challenge in small children, elderly, and immunocompromised patients, such as those who have received HCT (*Falsey et al., 2005; Hall et al., 2009; Shook and Lin, 2017; Khawaja and Chemaly, 2019*). Respiratory syncytial virus is one of the most common community respiratory viruses that may lead to death in HCT recipients, second only to influenza (*Khawaja and Chemaly, 2019*). The reported incidence of RSV infection in HCT recipients range from 5% to 49% depending on differing diagnostic methods, with 30% to 60% of RSV infections in HCT recipients causing LRTIs (*Khawaja and Chemaly, 2019*). The mortality rate of HCT recipients with LRTI ranges from 21% to 83% (*Khawaja and Chemaly, 2019*).

Currently, there is no vaccine or highly effective treatment available for RSV. At present, there are only two agents approved for the prevention or treatment of RSV infection, a prophylactic agent (palivizumab) and a therapeutic agent (aerosolized ribavirin), each having indications for use that are limited to the pediatric population. Aerosolized ribavirin, alone or in combination with palivizumab, has been used as a treatment of RSV in HCT recipients and retrospective studies show that the treatment may have some efficacy for preventing RSV-associated morbidity or mortality in this population (*Shah and Chemaly, 2011*). However, ribavirin-based treatments are controversial as aerosolized ribavirin is expensive, requires hospitalization, is considered to be potentially hazardous to health care workers, and does not have proven efficacy from randomized studies in HCT recipients (*Boeckh et al., 2007*).

EDP-938 is active against all RSV-A and RSV-B laboratory strains and clinical isolates tested *in vitro*. EDP-938 appears to inhibit RSV replication by modulating viral nucleoprotein, based on *in vitro* resistance studies, although the exact mechanism of action is under further investigation. EDP-938 has demonstrated *in vivo* efficacy in the RSV-infected African green monkey model.

To address the unmet medical need for more effective antiviral therapies for RSV and based on the promising early nonclinical safety and pharmacological profile, Enanta Pharmaceuticals, Inc. is investigating EDP-938 in humans as a potential treatment for RSV infection.

1.3 Nonclinical Studies

A summary of nonclinical studies is provided below. Additional information can be found in the Investigator's Brochure.

1.3.1 Nonclinical Pharmacology

EDP-938 is a novel nonfusion replication inhibitor of RSV. It is active *in vitro* against RSV-A and RSV-B laboratory strains and all clinical isolates tested. In primary human bronchial epithelial cells, EDP-938 has half-maximal effective concentration (EC_{50}) values of 21 nM against RSV-A Long strain, 23 nM against RSV-A M37 strain, and 64 nM against RSV-B Washington strain. It is highly specific for RSV with no cross activity against other RNA or DNA viruses and no significant cytotoxicity. EDP--938 inhibits RSV at a post entry replication step of the viral life cycle as confirmed by the time-of-addition study, and the activity appears to be mediated by viral nucleoprotein. An *in vitro* resistance study suggests that EDP-938 presents a higher barrier to resistance compared with viral fusion or L polymerase inhibitor with no cross resistance observed. The combination of EDP-938 with other classes of RSV inhibitors led to additive synergist antiviral effects *in vitro*. The *in vivo* efficacy of EDP-938- was demonstrated in the RSV infected African green monkey model, with >4 log_{10} viral load reduction after 6 days of treatment.

1.3.2 Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of EDP-938 following single intravenous and oral doses were determined in mice, rats, dogs, and monkeys. Oral bioavailability of EDP-938 at a single oral dose [redacted] was [redacted] in dogs, [redacted] in mice, [redacted] in rats, and [redacted] in monkeys. An evaluation of membrane permeability of EDP-938 performed using Caco2 cells showed [redacted] *in vitro* permeability [redacted]. Based on the outcome of these absorption studies, EDP-938 is projected to have a good oral absorption in humans.

[redacted]

[redacted]

EDP-938 showed no apparent inhibition of [redacted] in human liver microsomes (halfmaximal inhibitory concentration [IC_{50}] >10 µM). Preclinical studies also indicate that EDP-938 is a [redacted] substrate.

1.3.3 Safety Pharmacology

No safety pharmacology concerns have been identified following EDP-938 administration. There were no alerts from *in vivo* cardiovascular, neurologic, or respiratory safety pharmacology studies, and cell-based functional assays yielded IC_{50} values >20 µM for the NK1 and NK2 receptors. No secondary effects of toxicological concern were observed in the 28day repeat dose studies in [redacted]

1.3.4 Nonclinical Toxicology

[redacted]

1.4 Clinical Studies

Five Phase 1 clinical studies have been conducted:

- EDP-938-001: first-in-human (FIH) study in healthy adult subjects (n=68 treated with EDP-938),
- EDP 938-002 and EDP 938-003: drug-drug interaction (DDI) studies in healthy adult subjects (n=48 and n=72 treated with EDP-938 for these two studies, respectively),
- EDP 938-004: bioavailability study in healthy adult subjects (n=18 treated with EDP-938),
- EDP 938-007: DDI study in healthy adult subjects (n= 24 treated with EDP-938), and
- EDP 938-101: Phase 2a study in healthy adult subjects inoculated with RSV A Memphis 37b (virus challenge model) (n=118 treated with EDP-938).

Results of these studies are summarized below; refer to the Investigator's Brochure for further details. EDP-938 was administered as a suspension in all studies; it was also administered as a tablet formulation in Study EDP 938-004 (relative bioavailability study).

[redacted]

Study EDP 938-101 was a Phase 2a study designed to assess the efficacy, safety, and PK of multiple doses of orally administered EDP-938 in the RSV healthy subject challenge model. The primary objective of this two-part study was to evaluate the antiviral activity of EDP-938 compared with placebo in healthy adult subjects inoculated with RSV-A Memphis 37b.

In Part 1, 115 subjects were randomized to one of three treatment groups for 5 days of oral suspension dosing as follows: EDP-938 [redacted] for a total of 10 doses, n=38); EDP-938 [redacted], for a total of 10 doses, n=39); placebo (n=38) every 12 hours. Both EDP-938 treatment regimens demonstrated robustly lowered RSV RNA levels measured as AUCs compared with placebo ($p<0.001$), with no significant difference between the [redacted] regimens. Additionally, both EDP-938 regimens demonstrated robustly lower 10-point RSV total symptom score (TSS) AUCs compared with placebo ($p<0.001$), with no significant difference between the QD and BID regimens. The number of subjects with any AE was similar among EDP-938 and placebo recipients, ranging [redacted]. Only the treatment-emergent adverse events (TEAEs) of headache, diarrhea, dizziness, nausea, and URTI each occurred in at least 5 (4.4%) of the 114 subjects. Comparing the frequencies of these events in the EDP-938 [redacted] and placebo treatment groups, only headache ([redacted]), dizziness ([redacted]), and diarrhea [redacted]), respectively, were more common in one or both EDP-938 treatment groups compared with placebo. All TEAEs in EDP-938 recipients were mild except for a single event of moderate dyspepsia that was considered unrelated and resolved in follow-up.

In Part 2 of the study, 63 subjects were randomized into one of three treatment groups for 5 days of EDP-938 oral suspension with doses being informed by Part 1 data and dosing as follows: EDP-938 [redacted] for a total of 10 doses, n=21); EDP-938 [redacted] for a total of 10 doses, n=21); placebo every 12 hours (n=21). Both EDP-938 treatment regimens demonstrated robustly lower RSV RNA AUCs compared with placebo ($p<0.001$), with no significant difference between the [redacted] regimens. Additionally, both EDP-938 regimens demonstrated robustly lower 10-point RSV TSS AUCs compared with placebo ($p=0.001$ [QD regimen] and $p=0.003$ [BID regimen]), with no significant difference between the QD and BID regimens. The number of subjects with any AE was similar among EDP-938 and placebo recipients, ranging [redacted]. Only the TEAEs of nausea, dizziness, headache, and URTI occurred in at least 3 (4.8%) of the 63 subjects in Part 2. Comparing the frequencies of these events in the EDP-938 [redacted] and placebo treatment groups, only the frequencies of nausea ([redacted]), dizziness ([redacted]) and URTI ([redacted]), respectively, were more common in either EDP-938 arm compared with placebo. All TEAEs in EDP-938 recipients were mild except for a single event of vessel puncture site paraesthesia was considered moderate. All events resolved in follow-up. Therefore, both EDP-938 regimens were well tolerated with safety profiles that were comparable with placebo.

The systemic EDP-938 exposures were generally comparable to those observed in the FIH study at similar doses. There was no correlation between efficacy endpoints (viral load AUC and TSS) and exposure to EDP-938 (AUC).

In this Phase 2a study of healthy adults inoculated with RSV, all four EDP-938 regimens were well tolerated and demonstrated robust reductions in both RSV RNA levels and TSSs which were superior to placebo, with favorable PK profiles and safety profiles that were comparable with placebo.

1.5 Potential Risks and Benefits

EDP-938 is highly specific for RSV. *In vitro*, EDP-938 had no cross activity against other RNA or DNA viruses and no significant cytotoxicity. No safety pharmacology concerns have been identified following EDP-938 administration, and no secondary effects of toxicological concern were observed in the 28-day repeat-dose studies in mice, rats, or monkeys.

[redacted]

It is possible that exposure to EDP-938 may lead to RSV resistance to EDP-938 as may occur with any study of an antiviral. However, the genetic barrier of EDP-938 to development of resistance is considered to be high and the risk of resistance is considered to be low.

Additionally, to mitigate any risk to subjects, the following will be undertaken:

- A Data Monitoring Committee (DMC) will ensure the continuing safety of subjects enrolled to the study through scheduled and as needed evaluations of safety data. The DMC will include one or more physicians with expertise in transplant medicine.
- The EDP-938 dose selected for this study ([redacted] administered as a tablet formulation for subjects not taking azole antifungals that are moderate or strong CYP3A4 inhibitors, [redacted] for subjects taking azole antifungals that are moderate CYP3A4 inhibitors, and [redacted] for subjects taking azole antifungals that are strong CYP3A4 inhibitors; QD for 21 days) is expected to provide exposures within the range observed in the Phase 2a EDP 938-101 study. These systemic EDP---938 exposures are expected to be generally safe and efficacious. See Section 4.2.2 for more information about the rationale for the EDP-938 dose.

This is the first study that will evaluate the safety, PK, and efficacy of EDP-938 in HCT recipients, and consequently the efficacy and safety of EDP-938 in this population are not

known. Because EDP-938 has previously demonstrated clinical efficacy in the adult healthy subjects RSV challenge study, it is possible that subjects in the present study may have a more rapid clearance of RSV infection and a reduction in the symptoms associated with RSV infection compared with those who do not receive EDP-938. However, it is possible that no such effect will be observed. Additionally, subjects enrolled in the placebo treatment group will not be expected to derive any such benefit. Consequently, subjects enrolled to the study may experience no benefit with regard to impacting the rate of clearance of RSV or resolution of symptoms associated with RSV infection.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To evaluate the effect of EDP-938 on the development of lower respiratory tract complication (LRTC) in HCT subjects with an acute RSV infection of the upper respiratory tract

2.1.2 Secondary Objectives

- To evaluate the effect of EDP-938 on RSV viral load as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) of nasopharyngeal swab samples
- To evaluate the effect of EDP-938 on progression to respiratory failure or all-cause mortality
- To evaluate the progression of RSV infection using the InFLUenza Patient-Reported Outcome (FLU-PRO) questionnaire
- To evaluate the PK of EDP-938 [redacted]
- To evaluate the safety and tolerability of EDP-938

2.1.3 [redacted]

[redacted]

2.2 Endpoints

2.2.1 Primary Endpoint

- Incidence of LRTC through Day 28 defined as at least one of the following as determined by the Endpoint Adjudication Committee
  - LRTI by RSV
  - LRTI as secondary bacterial pneumonia
  - LRTI by unusual pathogens
  - LRTC of unknown etiology

2.2.2 Secondary Endpoints

- Change in RSV RNA viral load from Baseline through Day 49 in nasopharyngeal swab samples by RT-qPCR
- Incidence of subjects who develop respiratory failure of any cause requiring mechanical ventilation (invasive or noninvasive) or all-cause mortality through Day 49
- Incidence of subjects with RSV RNA viral load below the limit of detection in subjects receiving EDP-938 through Day 49
- Time to RSV RNA viral load below the limit of detection

[redacted]

- Plasma PK concentrations of EDP-938 and [redacted]
- Safety endpoints include, but are not limited to, AEs, serious adverse events (SAEs), vital sign measurements, pulse oximetry measurements, and clinical laboratory test results (including chemistry, hematology, and urinalysis)

2.2.3 [redacted]

[redacted]

[redacted]

3. SELECTION OF SUBJECTS

A total of approximately 200 subjects are planned to be enrolled into this study.

