



Clinical Study Protocol

EudraCT Number: 2022-002215-29

**A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY
TO EVALUATE THE EFFICACY AND SAFETY OF EDP-938 IN NON-HOSPITALIZED
ADULTS WITH ACUTE RESPIRATORY SYNCYTIAL VIRUS INFECTION WHO ARE
AT HIGH RISK FOR COMPLICATIONS**

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PROTOCOL APPROVAL- SPONSOR SIGNATORY

Study Title A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of EDP-938 in Non-hospitalized Adults with Acute Respiratory Syncytial Virus Infection who are at High Risk for Complications

Protocol Number EDP 938-104

Protocol Date and Version 30 October 2023, v4.1

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INVESTIGATOR 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.

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Study to Evaluate the Efficacy and Safety of EDP-938 in
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LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC ₀₋₂₄	area under the concentration-time curve from 0 to 24 hours
AUC _{0-inf}	area under the concentration-time curve from 0 to infinity
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EC50	half-maximal effective concentration
EC90	90% maximal effective concentration
ECG	Electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FDA	Food and Drug Administration
FEV ₁	forced expiratory volume in 1 second
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCV	hepatitis C virus
HDPE	high-density polyethylene
HRQOL	Health-Related Quality of Life
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
LD	loading dose

LLN	lower limit of normal
LRTD	lower respiratory tract disease
mITT	modified intent-to-treat (analysis population)
MMRM	mixed model for repeated measures
NAAT	nucleic acid amplification test
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NP	nasopharyngeal
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
PCR	polymerase chain reaction
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PND	postnatal day
PP	Per Protocol (analysis population)
PRO	patient-reported outcome
QD	once daily
QTcF	QT interval corrected for heart rate according to the Fridericia formula
RiiQ™	Respiratory Infection Intensity and Impact Questionnaire
RSV	respiratory syncytial virus
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	Safety (analysis population)
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome - coronavirus 2
SoA	schedule of assessments
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TND	target not detected
TSS	Total Symptom Score
ULN	upper limit of normal
URTD	upper respiratory tract disease
URTI	upper respiratory tract infection
VAS	visual analog scale
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 to Evaluate the Efficacy and Safety of EDP-938 in Non-hospitalized Adults with Acute Respiratory Syncytial Virus Infection who are at High Risk for Complications
Protocol Number: EDP 938-104
Phase of Development: 2b
Study Centers: This will be a multicenter global study.
Number of Subjects Planned: Approximately 180 subjects will be randomized.
Planned Study Population: Non-hospitalized adult subjects with up to 72 hours of respiratory tract infection symptoms, who test positive for respiratory syncytial virus (RSV) and negative for influenza virus and SARS-CoV-2, and who are at high risk for complications after RSV infection, which includes having at least one of the following risk factors: age ≥ 65 years; congestive heart failure (CHF) (New York Heart Association [NYHA] Class I to IV); chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Class I to III); or asthma. The total proportion of subjects either ≥ 65 to ≤ 74 years of age or patients with asthma combined will be capped at 20%.
Investigational Product, Dosage, and Mode of Administration: EDP-938 will be supplied as tablets for oral administration in a dose strength of 200 mg. The total dose administered will be 800 mg of EDP-938 or placebo once daily (QD) for 5 days.
Duration of Treatment: 5 days
Study Objectives: Primary Objective - To evaluate the effect of EDP-938 compared with placebo on the progression of RSV infection by assessment of clinical symptoms. Secondary Objectives - To evaluate the clinical efficacy of EDP-938 compared with placebo; - To evaluate the antiviral activity of EDP-938 compared with placebo; - To evaluate the pharmacokinetics (PK) of EDP-938;

- To evaluate the safety of EDP-938 compared with placebo.

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Criteria for Evaluation:

Primary Endpoint

- Time to