3.1 Subject Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled into this study:

1. An ICF signed and dated by the subject.
2. Male or female individuals aged between 16 and 75 years, inclusive.
3. Received an autologous HCT (within 6 months of signing ICF) or an allogeneic HCT (any time) using any conditioning regimen
4. Absolute lymphocyte count (ALC) <500 cells/ µL in allogeneic HCT recipients. Absolute lymphocyte count (ALC) <300 cells/ µL in autologous HCT recipients.
5. Laboratory confirmed RSV diagnosis from a respiratory sample within 3 days before signing the ICF. The RSV diagnosis can be determined by any validated laboratory method.
6. New onset of at least one of the following respiratory symptoms within 3 days before signing the ICF: nasopharyngeal discharge, nasopharyngeal congestion, sneezing, sinus congestion, sore throat, hoarseness, earache, cough, shortness of breath, respiratory wheeze, or worsening of one of these symptoms if present chronically (associated with a previously existing diagnosis [eg, chronic rhinorrhea, chronic lung disease]) in the 3 days before signing the ICF or at Screening.
7. No evidence of new abnormalities consistent with LRTI on chest imaging (chest x-ray and/or computed tomography) performed in the 2 days before signing the ICF. If there is no chest imaging available in the 2 days before signing the ICF, chest imaging (chest x-ray and/or computed tomography) must be obtained at the Screening visit.
8. Oxygen saturation ≥95% on room air.
9. A body mass index (BMI) ≥18 kg/m^2 and ≤40 kg/m^2 and a body weight of ≥50 kg
10. Negative urine pregnancy test for women of childbearing potential as defined in inclusion criterion 11.
11. A woman of childbearing potential who is sexually active with a male must agree to use two effective methods of contraception from the date of Screening until 30 days after her last dose of study drug. Effective methods of contraception are defined as follows:

    A condom for the male partner and at least one of the following for the female subject:

    a. Intrauterine device

    b. Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive (Note: hormonal contraception must be associated with the inhibition of ovulation)

The above does not apply to 1) a female subject who has a vasectomized male partner provided that partner is the sole sexual partner of the subject and the vasectomized partner has received medical assessment of surgical success or 2) a female subject who is of nonchildbearing potential (ie, physiologically incapable of becoming pregnant) as defined below:

a. Has had a complete hysterectomy ≥3 months before Screening,
b. Has had a bilateral oophorectomy (ovariectomy),
c. Has had a bilateral tubal ligation or fallopian tube inserts, or
d. Is postmenopausal (a total cessation of menses for at least 2 years; subjects with a cessation of menses between 1 to 2 years and a follicle-stimulating hormone [FSH] level of >35 mIU/mL will also be considered to be postmenopausal.)

12. A male subject who has not had a vasectomy and is sexually active with a woman of childbearing potential must agree to use effective contraception from the date of Screening to 90 days after his last dose of study drug. Effective contraception is defined as a condom and at least one of the following for a female partner:
    a. Intrauterine device
    b. Oral, injectable, implantable, transdermal, or intravaginal contraceptive (Note: hormonal contraception must be associated with the inhibition of ovulation).
13. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after his last dose of study drug.
14. Must be willing and able to adhere to the study assessments, visit schedules, prohibitions, and restrictions, as described in this protocol.

3.2 Subject Exclusion Criteria

Subjects will not be eligible to participate in the study if they meet any of the following criteria:

1. Admitted to the hospital primarily for a lower respiratory tract disease of any cause as determined by the Investigator.
2. Known to be concurrently infected with other respiratory viruses (eg, severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or other coronavirus, influenza, parainfluenza, human rhinovirus, adenovirus, human metapneumovirus) within 7 days before signing the ICF, as determined by local testing.
3. Clinically significant viremia, bacteremia, or fungemia, or bacterial or fungal pneumonia within 2 weeks before signing the ICF that has not been adequately treated, as determined by the Investigator.
4. Pregnant or nursing female subjects.
5. History of drug and/or alcohol abuse that, in the opinion of the Investigator, may prevent adherence to protocol activities.

6. Known positive human immunodeficiency virus (HIV).
7. Heart disease: any congenital heart disease, congenital long QT syndrome, or any clinical manifestation resulting in QT interval prolongation. Chronic heart failure or ischemic heart disease or cardiac disease occurring as a consequence of antineoplastic treatment and for which treatment medications have not added or increased in the last 3 months are not exclusionary.
8. Known malignant tumor that may interfere with the aims of the study or a subject completing the study.
9. Prior or planned ileal resection or bariatric surgery. Subjects who have undergone gastric surgeries that do not affect drug absorption (eg, gastric band or gastric sleeve procedures) will be allowed to participate if they are stable for at least 1 year before signing the ICF. Gastrectomy will be allowed if stable for at least 3 years before signing the ICF.
10. Estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) <50 mL/min as measured in the 3 days before signing the ICF or at Screening.
11. Alanine aminotransferase >5 × ULN as measured in the 3 days before signing the ICF or at Screening.
12. Twelve-lead ECG demonstrating a QT interval corrected for heart rate according to Fridericia (QTcF) that is >470 milliseconds or other clinically relevant abnormalities as judged by the Investigator at Screening.
13. Use of or intention to use any medication or supplement known to be a moderate or strong inducer or inhibitor of the CYP3A4 enzyme (Section 5.8) within 14 days before signing the ICF, with the exception of prophylactic azole antifungal therapies (e.g., fluconazole, itraconazole, ketoconazole, isavuconazole, posaconazole, and voriconazole), which are permitted with EDP-938 dose adjustment (Section 4.2.2).
14. Use of nonmarketed (according to region) or investigational agents, vaccines, biological products within 30 days or five half-lives before signing the ICF, whichever is longer.
15. Use of any investigational monoclonal anti-RSV antibodies within 4 months or five half-lives of signing the ICF, whichever is longer, or use of any investigational RSV vaccines after HCT.
16. Known hypersensitivity or allergy to EDP-938 or placebo or their excipients.
17. History of or currently experiencing a medical condition or any other finding (including laboratory test results) that, in the opinion of the Investigator, might confound the results of the study, pose an additional risk in administering study drug to the subject, could prevent, limit, or confound the protocol-specified assessments, or deems the subject unsuitable for the study.

4. STUDY DESIGN

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of EDP-938 in HCT recipients with acute RSV infection and symptoms of URTI.

The study has 3 periods:

- Screening Period will occur from Day -1 to Day 1. During this period, subjects will review and sign the ICF. Subjects will undergo screening assessments. Screening should be completed as soon as possible, and the subject will be randomized and administered the first dose of study drug within 24 hours of signing the ICF. A subject will be considered enrolled at the time of randomization.
- Treatment Period will begin with the first dose of study drug on Day 1 and will conclude with the End-of-Treatment (EOT) Visit on Day 21.
- Follow-up Period for safety will begin following the last dose of study drug and will conclude at the End-of-Study (EOS) visit on Day 49, 28 days following the last dose of study drug.

The end of the study will be defined as the last visit of the last subject enrolled.

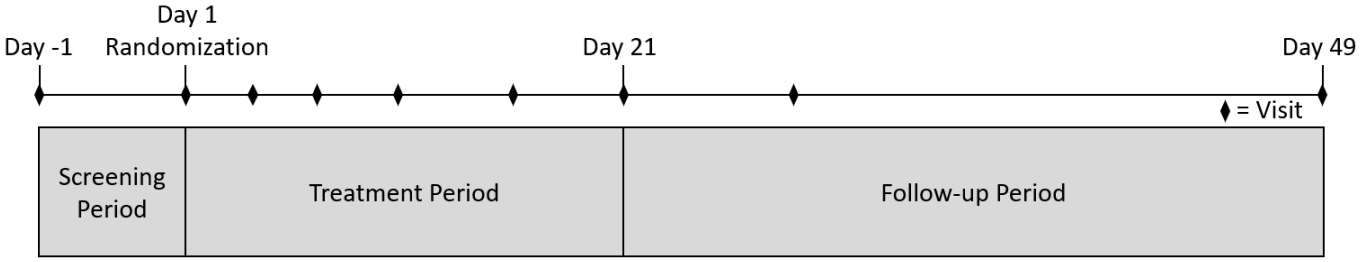
4.1 Dose and Treatment Schedule

Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomly assigned (2:1 ratio) on Day 1 to receive EDP-938 or placebo administered orally QD for a total of 21 days. The total dose administered QD will be either:

- [redacted] EDP-938 or placebo (for subjects not taking azole antifungals that are moderate or strong CYP3A4 inhibitors)
- [redacted] EDP-938 or placebo (for subjects taking azole antifungals that are moderate CYP3A4 inhibitors)
- [redacted] EDP-938 or placebo (for subjects taking azole antifungals that are strong CYP3A4 inhibitors)

Eligibility will be determined at the time of randomization. An overview of the study design is shown Figure 1. Study site visits and assessments are detailed in the Schedule of Assessments (SoA; Appendix 1).

Figure 1: Study Design



4.2 Rationale for Study Design

This proposed study will evaluate EDP-938 in adult subjects who have had an HCT and have an acute RSV infection of the upper respiratory tract. Subjects will be randomized to receive [redacted] EDP--938 or placebo in a 2:1 ratio (see Section 4.1).

4.2.1 Justification of Study Design, Endpoints, and Subject Population

Respiratory syncytial virus is one of the most common community respiratory viruses that may lead to serious infection or death in HCT recipients and which is second only to influenza. Estimates of mortality rates associated with RSV LRTI range from 21% to 83%. It is estimated that approximately 1 to 2 out of every 3 HCT patients develop LRTI (*Khawaja and Chemaly, 2019*).

Despite the significant medical need, there is no vaccine or highly effective treatment currently available for RSV. At present, there are only two agents approved for the prevention or treatment of RSV infection, a prophylactic agent (palivizumab) and a therapeutic agent (aerosolized ribavirin), each having indications for use that are limited to the pediatric population. Consequently, physicians have no safe and highly effective treatment for RSV infection. This is an issue of significant concern for patients at risk of severe RSV disease, including the elderly, those with chronic lung and/or heart diseases, immunosuppressed individuals including HCT recipients, and pediatric patients. In these populations, RSV infection may be associated with significant morbidity and even mortality.

This Phase 2b study aims to evaluate the efficacy and safety of EDP--938 in HCT recipients with acute RSV infection of the upper respiratory tract. In order to more fully investigate the efficacy of EDP--938, and noting the lack of an approved, safe and effective RSV therapy, a double-blind, placebo-controlled study design was selected, where subjects will be randomized to receive [redacted] EDP--938 or placebo in a 2:1 fashion (see Section 4.1). The study endpoints include efficacy and safety assessments. The primary endpoint is the incidence of LRTC. This endpoint will be based on an assessment of respiratory outcomes and will be adjudicated by an independent Endpoint Adjudication Committee blinded to treatment assignment. The secondary endpoint of RSV RNA viral load will be used to assess antiviral efficacy. RSV RNA viral load assessment was similarly employed in the Phase 2a EDP 938-101 study. Clinical efficacy will be assessed using [redacted] and

other measures of disease progression, including incidences of respiratory failure and all-cause mortality. Safety and PK assessments will also be summarized in relation to study treatment group.

Among HCT patients with an acute RSV URTI, those with lower lymphocyte counts, in particular, are considered at greater risk of progression to LTRI and were previously demonstrated to benefit from an investigational fusion inhibitor (*Chemaly et al., 2019*; *Ison and Hirsch, 2019*). Consequently, the eligible population will comprise adults who have received an HCT and are lymphopenic with an ALC <500 cells/µL and are diagnosed with RSV with new onset of respiratory symptom(s). This includes subjects who have oxygen saturation ≥95% on room air and a BMI up to 40 kg/m^2. Subjects with new abnormalities consistent with LRTI on chest imaging and those who have been admitted to the hospital for a lower respiratory tract disease of any cause are excluded. Subjects known to be positive for other respiratory viruses, (eg, influenza, adenovirus, SARS CoV-2) or who have clinically significant viremia, bacteremia, fungemia, or bacterial or fungal pneumonia, are also excluded. Subjects with known HIV are excluded because the impact of HIV infection on the clearance of RSV in HCT patients is not known. Also excluded are subjects with defined renal, cardiac, and hepatic conditions, or any historical or current medical condition that, in the opinion of the Investigator, deems the subject unsuitable for the study.

Previous data suggest that in HCT patients with acute RSV, the therapeutic window from symptom onset to initiation of treatment may be short (*Chemaly et al. 2019; Marty et al. 2019*). Because the window for optimal intervention for RSV infection may be limited, the screening process is optimized to allow rapid identification of subjects with RSV and who are otherwise appropriate for the study so that EDP-938 or placebo can be initiated at the earliest possible timepoint. The timeframe from onset of symptoms to signing the ICF is not more than 3 days and subjects are to be randomized and administered the first dose of study drug within 24 hours of signing the ICF.

A dosing duration of 21 days has been selected as there is evidence that clearance of respiratory viruses may be slower in HCT patients than in healthy subjects (*Chemaly et al., 2019*; EDP 938-101). Although a 21-day treatment duration is longer than EDP-938 has been previously dosed, EDP-938 was demonstrated to be generally safe and efficacious in the Phase 2a EDP 938-101 study (see Section 1.4), in which healthy adult subjects were inoculated with RSV and received EDP-938 [redacted] for up to 5 days and EDP-938 was observed to be generally safe and well tolerated in healthy adult subjects for up to 7 days of dosing in the FIH EDP-938-001 study (see Section 1.4). Also, EDP-938 was well-tolerated in preclinical repeat-dose general toxicology studies with no adverse effects observed in any species evaluated (mice, rats, monkeys) at up to the highest dose administered per species at up to 28-days dosing duration.

The double-blind design utilizing a matched placebo for EDP-938 will allow for the most unbiased assessment of the clinical safety profile of EDP-938. Subject safety will be monitored through regularly scheduled assessments of AEs, safety laboratory tests, and the inclusion of a DMC whose activities will be defined in a separate DMC charter.

HCT recipients are immunocompromised, resulting in an increased propensity to develop opportunistic infections, including invasive fungal infections (IFI). Currently, azole antifungals are the preferred agents for prophylaxis of IFI (*Busca and Pagano, 2016; Kontoyiannis, 2011*). Azole antifungals are known inhibitors of [redacted], the main enzyme involved in EDP-938 metabolism. Given that a high proportion of HCT recipients are expected to be on prophylactic antifungal therapy with azoles, these agents are allowed in the current study with EDP-938 dose adjustment (Section 4.2.2).

Observational studies, small case series, and uncontrolled trials in adult HCT recipients with RSV infection suggest that early use of ribavirin (oral or inhaled) (*Casey et al., 2013; Foolad et al., 2019; Gorcea et al., 2017; Gueller et al., 2013; McColl et al., 1998; D. P. Shah et al., 2013; Waghmare et al., 2013*) or ribavirin in combination with other agents (*Ghosh et al., 2000; Khawaja & Chemaly, 2019; Ljungman et al., 2001; J. N. Shah & Chemaly, 2011; Whimbey et al., 1995*) are associated with reduced morbidity and mortality. In Study EDP 938-103, the use of ribavirin is allowed as per the discretion of the investigator.

4.2.2 Justification of EDP-938 Dose

EDP-938 has been comprehensively characterized in preclinical and clinical studies. EDP-938 regimens were generally well tolerated with a consistent safety profile that has now been observed in approximately 320 subjects exposed to single or multiple doses of EDP-938 for up to 7 days.

[redacted]

[redacted]

[redacted] recipients are immunocompromised (*Busca and Pagano, 2016; Kontoyiannis, 2011)*, they are often prescribed azole antifungals for the prophylaxis for IFI. Azole antifungals are known inhibitors of [redacted], the main enzyme involved in EDP-938 metabolism. When coadministered with itraconazole (a strong [redacted] inhibitor) and fluconazole (a moderate [redacted] inhibitor), EDP-938 systemic exposures ($AUC_{0\text{-}inf}$) increased by approximately [redacted], respectively (Studies EDP 938-003 and EDP 938-007). Based on these results, EDP-938 dose adjustment is required for enrolled HCT recipients who are taking stable doses of prophylactic azole antifungals that are moderate or strong [redacted] inhibitors. For subjects taking azole antifungals, the following dose adjustments are expected to provide exposures similar to the [redacted] dose: for azole antifungals that are moderate CYP3A4 inhibitors (e.g. fluconazole, isavuconazole), the EDP-938 dose will be [redacted] (or placebo) to account for a [redacted] increase in exposure. For subjects taking azole antifungals that are strong [redacted] inhibitors (e.g., itraconazole, ketoconazole, posaconazole, and voriconazole), the EDP-938 dose will be [redacted] (or placebo), to account for a [redacted] increase in exposure. No adjustment of EDP-938 dose is needed when coadministered with azoles that are weak [redacted] inhibitors (e.g., clotrimazole).

Echinocandins do not affect [redacted]; therefore, prophylactic treatment with an echinocandin (caspofungin, anidulafungin, micafungin) is allowed. Subjects receiving treatment with an echinocandin will receive EDP-938 at a dose of [redacted].

In summary, based on the PK data from Studies EDP 938-001, -003, -004, -007, and -101, and accounting for the formulation difference and modest food effect observed in Study EDP 938-004, an EDP-938 dose of [redacted] tablet (for subjects not taking azoles that are moderate or strong [redacted] inhibitors), a dose of [redacted] tablet (for subjects taking azoles that are moderate [redacted] inhibitors), or [redacted] tablet (for subjects taking azoles that are strong [redacted] inhibitors) can be administered without regard to food, and are expected to provide exposures similar to the [redacted] suspension formulation used in Study EDP 938-101. These systemic EDP-938 exposures are expected to be generally safe and efficacious.

5. STUDY DRUG AND TREATMENT OF SUBJECTS

5.1 Description of Study Drug

EDP-938 drug product tablets [redacted]

5.2 Packaging and Labeling

EDP-938- drug product tablets and the corresponding placebo tablets are supplied as [redacted] tablets and [redacted] tablets in [redacted]

All the drug product manufacturing, packaging, and release testing are conducted under Current Good Manufacturing Practice regulations. EDP-938- drug products are labeled according to the regulatory guidelines for labeling of investigational products.

5.3 Storage

EDP-938 and placebo tablets will be shipped and stored at the site at [redacted] Additional information can be found in the in the Pharmacy Manual.

Subjects will be instructed to store study drug in the original bottle at [redacted].

5.4 Accountability

Site staff will maintain adequate records of the receipt and disposition of all study drug shipped to and/or procured by the site for this study.

Site and/or pharmacy records (as appropriate for the site) must include dates, bottle numbers, lot numbers, quantities received, quantities dispensed, date and time of administration (Section 5.7), and the identification number of each subject who has received each lot of study drug.

Unused study drug must not be discarded until the end of the study after full drug accountability is performed. Study drug that is dispensed to a subject, but not administered or completely ingested by the subject, must be returned to the pharmacy and the amount remaining recorded in the source documents.

In addition, for drug accountability, subjects should bring study drug (including empty bottles) with them to the study site.

5.5 Handling and Disposal

Study drug must not be used for any purpose other than for administration to subjects enrolled into this clinical study. All study drug bottles that are opened and returned by subjects as well as those that are not opened or assigned to subjects will be retained at the site according to instructions provided by Enanta Pharmaceuticals, Inc. or designees until monitored by the Study Monitor. Full accountability of all study drug distributed to subjects will be documented per Section 5.4.

Enanta Pharmaceuticals, Inc. will provide instructions for the return or destruction of any unused study drug. If Enanta Pharmaceuticals, Inc. authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Enanta Pharmaceuticals, Inc., and, that the destruction was adequately documented.

5.6 Treatment Assignment/Randomization

Subjects will be randomized to a treatment group using an Interactive Web Response System (IWRS). Subjects will be randomized in a 2:1 ratio to the EDP-938 or placebo treatment group as shown below:

- Treatment Group 1 (approximately 130 subjects): either [redacted] (see Section 4.1) of EDP-938 orally QD for 21 days
- Treatment Group 2 (approximately 70 subjects): Placebo orally QD for 21 days

In addition, subject randomization will be stratified based on ribavirin treatment (presence or absence) and ALC (<200 or ≥200 cells/μL) at Screening.

During the Screening Period, subjects will be identified by a unique screening number assigned by the clinical site. Subjects who have completed screening assessments and are eligible for participation in the study will be randomized before the first dose of study drug (Day 1) and assigned a unique four-digit subject number that will be used to identify the subject throughout the study.

5.7 Study Drug Dose and Administration

Complete instructions for dispensing and administering study drug are presented in the study-specific Pharmacy Manual.

Following randomization on Day 1, subjects will receive the first dose of EDP-938 or placebo orally while at the study site. After the first dose, subjects will be instructed to take the study drug orally QD on each of the 20 subsequent days. Subjects will be instructed to take the study drug at approximately the same time every day (±1 hour).

Study site visits should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site. If a visit occurs within 4 hours of the scheduled dosing time, the subject should take the study drug at the site during the visit. If a visit occurs more than 4 hours before or after the scheduled dosing time, the subject should take study drug at the

scheduled time at home. The time and date of doses of study drug taken at the study site should be recorded by site staff in source.

If a subject forgets to take their study drug at the scheduled time, the dose should be taken as soon as the subject remembers; however, the following rules apply:

- No more than one dose should be taken on any calendar day and
- There must be a minimum of 16 hours between doses.

Site staff will record the time and date of all study drug doses taken at the site. Subjects that took study drug at home on the day of a study visit should be asked for the time that dose was self-administered and record it in the electronic case report form (eCRF).

5.7.1 Dispensing of Study Drug

EDP-938 and placebo must be dispensed by a licensed investigational pharmacist or other authorized site staff with appropriate training. Subjects will receive instructions on study drug storage (see Section 5.3) and dosing (see Section 5.7).

5.7.2 Treatment Compliance

Both accountability and study drug compliance will be reviewed at each study site visit as indicated in the SoA (Appendix 1). The number of tablets will be counted, and the site staff will ask the subjects why any doses were missed, if applicable. Any potential reasons for lack of compliance with dosing will be monitored and followed up by the site staff. Compliance assessment may be completed at the study site or by a study site personnel via a home visit.

For any subject considered to demonstrate continued noncompliance of study drug dosing despite continued educational efforts, the Investigator should contact [redacted] the Sponsor's Medical Monitor to discuss possible discontinuation of the subject from the study.

5.8 Prohibited Medications

Following drugs, including over-the-counter medications and supplements with equivalent efficacy, will be prohibited before the study and from the first dose of study drug on Day 1 through Day 49 or early termination:

- Use of or intention to use any medication or supplement known to be a moderate or strong inducer or inhibitor of the [redacted] enzyme within 14 days before signing the ICF and throughout the study, with the exception of prophylactic azole antifungal therapies (e.g., fluconazole, itraconazole, ketoconazole, isavuconazole, posaconazole, and voriconazole), which are permitted with EDP-938 dose adjustment (Section 4.2.2).
- Treatment with azole antifungals that are weak inhibitors of [redacted] (e.g., clotrimazole) is allowed without EDP-938 dose adjustment.

- For HCT recipients on prophylactic antifungal therapy with azole antifungals, treatment with additional moderate or strong inhibitors of [redacted] outside the azole antifungal class is exclusionary within 14 days of signing the ICF and throughout the duration of the study.
- For subjects not on prophylactic antifungal therapy with azole antifungals at screening, initiation of new azole antifungals that are moderate or strong inhibitors of [redacted] is prohibited. If treatment with these agents is considered medically necessary after Day 1, dosing with EDP-938 should be discontinued.
- A comprehensive list of [redacted] inducers and inhibitors can be found at: *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*.
- Cyclosporine, a moderate [redacted] inhibitor, has been shown in a Phase 1 DDI study (EDP 938-002) evaluating the effect of cyclosporine on EDP-938 levels to have no apparent effect on the EDP-938 peak exposure and a weak effect on EDP-938 systemic exposures [redacted]. In the same study, (EDP -938-002) coadministration with prednisone, a weak[redacted] inducer, showed no apparent effect on EDP-938 exposure. Based on these results, no dose adjustments of EDP-938 when it is coadministered with cyclosporine or prednisone will be necessary.
- Use of nonmarketed (according to region) or investigational agents, vaccines, biological products within 30 days or five half-lives before signing the ICF, whichever is longer, and throughout the study.
- Use of any investigational monoclonal anti-RSV antibodies within 4 months or five half-lives of signing the ICF, whichever is longer, or use of any investigational RSV vaccines after HCT, and throughout the study.

6. BLINDING

6.1 Maintaining the Blind

The study will be double-blinded, meaning that the subjects, investigators, and site staff will be blinded to treatment assignment until the completion of the study. All site staff will be blinded to treatment assignment except for the following individuals:

- Unblinded Enanta/[redacted] statistician for purpose of generating and monitoring the randomization list
- Unblinded Enanta representatives not associated with the day-to-day conduct of the study as outlined in a separate DMC charter
- Unblinded members of the DMC for purposes of unblinded data review
- Unblinded Drug Supply Chain personnel for the purpose of monitoring drug supplies
- Enanta, [redacted], and Regulatory Affairs representatives when required to satisfy regulatory reporting requirements
- Bioanalytical laboratory for the purpose of measuring drug concentrations

During the study, investigators, site personnel, and blinded contract research organization/Sponsor staff will not have access to results for individual subjects that could impact clinician assessments, including results for RSV viral load, confirmatory respiratory pathogen panel testing, biomarkers, and PK.

6.2 Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will use the IWRS process. Using the IWRS will allow the Investigator to have immediate access to the unblinding system.

Unblinding of individual subject treatment by the Investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In situations where the urgency of the case requires immediate action, investigators should use their best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding. In emergency situations, the decision to unblind resides solely with the Investigator.

For unblinding, sites at all locations should call the following [redacted] Medical Monitor 24/7 global medical coverage hotline:

[redacted] **Medical Monitor 24-Hour Safety Hotline for Protocol Inquiries**	
Europe, Middle East and Africa (EMEA) and Asia-Pacific (APAC)	[redacted]
United States	[redacted]
Latin America	[redacted]

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the [redacted] Medical Monitor should be notified within 24 hours of unblinding of

the treatment and should inform the Sponsor's Medical Monitor. Information relating to unblinding (eg, the reason, date) should be clearly recorded in the subject's study file. In addition, the Investigator should consider whether the clinical event that prompted unblinding should be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report as described in Section 9.2.

The [redacted] Safety and Risk Management group will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Enanta Pharmaceuticals, Inc. may unblind individual subjects at any time for matters relating to safety concerns.

7. STUDY CONDUCT AND VISIT SCHEDULE

7.1 Study Site Visits

Details of assessments at each study site visit are presented in the SoA (Appendix 1). Study sites will be responsible for following up with subjects for any missed study site visits.

7.1.1 Screening Period (Day-1 to Day 1)

Screening procedures (from Day-1 to Day 1) will occur after the subject signs and dates an institutional review board (IRB)- or ethics committee (EC)-approved ICF and provides authorization to use protected health information (see Section 12.1.3). The ICFs will be completed before conduct of any study-specific procedures.

After signing the ICF, screening assessments will be assessed within 24 hours before dosing. Some procedures performed as part of standard-of-care before Screening may be used in determining study eligibility, such as RSV diagnostic test or safety laboratory tests performed up to 3 days before informed consent and chest imaging performed within 2 days before informed consent, as specified in Section 8 and the SoA (Appendix 1). As required, screening safety laboratory test samples will be sent to the local laboratory for expedited testing.

After signing the ICF, Screening should be completed as soon as possible, and the subject will be randomized and administered the first dose of study drug within 24 hours of signing the ICF.

7.1.2 Treatment Period (Days 1 to 21)

Study Site Visits (Days 1, 4, 7, 11, 16, and 21):

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized 2:1 to receive [redacted] EDP-938 or placebo administered orally for 21 days. Subject randomization will be stratified by ribavirin treatment (presence or absence) and ALC (<200 or ≥200 cells/µL). Presence of ribavirin treatment will be defined as ≥1 dose of ribavirin (oral, intravenous, or aerosolized) before randomization or with written orders for the initiation of therapy at the time of randomization.

The study drug treatment duration is 21 days, during which 6 study visits will be performed.

Randomized subjects will be assigned to an electronic device [redacted].

Following randomization on Day 1, subjects must complete baseline assessments before receiving the first dose of EDP-938 or placebo. Although prior local safety laboratory test results may have been used to determine eligibility, separate safety laboratory samples must be collected and sent to the central laboratory for baseline assessment. If Screening and randomization/first dose occur on the same day (Day 1), then screening assessments for vital signs and pulse oximetry will be used as baseline values. If Screening (Day -1) and randomization/first dose

(Day 1) occur on different calendar days within a 24-hour period, then vital signs and pulse oximetry will be performed again on Day 1 (predose).

Subjects will receive the first dose of study drug while at the study site and will be instructed to take EDP-938 or placebo QD at approximately the same time every day (±1 hour) on each of the 20 subsequent days. The subject will also receive instructions on the appropriate storage and transport of study drug. At each study visit, subjects should bring their study drug with them as part of their study site visit for drug accountability and for dosing of study drug. If a subject is unable to attend a study site visit, a home visit by study site personnel may be arranged, if feasible.

Except for Screening and Day 1 visits, visit assessments for other visits may be completed at the study site or by study site personnel via a home visit, if feasible.

During study visits throughout the Treatment Period, safety assessments, blood collections, and nasopharyngeal swab collections will be conducted as specified in the SoA (Appendix 1). Safety evaluations will include assessment of clinical laboratory findings, physical examination findings (as applicable), vital sign measurements, pulse oximetry measurements, AEs, and concomitant medications. Other assessments include incidences of hospitalization, ICU admissions or utilization of ICU care for >24 hours, incidences of MAARI, standard of care test results (eg, chest imaging reports, laboratory tests, ECGs), mechanical ventilation, and supplemental oxygen use (≥2 L/min for >24 hours).

All study assessments during the Treatment Period are detailed in the SoA (Appendix 1).

7.1.3 Follow-up Period (Days 22 to 49)

Study Site Visits (Days 28 and 49):

Follow-up visits will occur 1 and 4 (EOS visit) weeks after the last dose of study drug for all subjects including those who discontinue treatment early (ie, before completing 21 days of dosing). Visit assessments may be completed at the study site or by study site personnel via a home visit, if feasible.

All study assessments during the Follow-up Period are detailed in the SoA (Appendix 1).

Any subject with ongoing AEs/SAEs at the EOS visit should be followed up until resolution of their AE/SAE or until the Investigator has determined that the event has stabilized as discussed in Section 9.3.

7.2 Subject Withdrawal/Early Termination/Completion

Subjects will be considered to have completed treatment if they did not permanently discontinue treatment before the EOT visit. Subjects will have completed the study if they completed the full Treatment Period and full Follow-up Period.

If a subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be

collected. Enanta Pharmaceuticals, Inc. may retain and continue to use any data collected before such withdrawal of consent.

Any randomized subjects who withdraw or are withdrawn from the study will not be replaced.

7.2.1 Withdrawal Criteria

Reasons for discontinuation include but are not limited to the following:

- AE
- Lack of efficacy
- Lost to follow-up
- Withdrawal by subject
- Protocol deviation (including noncompliance with study drug or study procedures)
- Pregnancy
- Study terminated by the Sponsor
- Other

7.2.2 Procedures for Early Discontinuation or Early Termination of Treatment

Subjects who discontinue treatment before completing 21 days of dosing should return to the study site within 24 hours after the last dose of study treatment to complete an EOT visit, including EOT PK sample collection. Subjects should then return to the clinic for the Follow-up Visit 1 (EOT + 1 week) and the EOS visit 4 weeks following the last dose of the study drug.

Subjects who discontinue the study before Day 28 should return to the site within 48 hours to complete Follow-up Visit 1 (EOT + 1 week) procedures. Subjects who discontinue the study early between Day 28 and Day 49 should return to the study site within 48 hours to complete the EOS procedures (see Appendix 1). Any subject who withdraws with ongoing AEs/SAEs should be followed until resolution of their AE(s) or until the Investigator has determined that the AE(s) has stabilized.

Site staff will attempt to contact any subject who does not return to the site for the EOS visit at least three times using the subject's preferred method of communication, followed by a letter requiring delivery notification if the three attempts were unsuccessful. Any subject who still cannot be reached following those attempts will be considered lost to follow-up. These subjects will be included in the PK and safety analysis as indicated in Section 11.3.

7.2.3 Documentation of Withdrawal of Subjects

The reason for early withdrawal/termination/lost to follow-up of any subject from the study must be documented in source and on the appropriate eCRF. If the reason for early withdrawal is an

AE or an abnormal laboratory value, the specific event or test result, if available, should be recorded on the AE eCRF and the subject should be monitored until the event is resolved or deemed stable by the Investigator.

8. STUDY PROCEDURES/EVALUATIONS

8.1 Timing of Assessments

The timing of assessments is shown in the SoA (Appendix 1).

8.2 Demographics and Medical History

Demographics and baseline characteristics including year of birth and age, gender or sex, race (if available), ethnicity (if available), medical history, and smoking history will be obtained from each subject and entered in the eCRF as reported at Screening. Significant medical history will be obtained by consulting with the subject. As a general rule, all medical events occurring within the last 6 months should be recorded. For events that occurred more than 6 months ago (and that are not ongoing), only significant or relevant events should be recorded on source and entered in the eCRF. Any items in the history that are still ongoing should be noted as such in the eCRF. All surgeries occurring in adulthood should be recorded in the eCRF, whereas surgical methods of contraception, if applicable, should only be documented in the source documents.

If there is a question concerning a subject's medical history, then medical records may be requested from the subject's primary care physician, as appropriate.

8.2.1 Prior and Concomitant Therapies

Prior therapies will include medications and other therapies (including surgeries and other interventions) that end prior to the first dose of study drug. Concomitant therapies will include medications and other therapies (including surgeries and other interventions) ongoing at the first dose of study drug or started any time after the first dose of study drug.

Any medication or therapy taken within 1 month of signing the ICF and during the study through the end of the study will be recorded with indication, dosage, route of administration, and start and stop dates of administration. Only relevant medications and therapies should be recorded if they were discontinued more than 1 month before signing the ICF. Any therapies, including supplemental oxygen, administered while the subject is participating on the study will also be documented in source and reported on the eCRF. All subjects will be questioned about concomitant therapies at each study site visit.

8.3 Clinical Evaluations

8.3.1 Chest Imaging

Chest imaging (CXR and/or CT) obtained within 2 days before signing the ICF may be used to determine a subject's eligibility. If chest imaging is not available or was not obtained during standard care within 2 days before signing the ICF, it must be obtained at Screening.

8.3.2 Vital Sign Measurements

Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Vital signs will be measured at times shown in the SoA (Appendix 1) after the subject has been supine for a minimum of 5 minutes. Pulse oximetry will be performed to measure oxygen saturation as indicated in the SoA (Appendix 1).

8.3.3 Electrocardiograms

A resting 12-lead ECG will be performed locally and recorded as specified in the SoA (Appendix 1) after the subject has been supine for 5 minutes and before dosing. A standard bedside 12-lead ECG machine that calculates heart rate and measures PR, QRS, QT, RR, and QTcF intervals will be used.

At Screening on Day 1, the Investigator or designee should review the ECG for gross abnormalities and interval measurements of concern (absolute readings). The clinical interpretation by the Investigator or designee of the ECGs should be recorded on a hard copy of the ECG (ie, clinically significant or not clinically significant).

An ECG may be repeated at the discretion of the Investigator to address suspected errors in performance. Before dosing, the screening ECG must be reviewed by the Investigator or designee to confirm that no clinically significant cardiac abnormalities are present.

8.3.4 Physical Examination

The Investigator or designee will perform the physical examination. A full physical examination will be conducted at Screening and will include examination of all pertinent body systems. Any subsequent physical examinations performed at the discretion of the Investigator will be targeted to new signs and symptoms including specific assessments of any changes from previous status. Clinically significant abnormalities should be recorded as AEs.

The physical examination performed at Screening will be used as the baseline assessment. If Screening (Day -1) and Randomization/first dose (Day 1) occur on different calendar days within a 24-hour period, a subsequent physical examination will not be required unless it is deemed necessary by the Investigator due to new signs and symptoms or for specific assessments of changes from previous status.

8.3.5 Height, Weight, and Body Mass Index

Height and body weight should be obtained with the subject in light clothes and no shoes. Height will be documented at Screening only whereas weight will be measured at all visits.

Body mass index will be calculated at Screening (to assess eligibility) and all other visits according to the following equation:

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$$

8.3.6 Adverse Events

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in Section 9.1 of this protocol. All AEs and SAEs must be recorded in the source documents and eCRF as described in Section 9.2. At all study site visits, the Investigator or designee should inquire about the occurrence of AEs. The following are examples of open-ended questions that may be used to obtain this information: "How are you feeling?"; "Have you had any medical problems recently?"; and "Have you taken any new medicines since your last visit/assessment?"

It is the Investigator's responsibility to ensure any necessary additional therapeutic measures and follow-up procedures are performed and documented in the subject source notes and eCRF.

8.3.7 Lower Respiratory Tract Complications Clinical Source for Endpoint Adjudication Committee Review

During the course of the study, it is anticipated that chest images, and other clinical evaluations and laboratory tests will be performed as part of standard of care if there is any concern of a LRTCs. In addition to eCRF data relevant to safety assessments, the following source will be submitted to adjudicators:

- Chest images: Images and results for chest imaging used for Screening and eligibility, including the comparison chest imaging, and all scans done as part of the standard of care while subjects are on study, will be collected and stored electronically for review by the Endpoint Adjudication Committee.
- Results of all local microbiological tests performed while on study (all bacterial, viral, fungal, parasitic, or other test results from samples obtained from any respiratory specimen [eg, bronchoalveolar lavage, sputum, pleural fluid, lung tissue] and from blood specimens, including bacterial culture, viral polymerase chain reaction, and serology studies).
- Clinical notes with range of dates, including outpatient notes with vital signs, outpatient laboratory and hospital discharge summaries, as appropriate.
- Autopsy reports (if performed).
- Other supporting documentation, as requested, including by the Endpoint Adjudication Committee.

8.3.8 [redacted]

[redacted]

[redacted]

8.3.9 Collection of Swabs and Blood Samples for Virology Assessments

Refer to Section 8.5 for samples that will be collected for diagnosis and virology assessments. Nasopharyngeal swabs (one from each nostril) for virology assessments will be collected predose at visits specified in the SoA (Appendix 1). The RSV specific tests are indicated in Table 1.

Residual volume from the nasopharyngeal swab sample collection may be stored [redacted].

8.4 Laboratory Procedures

At Screening, clinical laboratory evaluations of blood samples will be performed at the local site laboratory for expedited testing and reporting if existing values collected in the 3 days before signing the ICF are not available to assess eligibility. Clinical laboratory evaluations to be assessed at Screening are noted in Table 1 with "a" and described in corresponding footnote a.

On Day 1, randomized subjects will undergo the clinical laboratory evaluations of blood and urine samples specified in Table 1, which will be performed at the central laboratory(ies) as a baseline measurement. Subsequent clinical laboratory evaluations will be performed by the central laboratory(ies). Only central laboratory values will be collected for analysis.

The Day 1 collection of blood and urine will be completed before administration of study drug.

A Laboratory Manual will be provided to the site detailing kit contents, reordering supplies, sample collection, handling, storage, and shipment instructions. All unblinded laboratory values will be reviewed by the Investigator, documented, and the results maintained in the source documents. All out-of-range laboratory findings require an interpretation as to whether or not they are of clinical significance. Clinically significant laboratory findings in the opinion of the Investigator should be recorded as an AE (or SAE as appropriate) (see Section 9.1).

8.4.1 Safety Laboratory Panels

Safety laboratory tests include chemistry, hematology, and urinalysis. Blood samples will be collected for analysis of the analytes as shown in Table 1. Samples will be collected from all subjects randomized into the study.

Blood and urine samples for clinical laboratory assessments will be collected according to the SoA (Appendix 1) and processed as indicated in the Laboratory Manual. Estimated glomerular filtration rate will be calculated using the MDRD equation.

8.4.2 Pregnancy and Menopausal Laboratory Testing

All female subjects of childbearing potential will undergo a urine pregnancy test at Screening, Day 28 (EOT + 1 week), and at the EOS (EOT + 4 weeks) visit. In addition, on Day 1, a blood sample will be collected for a serum pregnancy test to be performed by the central laboratory. The screening urine pregnancy test results will be used to qualify subjects at study entry.

To confirm nonsurgical postmenopausal status for women stating that they are amenorrhoeic for 1 to 2 years, documentation of FSH levels >35 mIU/mL will be required. Where such documentation is not available, FSH levels will be measured on Day 1. In such subjects, urine and serum pregnancy testing should also be performed at Screening, and these subjects will be required to follow appropriate contraceptive practices for women of childbearing potential until a confirming FSH level is available.

8.4.3 Calcineurin Inhibitor and mTOR Inhibitor Levels

For subjects taking a calcineurin inhibitor (CNI) and/or mTOR inhibitor, blood samples will be harvested at timepoints indicated in the SoA (Appendix 1) and sent to both the central and local laboratories where the CNI and mTOR inhibitor levels will be measured. Management of CNI and mTOR inhibitor levels (including obtaining additional CNI or mTOR inhibitor levels as clinically indicated) will be at the Investigator's discretion based on levels reported by the local laboratory.

Table 1: Clinical and Respiratory Syncytial Virus Laboratory Evaluations

CHEMISTRY PANEL	**HEMATOLOGY PANEL**
Alanine aminotransferase[a] Albumin, serum[a] Alkaline phosphatase, serum [a] Amylase[a] Aspartate aminotransferase[a] Bilirubin, total and direct[a] BUN[a] BUN/creatinine ratio (calculation) Calcium, serum Creatine kinase Creatinine, serum[a] Glomerular filtration rate, estimated Uric acid Electrolyte panel (sodium, potassium, chloride, bicarbonate)[a] Phosphorus Gamma glutamyl transferase Globulin, total Glucose, serum[a] Cholesterol Triglycerides Lactate dehydrogenase Lipase Protein, total serum Calcineurin and mTOR inhibitors[b]	Hemoglobin[a] Hematocrit[a] Differential white blood cell count, percentage and absolute (basophils, eosinophils, lymphocytes, monocytes, neutrophils)[a] Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count[a] Red blood cell count White blood cell count[a] International normalized ratio[a] Prothrombin time[a] Activated thromboplastin time[a]
	RSV-SPECIFIC TESTS RSV diagnostic test (nasopharyngeal or other appropriate secretions), if necessary Confirmatory respiratory pathogen panel RSV RNA quantitation of viral load (nasopharyngeal secretions) RSV RNA quantitation of live viral load using cell-based infectivity assay (nasopharyngeal secretions) RSV subgroup/genotype determination (nasopharyngeal secretions) Viral resistance (nasopharyngeal secretions, archived) RSV serology (neutralizing antibodies, serum, archived)
URINALYSIS Routine urinalysis to include: color and appearance, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, protein, urobilinogen, microscopic examination (including red blood cells and white blood cells)	**PREGNANCY AND OTHER TESTS** Urine pregnancy test Serum pregnancy test (only Day 1 and to the central laboratory) Follicle-stimulating hormone

Abbreviations: BUN = blood urea nitrogen; mTOR = mammalian target of rapamycin; RSV = respiratory syncytial virus.

[a] If existing values collecting in the 3 days before signing the ICF are not available for these identified tests to assess eligibility at Screening, blood and urine samples for these tests should be taken and sent to the local laboratory for testing and reporting in an expedited manner.

[b] Samples will be collected and analyzed only for subjects taking calcineurin and mTOR inhibitor(s).

8.5 Virology Assessments

Virology assessments and tests (Table 1) will be performed using nasopharyngeal or other appropriate swab (rapid diagnostic screen) or nasopharyngeal swab samples (other virology assessments) and serology samples collected at Screening and at timepoints indicated in the SoA (Appendix 1). The tests are further described in the Laboratory Manual, including swab collection, sampling, and handling procedures. Multiple nasopharyngeal swab samples may be collected at each timepoint. With the exception of the rapid diagnostic screen for RSV that will be performed at the local site laboratory, all other virology/RSV assessments will be analyzed at the central laboratory(ies).

8.5.1 Respiratory Syncytial Virus Rapid Diagnostic Test

RSV diagnostic testing determined in the 3 days before signing the ICF or at Screening may be used to assess eligibility. Subjects who were not tested for RSV as standard of care in the 3 days before signing the ICF may consent to the study and be tested for RSV during the Screening visit. A nasopharyngeal or other appropriate swab sample will be collected to obtain respiratory secretions. Subjects whose swab sample tests positive for RSV may proceed for further screening assessments. Results will be recorded in the source documents.

8.5.2 Confirmatory Respiratory Pathogen Panel

Following randomization on Day 1, a nasopharyngeal swab sample(s) will be obtained before taking the first dose of EDP-938 or placebo for central laboratory analysis and confirmation of respiratory pathogens recovered. This testing will be performed to identify other nasopharyngeal co-pathogens that may include adenovirus, coronavirus including SARS-CoV-2, human metapneumovirus, human rhinovirus/enterovirus, parainfluenza virus, *Chlamydophila pneumoniae*, and/or *Mycoplasma pneumoniae*, which may impact the course of a subject's illness. Refer to the Laboratory Manual for further details.

8.5.3 Respiratory Syncytial Virus Viral Load Quantification

The RSV viral load will be measured in nasopharyngeal swabs by an infectious virus cell-based infectivity assay and RT-qPCR assay at the timepoints specified in the SoA (Appendix 1). The RT-qPCR will also be used to determine viral dynamics (eg, peak viral load and time to peak). Refer to the Laboratory Manual for further details.

8.5.4 Respiratory Syncytial Virus Subgroup/Genotype Determination

Nasopharyngeal swab sample(s) at Baseline (Day 1) will be analyzed to determine the subgroup (A or B) and genotype of RSV.

8.5.5 Viral Resistance

Nasopharyngeal swab sample(s) may be analyzed for potential viral resistance monitoring assessment. Resistance monitoring assessment, if performed, will be conducted by population and/or deep sequencing of the RSV gene to monitor for treatment-emergent RAVs. Phenotypic analysis using reverse genetics system may also be performed to determine the susceptibility of the RAVs to EDP-938. Refer to the Laboratory Manual for further details.

8.5.6 Respiratory Syncytial Virus Serology

At the timepoints specified in the SoA (Appendix 1), samples will be collected for RSV serology assessment using the RSV neutralization antibody assay. Refer to the Laboratory Manual for further details.

8.6 Pharmacokinetic Samples

Blood (plasma) samples for PK analysis will be collected as outlined in the SoA (Appendix 1).

On Day 1, Day 7, and Day 21, two samples will be collected: one predose, collected within 1 hour before dosing (preferably within 30 minutes of dosing if possible) and at the same approximate time as that of the nasopharyngeal swab collection; and one postdose sample collected 1 to 3 hour post dose.

At all other visits, one predose plasma PK sample will be collected at the same approximate time as that of the nasopharyngeal swab collection. Subjects who discontinue treatment before completing 21 days of dosing should return to the study site within 24 hours from the last dose of study treatment to complete an EOT visit. One plasma PK sample will be collected at the same approximate time as that of the nasopharyngeal swab collection.

The time and date of PK sample collection should be recorded in source and in the eCRF. Study drug (EDP-938 or placebo) should be administered during the study visit on days when clinic visits occur. Study visits should be scheduled close to the time that the subject normally takes the study drug so that dosing expected on the day of the visit can occur during the visit. In addition, the site should record the date and time of last dose taken before the PK sample collection. See Section 5.7 for additional dosing details.

Blood samples will be collected and processed to measure plasma concentrations of EDP-938 [redacted] according to the procedures provided and/or approved by Enanta Pharmaceuticals, Inc. Additional details will be provided in the Laboratory Manual.

EDP-938 [redacted] in human plasma will be quantified by high-performance liquid chromatography with tandem mass spectrometric detection. The method will be fully validated by assessment of precision, accuracy, sensitivity, and specificity of EDP-938 [redacted] by the laboratory selected by Enanta Pharmaceuticals, Inc.

Pharmacokinetic samples may be stored and used for [redacted] and/or further evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical study report (CSR).

8.7 [redacted]

[redacted]

8.8 Endpoint Adjudication Committee

Blinded reviewers will review relevant clinical data and source documentation to determine whether a LRTC has developed. These relevant clinical data and documentation (ie, clinical notes, radiology reports, and microbiology results) will be used to determine if one of the following has occurred:

- Primary RSV LRTI
    - New findings on chest imaging compared with screening baseline chest image consistent with a viral LRTI AND
    - Positive RSV test from lower respiratory tract within ±7 days of new chest image findings
- Secondary bacterial LRTI
    - New findings on chest imaging compared with screening baseline chest image consistent with a bacterial LRTI AND
    - Evidence of a significant bacterial infection in lower respiratory tract within ±7 days of new chest image findings
- LRTI due to unusual pathogen
    - New findings on chest imaging compared with screening baseline chest image consistent with a lower respiratory tract infection AND
    - Positive microbiologic test for atypical bacteria, fungus, or other respiratory viruses within ±7 days of new chest image findings
- LRTC due to unknown etiology
    - New findings on chest imaging compared with screening baseline chest image consistent with an LRTI, inflammatory process or some other clinically significant pulmonary process AND
    - No organisms documented from lower respiratory tract

Detailed definitions for each of the above diagnoses will be provided to the adjudication committee in the Endpoint Adjudication Committee Charter.

9. SAFETY MONITORING AND REPORTING

9.1 Definitions

9.1.1 Pretreatment Events

A pretreatment event is any event that meets the criteria for an AE/SAE and occurs after the subject signs the ICF but before receiving the first administration of study drug.

9.1.2 Adverse Events

An AE is any event, side effect, or untoward medical occurrence in a subject enrolled in a clinical study whether or not it is considered to have a causal relationship to the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory finding outside of normal range with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the Investigator, including those requiring therapeutic intervention, physical examination finding, or disease temporally associated with the use of the study drug, whether or not the event is considered related to the study drug.

The occurrence of AEs should be sought by nondirective questioning of the subject at each study site visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between study site visits or through physical examination, laboratory test, or other assessments.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier than planned).

9.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death: This includes deaths that appear to be completely unrelated to study drug (eg, a car accident)
- Is a life-threatening event: An event that places the subject at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolonged hospitalization of an existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication
    - RSV disease progression

  - Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Results in permanent or prolonged (at least 28 days in duration) disability or incapacity
- Is a congenital anomaly or birth defect in the offspring of a study subject
- Medically important event: An event that may not be immediately life-threatening, or result in death or hospitalization, or require intervention to prevent one of the outcomes listed above but is considered medically significant for other reasons. An opportunistic or otherwise unusual infection for the Investigator's practice, such as tuberculosis, will be considered medically significant.

The term severe is used to describe the intensity of a specific event (as in mild, moderate, or severe); the event itself, however, may be of minor medical significance (such as severe headache). This is not the same as serious, which is based on outcome of the event, as described above. Seriousness, not intensity, serves as a guide for defining regulatory reporting obligations.

9.2 Documenting and Reporting of Adverse Events (Including Serious Adverse Events)

Adverse events will be evaluated and documented using the grading scales contained in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.

9.2.1 Documenting and Reporting Adverse Events

All AEs reported from the time of informed consent to the EOS visit for each subject will be recorded in the subject's source documents. For subjects who do not receive study drug (ie, alternates or screen failures), AEs will only be recorded in the source documents. For subjects enrolled into the study (ie, randomized), all AEs will be recorded in the subject's AE eCRF and the SAE form (if applicable). The site should record all AEs regardless of the intensity, seriousness, or relationship to study drug.

Adverse events (serious and nonserious) will be graded in accordance with the NCI-CTCAE scale as follows:

- **Mild** (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Moderate** (Grade 2): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

- **Severe** (Grade 3): severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- **Life threatening** (Grade 4): life-threatening consequences; urgent intervention indicated
- **Death** (Grade 5): death related to the AE

Any recurrence of an AE with similar causality to study drug will be reported as recurrence or exacerbation of the initial event, and not as a new event. Whenever possible, AEs will be reported as a specific diagnosis or syndrome (eg, flu syndrome) rather than as individual signs or symptoms. If no specific diagnosis or syndrome is identified, AEs should be reported as separate and individual events.

An AE includes the following:

- Progression or exacerbation of the subject's underlying disease. Clinical sequelae that result from disease progression, such as pleural effusion or small bowel obstruction, are reportable as AEs
- Pre-existing event that increases in frequency or intensity
- Condition detected or diagnosed during the study period, even though it may have been present, in retrospect, before the first dose of study drug
- Laboratory abnormalities outside of normal limits with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the Investigator, including those requiring therapeutic intervention

The following events will not be identified as AEs in this study:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, etc); however, the condition (the "triggering event") that leads to the procedure may be an AE
- Pre-existing conditions present or detected before the first dose of study drug that do not worsen

9.2.2 Assigning Attribution of Adverse Events

The Investigator must attempt to determine the cause of each event. Every effort will be made by the Investigator to assess the relationship of each AE to study drug. To ensure consistency of AE/SAE causality assessments, the Investigator should apply the following guidelines:

- **Related:** There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug have been ruled out, and/or the event reappeared on re-exposure to the study drug.

- **Possibly related:** There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
- **Unlikely related:** The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.
- **Not related:** The event is related to an etiology other than the study drug (the alternative etiology must be documented in the study subject's medical record).

9.2.3 Classifying Action Taken With Study Drug

In the case of an AE, the actions that can be taken with study drug by the Investigator or designee are defined in Table 2.

Table 2: Options for Action Taken With Study Drug

Classification	Definition
Dose not changed	Study drug dose not changed in response to the adverse event.
Drug interrupted	Study drug administration interrupted in response to an adverse event.
Drug withdrawn	Study drug administration permanently discontinued in response to an adverse event.
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances when no opportunity to decide whether to continue, interrupt, or withdraw treatment was possible such as when the investigational treatment had been completed before the adverse event began.

9.2.4 Classifying Adverse Event Outcome

For every AE/SAE, the possible outcomes of the event and the definition of the outcome are shown in Table 3. One outcome must be entered into the appropriate field on the AE and (if appropriate) SAE form for each event.

Table 3: Classification and Definition of Adverse Event Outcomes

Classification	Definition
Recovered/resolved	Resolution of an adverse event with no residual signs or symptoms
Recovered/resolved with sequelae	Resolution of an adverse event with residual signs or symptoms
Is Recovering/is resolving	Incomplete improvement to date but adverse event continues to improve/resolve and complete resolution is expected over time
Not Recovered/not resolved	Either incomplete improvement or no improvement of an adverse event, such that it remains ongoing
Fatal	Outcome of an adverse event is death. "Fatal" should be used when death is at least possibly related to the adverse event
Unknown	Outcome of an adverse event is not known (eg, a subject lost to follow-up)

9.2.5 Documenting and Reporting Serious Pretreatment Events and Serious Adverse Events

All SAEs that occur after obtaining informed consent through the EOS visit, regardless of causality, must be reported by the Investigator or designee to [redacted] and Enanta Pharmaceuticals, Inc. In addition, all SAEs, including those that result in death, that occur after the EOS visit and that are considered related to study drug must be reported to [redacted] and Enanta Pharmaceuticals, Inc. within 24 hours of learning of its occurrence. Additional details are provided in the Safety Management Plan. The SAE form should be sent to [redacted].

Serious Adverse Event and Pregnancy Reporting	
[redacted]	Email at [redacted] Faxed to [redacted] Phone contact is [redacted]

All SAEs will be recorded on the SAE form using a recognized medical term or diagnosis that accurately reflects the event. All SAEs will be assessed by the Investigator for severity, relationship to the investigational study drug, and possible etiologies. On the SAE form, relationship to study drug will be assessed only as related or not related. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing.

For purposes of regulatory safety monitoring, the Investigator is required to follow up the event to resolution and report the outcome of the event to [redacted], and Enanta Pharmaceuticals, Inc. using the SAE form.

The Investigator or designee is responsible for notifying the Sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE form should be completed for new/initial events as well as to report follow-up information on previously reported events. The Investigator or designee is asked to report follow-up information as it becomes available.

Enanta Pharmaceuticals, Inc. or its designee, as study Sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (ie, SUSARs) involving the study drug to all regulatory authorities, and participating investigators, in accordance with United States Food and Drug Administration (FDA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and/or local regulatory requirements, as applicable.

9.2.6 Documenting and Reporting of Pregnancy

Subjects will be counseled to inform the Investigator of any pregnancy that occurs during study drug and for 90 days after the last dose of study drug.

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. The Investigator or designee must notify [redacted] (Section 9.2.5), the Sponsor's Medical Monitor, and [redacted] within 1 business day of the sites' knowledge of the subject's (or partner's) pregnancy, by utilizing the study-specified pregnancy report form.

If confirmed to be on active drug, the subject or partner will be followed up until the end of the pregnancy and the infant will be followed up for 3 months after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

9.3 Follow-up of Adverse Events and Serious Adverse Events

All AEs (serious and nonserious) will be followed up until resolution or otherwise explained (see Table 3), the subject dies, the event stabilizes and is not expected to further resolve with the maximum time limit for stabilization defined as 30 days after the occurrence of the event, or when alternative therapy is instituted, whichever occurs first. If alternative therapy is instituted, it should be documented. Enanta Pharmaceuticals, Inc. may request that the Investigator perform or arrange for supplemental measurements or evaluations to further clarify the nature of the event.

9.4 Data Monitoring Committee

Safety data from this study will be reviewed by a DMC throughout the study. The DMC will be headed by a DMC Chair and will include one or more physicians with expertise in transplant medicine, consisting of expert(s) independent from the Sponsor. Procedures for data review, including timing and potential outcomes, roles and responsibilities, and interactions with the Sponsor and PPD, will be governed by a separate DMC charter.

10. STUDY STOPPING AND DISCONTINUATION RULES

10.1 Study Stopping Rules

If either of the following events occur, enrollment will be paused pending a full review of all available clinical safety data and discussion with the DMC:

- One subject has a Grade 4 AE or SAE that is judged as possibly related to study drug
- Two subjects experience the same Grade 3 AE that is judged as possibly related to study drug

Unless the subject's randomization code is unblinded by the Sponsor for clinical reasons, only the DMC will have access to unblinded data.

10.2 Site or Study Discontinuation

10.2.1 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Incidence or severity of AEs in this study indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- Decision from the IRB/EC or regulatory authority to terminate the study

If the study is suspended or terminated for safety reasons, Enanta Pharmaceuticals, Inc. will promptly notify the investigators and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator is responsible for promptly informing the IRB/EC and providing the reasons for the suspension or termination of the study.

10.2.2 Site Termination

A single site may warrant termination under the following conditions:

- Failure of the site to enroll subjects into the study at an acceptable rate
- Failure of the site to comply with pertinent governmental regulations as appropriate

- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or governmental authority
- Failure to adhere to the protocol requirements
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study

10.2.3 Study Termination Procedures

If the study is terminated by Enanta Pharmaceuticals, Inc. for one of the reasons listed previously, or upon completion of the study, the following activities must be conducted by the Study Monitor and/or site staff:

- Return of all study data to Enanta Pharmaceuticals, Inc. or designee
- Respond to and complete all requests for data clarifications
- Accountability and final disposition of used and unused study drug
- Review of site records for completeness
- Shipment of all applicable biological samples (including PK samples) to the designated laboratory

11. STATISTICAL CONSIDERATIONS

11.1 General Considerations

Statistical analysis of this study will be the responsibility of Enanta Pharmaceuticals, Inc. or its designee. Details of the statistical analysis methods will be described in the statistical analysis plan (SAP) document.

Continuous endpoints will be summarized using n, mean, standard deviation, median, 25^{th} quartile, 75^{th} quartile, minimum, and maximum values. Categorical endpoints will be summarized by the number of subjects meeting the endpoint and the percentage of subjects out of the appropriate population. The denominator will be displayed when needed. Statistical inference will be performed as appropriate. Inferential testing will be conducted using a two-sided alpha of 0.05, unless stated otherwise. Reference to stratification factors will include ribavirin treatment (presence or absence) and ALC (<200 or ≥200 cells/μL) at Screening.

Any change to the data analysis methods described in the protocol will require an amendment if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR or SAP. The SAP will be developed and finalized before database lock. Changes to the SAP may not be made after unblinding of treatment assignments (after database lock).

11.2 Sample Size Considerations

Assuming an LRTC rate of 30% for placebo, then a 20% reduction with 90% power and a two-sided alpha at 0.05 using a unpooled z-test, with a ratio of 2:1 would require approximately 160 subjects. Assuming a 15% dropout rate a total of 190 subjects will be randomized.

11.3 Analysis Populations

The following analysis populations are planned:

- *Intent-to-Treat (ITT) Population:* All subjects who receive at least one dose of study drug. Subjects will be analyzed as treated. The ITT Population is designated as the primary efficacy population.
- *Per Protocol Population:* All subjects who are randomized and receive all planned doses of study drug and do not have major protocol deviations that may unduly influence outcome. Subjects will be analyzed in the treatment group that corresponds to the study drug received during the study.
- *Safety (SAF) Population:* All subjects who receive at least one dose of study drug. Subjects will be analyzed in the treatment group that corresponds to the study drug received during the study.
- *Pharmacokinetic (PK) Population:* All subjects receiving active study drug and having any measurable plasma concentration of study drug at any timepoint.

11.4 Subject Disposition and Demographic Data

The number of subjects screened, randomized, and in the SAF and PK Populations will be summarized using frequencies and percentages. The denominator for the calculation of percentages will be from the number of subjects randomized.

The following categories will also be summarized for subject disposition:

- Completed study drug per the protocol
- Discontinued study drug early and the reason for discontinuation
- Completed the study
- Discontinued from the study early and the reason for discontinuation

Subject demographics will be summarized by treatment group for all subjects in the SAF Population. Appropriate baseline characteristics will be included in addition to demographic characteristics. No statistical testing will be performed.

11.5 Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized to blinded treatment on Day 1 in a 2:1 ratio to [redacted] EDP-938 or placebo. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign investigational product to each subject. To achieve between group comparability, the randomization will be stratified by presence or absence of ribavirin treatment.

11.6 Efficacy Analyses

11.6.1 Primary Efficacy Analyses

The proportion of LRTC between EDP-938 and placebo will be compared using a Cochran Mantel-Haenszel test with ribavirin treatment (presence or absence) and ALC (<200 or ≥200 cells/μL) as stratification factors. The primary analysis will be using the ITT Population based on the results of the Endpoint Adjudication Committee. Subjects with missing LRTC data will be treated as a nonresponse. A Fisher's exact test will be used to compare groups within each strata. A two-sided 95% confidence intervals for the odds ratio between groups based on stratum adjusted Mantel Haenszel proportions. Frequency and proportion of subjects who develop LRTC will be provided using 95% confidence intervals based on the normal approximation method. If stratification leads to small cell sizes a modification of the strata may be performed. This will be described in detail in the SAP.

11.6.2 Secondary Efficacy Analyses

[redacted] TSS AUC will be calculated for overall and individual components. All parameters will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and stratification factors as fixed effects and the baseline TSS as a covariate. Treatment groups will be compared using a type III sum-of-squares. Other sensitivity analysis may include a mixed model repeated measures analysis on the change from Baseline over all visits.

The RSV RNA viral load AUC measured in nasopharyngeal swab samples by RT-qPCR will be measured. The trapezoid rule will be used to calculate the AUC of the RSV RNA viral load. An ANCOVA model with treatment group and stratification factors as fixed effects, and the baseline RSV RNA viral load as a covariate will be performed. Treatment groups will be compared using a type III sum-of-squares. The proportion of subjects with RSV RNA below the limit of detection will be analyzed on days collected. Treatment groups will be compared using a Cochran-Mantel-Haenszel test controlling for the stratification factors

11.7 Safety Analyses

Statistical methods for the safety analyses will be primarily descriptive in nature. Safety data, including AEs, SAEs, vital sign measurements, concomitant medications, and laboratory values, will be summarized separately by treatment group. Change from Baseline will be included in summary tables for vital sign measurements and laboratory parameters. Shift tables will also be generated by laboratory analyte. All laboratory data will be included in the data listings, and all test values outside the normal range will be flagged.

11.7.1 Adverse Events

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities system organ class and preferred term by treatment group. All subjects in the SAF Population will be included in the summaries. Treatment-emergent AEs (TEAEs) are defined as reported AEs that first occurred or worsened during the post-Baseline phase compared with Baseline. The maximum severity at Baseline will be used as baseline severity. If the maximum severity during post-Baseline is greater than the maximum baseline severity, then the event is considered treatment emergent. No statistical testing will be performed.

Summaries of AEs will include the following at a minimum:

- An overall summary of AEs with a line for each of the categories provided below:
    - TEAEs
    - Related TEAEs
    - Maximum severity TEAE
    - TEAEs by severity
    - TEAEs leading to study drug discontinuation

- AEs leading to death
- SAEs
- Related treatment-emergent SAEs

11.7.2 Clinical Laboratory Data

Laboratory assessments will be reported as mean change from Baseline across scheduled visits, and as the incidence rate of shift change from Baseline. Shift from Baseline tables will be generated for each treatment group for selected analytes. Laboratory shifts will be displayed as treatment-emergent abnormal, high, or low results. The following details the summary types where LLN = lower limit of normal and ULN = upper limit of normal.

For categorical tests: Treatment-emergent abnormal is defined as a change from normal at Baseline to abnormal at any post-Baseline visit.

For continuous tests:

- Treatment-emergent high is defined as a change from a result less than or equal to the high limit at Baseline to a value greater than the high limit at any time post-Baseline.

  Results will be reported according to any value greater than the high limit, any value greater than 2× ULN and 3× ULN.

- Treatment-emergent low is defined as a change from a result greater than or equal to the low limit at Baseline to a value less than the low limit at any time post-Baseline.

  Results will be reported to any value less than the lower limit, any value less than 2× LLN and 3× LLN.

11.7.3 Vital Sign Measurements

The incidence rate of subjects with treatment-emergent vital sign changes at any post-Baseline visit will be summarized. Specific criteria for the classification of treatment emergent will be documented in the SAP. Vital sign observed, change, and percentage change will be summarized by treatment over visits. Pulse oximetry measurements will be summarized by visit and treatment.

11.7.4 Electrocardiograms

Screening ECG data will be provided in data listings.

11.7.5 Concomitant Medications

The number and percentage of subjects taking concomitant medications will be coded according to the latest World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification level 4 and WHO preferred term. Summaries will be provided by ATC Level 4 and preferred term. Subjects in the SAF Population will be summarized by treatment group.

11.7.6 Physical Examinations

Physical examination data will be provided in data listings.

11.8 Pharmacokinetic Analyses

Summary of plasma PK concentration data will be descriptive in nature. Mean plasma concentration-time figures may be created for EDP-938 [redacted], as allowed by the data. Additional details will be provided in the SAP.

11.9 Subgroup and Covariate Analyses

Subgroup analyses will be performed on the primary and secondary endpoints, primarily. A logistic regression model will be planned when categorical endpoints are analyzed. For continuous endpoints, an ANCOVA model with treatment group and stratification factor as fixed effects in the model, with subgroup and subgroup-by-treatment interaction. Various study populations may be used. Forest plots will be provided to visually describe the association.

11.10 [redacted]

[redacted]

11.11 Interim Analyses

An interim analysis may be conducted, if deemed necessary by the Sponsor.

12. STUDY ADMINISTRATION

12.1 Ethical Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in compliance with this protocol, principles of E6 Good Clinical Practice: Consolidated Guidance (ICH-GCP), Declaration of Helsinki, and all applicable local laws and regulations governing clinical studies.

12.1.2 Ethical Review

It is the Investigator's responsibility to ensure that this protocol is reviewed and approved by an appropriate IRB/EC that conforms to the regulations set forth in FDA 21 Code of Federal Regulations (CFR) Part 56 and other national, country, and regional regulations as applicable. The Investigator must also submit the ICF, any other written documentation provided to the subject, and all advertisements that may be used for study-specific recruitment to the IRB/EC for review and approval before commencing study-specific assessments. If it is necessary to amend the protocol during the study, then it is the responsibility of the Investigator to ensure that IRB/EC approval is obtained before implementation of the amended procedures. It is also the responsibility of the Investigator to provide the IRB/EC with any SAE or Investigational New Drug safety reports. A copy of the ICF approved by the IRB/EC must be forwarded to Enanta Pharmaceuticals, Inc. for regulatory purposes.

12.1.3 Written Informed Consent

The Investigator or designee must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in 21 CFR Part 50, and other applicable national and local regulations governing informed consent.

Each subject must provide a signed and dated ICF before enrollment into this study. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time. In accordance with individual local and national subject privacy regulations, the Investigator or designee must explain to each subject before Screening that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Enanta Pharmaceuticals, Inc. and its designee, regulatory agencies, and IRBs/ECs. As the study Sponsor, Enanta Pharmaceuticals, Inc. will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing

from the subject or subject's legal guardian and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

12.1.4 Investigator Compliance

No modifications to the protocol should be made without the approval of both the Investigator and Enanta Pharmaceuticals, Inc. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (ie, efficacy assessments) will require IRB/EC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects.

If circumstances require an immediate departure from protocol procedures, the Investigator will contact Enanta Pharmaceuticals, Inc. and/or its designee to discuss the planned course of action. Contact should be made before the implementation of any changes when possible. Any departures from protocol must be fully documented in the source documents and reported to Enanta Pharmaceuticals, Inc. or its designee and the IRB/EC as required.

12.2 Data Collection

Study data will be entered into an eCRF by site staff. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Subjects who did not randomize will not be entered into the clinical database. Reasons for screen failure will be collected in the interactive response technology (IRT) system. In addition, criteria for confirming RSV eligibility will be collected in IRT.

Source documentation supporting the clinical data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, other observations, and subject status. The Investigator or designated representative should complete the eCRF as soon as possible after information is collected. An explanation should be provided for all missing data.

After the subject has completed the study, the Investigator must review and sign the signature page of the eCRF indicating that he or she has reviewed the completed eCRF and pertinent clinical data for that subject and that, to the best of his or her knowledge, all data recorded in the eCRF accurately reflects the subject's clinical performance in the study.

Sites are responsible for abiding by the rules and regulations of their IRB/EC for recording and reporting protocol deviations. All deviations reported to the IRB/EC must be reported to Enanta Pharmaceuticals, Inc. and/or their designee and recorded as deviations as appropriate.

12.3 Study Monitoring

Representatives of Enanta Pharmaceuticals, Inc. or its designees will monitor this study until completion. Monitoring will be conducted through both on-site and remote visits with the Investigator and site staff as well as any appropriate communications by mail, fax, email, or

telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. The Study Monitor will ensure that the investigation is conducted according to protocol and regulatory requirements, and as described in the Study Monitoring Plan.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/EC, representatives of Enanta Pharmaceuticals, Inc., its designated agent, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or study site records of all subjects enrolled into this study. A statement to this effect will be included in the ICF authorizing the use of protected health information.

12.4 Quality Assurance

At its discretion, Enanta Pharmaceuticals, Inc. or its designees may conduct a quality assurance audit of this study. If such an audit occurs, the Investigator will give the auditor direct access to all relevant documents and will allocate his or her time and the time of his or her site staff to the auditor as required. In addition, regulatory agencies may conduct an inspection of this study. If such an inspection occurs, the Investigator will notify the Sponsor [redacted] and will allow the inspector direct access to all source documents, eCRFs, and other study documentation for source data check and/or on-site audit inspection.

12.5 Retention of Records

The site will retain a copy of all study records in a safe, secure, and accessible location for a minimum of 2 years after notification by Enanta Pharmaceuticals, Inc. that the investigations of EDP-938 have been discontinued or for 2 years following marketing approval of the drug, after which time, Enanta Pharmaceuticals, Inc. will be contacted for instructions on the disposition of study materials. Study records will contain all of the appropriate documents as detailed in Section 8.0 of the ICH-GCP E6.

12.6 Information Disclosure

12.6.1 Confidentiality

Subject names or any other identifiers will remain confidential and will not be supplied to Enanta Pharmaceuticals, Inc. or its designees. Only subject number and year of birth with age will be recorded on the eCRF. If the subject name appears on any other document collected (eg, unit discharge summary), it must be obliterated before the document is transmitted to Enanta Pharmaceuticals, Inc. or its designees. All study findings will be stored in electronic databases. As indicated in the ICF, subjects will give permission for representatives of the Sponsor, regulatory authorities, and the IRB/EC to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection

will be handled in the strictest confidence and in accordance with local data protection/privacy laws.

Individual subject medical information obtained during this study is confidential and its disclosure to third parties other than those mentioned in the preceding paragraph is prohibited. Medical information obtained during this study may be provided to the subject's personal physician or other appropriate medical personnel when required in connection with the subject's continued health and welfare and with the subject's prior knowledge and permission.

12.6.2 Publication Policy

It is the intention of Enanta Pharmaceuticals, Inc. to publish the results of this study in their entirety within a reasonable period of time following conclusion of the study. The Sponsor will determine when and where data will be first disclosed.

All information generated from this study is the proprietary property of Enanta Pharmaceuticals, Inc. The Sponsor, Enanta Pharmaceuticals, Inc. reserves the right, among other things, to the following:

- Modify or amend study material to ensure that no confidential or proprietary information is disclosed
- Ensure that the reported data are factually correct
- Utilize the information generated from or as a result of this study in any manner it deems appropriate, including but not limited to regulatory submissions, annual reports, and other scientific or business affairs of the company
- Modify the publication or disclosure or delay it a sufficient time to allow Enanta Pharmaceuticals, Inc.to seek patent protection of any invention contained therein

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14. APPENDICES

Appendix 1: Schedule of Assessments

Period	Screening	Treatment						Follow-up	
Visit	Screening	V1	V2	V3	V4	V5	V6	FU V1 (EOT +1wk)	FU V2 (EOT +4wks)
Day	D-1 to D1 Screening	D1 Randomization[a]	D4	D7±1d	D11±1d	D16±1d	D21+1d EOT[b]	D28±1d	D49±2d EOS[b]
Study site visit	X	X	X	X	X	X	X	X	X
Informed consent form	X								
Demographics, medical history[c]	X								
Smoking history	X								
Local RSV diagnostic test[d]	X								
Chest Imaging[e]	X								
Vital sign measurements and pulse oximetry[f]	X	X[g]	X	X	X	X	X	X	
Physical examination[h]	X	X[i]	X	X	X	X	X	X	
Safety laboratory tests[j]	X	X[k]	X	X	X	X	X	X	
Height[l]	X								
Weight and BMI[l]	X		X	X	X	X	X	X	
Pregnancy test[m]	X	X						X	X
FSH[n]		X							
12-Lead ECG (resting)	X		X		X		X	X	
Randomization[o]		X							
[redacted]									
Nasopharyngeal swab collection[q]		X	X	X	X	X	X	X	X
RSV serology collection		X						X	
[redacted]									
Study drug dosing[s]		X	X	X	X	X	X		
Study drug accountability[t]		X	X	X	X	X	X		
PK sample collection[u]		X	X	X	X	X	X		
CNI and mTOR sample[v]		X	X	X	X	X	X	X	

Period	Screening	Treatment						Follow-up	
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**FU V1 (EOT +1wk)**	**FU V2 (EOT +4wks)**
Day	**D-1 to D1 Screening**	**D1 Randomization[a]**	**D4**	**D7±1d**	**D11±1d**	**D16±1d**	**D21+1d EOT[b]**	**D28±1d**	**D49±2d EOS[b]**
Assess ICU admissions, hospitalizations, MAARI, standard of care test results, mechanical ventilation, and supplemental oxygen[w]		X	X	X	X	X	X	X	X
Prior/concomitant therapies[x]	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; CNI = calcineurin inhibitors; D/d = Day/day; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; eCRF = electronic case report form; EOS = End-of-Study; EOT = End-of-Treatment; FLU-PRO = InFLUenza Patient-Reported Outcome; FSH = follicle-stimulating hormone; FU = follow-up; ICF = informed consent form; ICU = intensive care unit; MAARI = medically attended acute respiratory infection; mTOR = mammalian target of rapamycin; PK = pharmacokinetic; RSV = respiratory syncytial virus; V = visit. Note: Refer to the Laboratory Manual for sample collection and processing details.

[a] Day 1 assessments to be performed in randomized subjects.

[b] Subjects who discontinue treatment early (ie, before completing 21 days of dosing) should return to the study site within 24 hours from the last dose of study treatment to complete an EOT visit. They should then return to the clinic for the Follow-up Visit 1 (EOT + 1 week) and the EOS visit 4 weeks following the last dose of the study drug. Subjects who discontinue the study before Day 28 should return to the site within 48 hours to complete Follow-up Visit 1 (EOT + 1 week) procedures. Subjects who discontinue the study early between Day 28 and Day 49 should return to the study site within 48 hours to complete the EOS procedures.

[c] Significant medical history, including surgical history, will be obtained by consulting with the subject. Refer to Section 8.2 of protocol.

[d] RSV diagnostic testing determined in the 3 days before signing the ICF or at Screening may be used to assess eligibility. Subjects who were not tested for RSV as standard of care in the 3 days before signing the ICF may consent to the study and be tested for RSV during the Screening visit.

[e] If available, chest imaging obtained within 2 days before signing the ICF may be used to determine eligibility. If chest imaging is not available or was not obtained during standard care within 2 days before signing the ICF, a chest image (chest x-ray and/or computed tomorgraphy) must be obtained at Screening.

[f] Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Vital signs will be measured after the subject has been supine for a minimum of 5 minutes. For pulse oximetry assessments, record oxygen support level if not done on room air.

[g] If Screening and randomization/first dose occur on the same day (Day 1), then vital signs and pulse oximetry measured at Screening will be used as baseline values. If Screening (Day -1) and randomization/first dose (Day 1) occur on different calendar days within a 24-hour period, then vital signs and pulse oximetry will be performed again on Day 1 predose.

[h] A physical examination will be performed at Screening. Any subsequent physical examinations performed at the discretion of the Investigator will be targeted to new signs and symptoms including specific assessments of any changes from previous status.

[i] The physical examination performed at Screening will be used as the baseline assessment. If Screening (Day -1) and Randomization/first dose (Day 1) occur on different calendar days within a 24-hour period, a subsequent physical examination will not be required unless it is deemed necessary by the Investigator due to new signs and symptoms or for specific assessments of changes from previous status.

[j] Safety laboratory tests include chemistry, hematology, and urinalysis. Existing values collected in the 3 days before signing the ICF or at Screening may be used to assess eligibility.

[k] Although prior local safety laboratory test results may have been used to determine eligibility, separate safety laboratory samples must be collected before first dose and sent to the central laboratory for baseline assessment at Day 1.

[l] Height will be documented at Screening only. The BMI will be calculated at Screening (to assess eligibility) and other visits according to the following equation: BMI = (weight in kg)/(height in m^2).

[m] Pregnancy testing will be performed in female subjects of childbearing potential. A urine pregnancy test will be performed at Screening, Day 28, and at the EOS visit. In addition, on Day 1, blood will be collected for a serum pregnancy test to be performed by the central laboratory. The screening urine pregnancy test results will be used to qualify subjects at study entry. Refer to Section 8.4.2 of the protocol for pregnancy testing requirements for postmenopausal females.

[n] FSH should be tested in postmenopausal females. Refer to Section 8.4.2 of the protocol.

[o] Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized 2:1 to receive [redacted] 800 mg of EDP-938 or placebo. Subject randomization will be stratified by ribavirin treatment (presence or absence) and absolute lymphocyte count (<200 or ≥200 cells/µL) at Screening.

[redacted]

[q] Two nasal/nasopharyngeal swabs, one from each nostril, will be collected predose at each visit. [redacted].

[r] Subject participation is optional. Subjects will be required to review and sign a separate ICF for this assessment. Day 1 and 21 samples should be collected predose.

[s] Study drug (EDP-938 or placebo) should be administered during the study visit on days when clinic visits occur. Study visits should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur during the visit. See Section 5.7 for additional dosing details.

[t] Subjects should bring their study drug with them as part of their study site visit for drug accountability and for dosing of study drug. Study drug accountability will occur through a tablet count at each visit during Treatment and up through the Day 21 EOT visit.

[u] On Day 1, Day 7, and Day 21, two samples will be collected: one predose, collected within 1 hour before dosing (preferably within 30 minutes of dosing if possible) and at the same approximate time as that of the nasopharyngeal swab collection; and one postdose, collected 1-3 hours postdose. At all other visits, one predose plasma PK sample will be collected at the same approximate time as that of the nasopharyngeal swab collection. Time and date of collection should be recorded in source and in the eCRF. Subjects who discontinue treatment early (before completing 21 days of dosing) should return to the study site within 24 hours after the last dose of study treatment to complete an EOT visit. One plasma PK sample will be collected at the same approximate time as that of the nasopharyngeal swab collection.

[v] For subjects taking CNI and/or mTOR inhibitor, a blood sample will be collected to be analyzed at the local laboratory for CNI and/or mTOR inhibitor blood levels and a separate sample will be collected for analysis at the central laboratory.

[w] Standard of care test results may include chest imaging reports, laboratory tests, electrocardiogram , or other assessments.

[x] Prior therapies will include medications and other therapies (including surgeries and other interventions) that end prior to the first dose of study drug. Concomitant therapies will include medications and other therapies (including surgeries and other interventions) ongoing at the first dose of study drug or started any time after the first dose of study drug. Any medication or therapy (including surgeries and other interventions) taken within 1 month of signing the ICF (Screening) and during the study through the end of the study will be recorded.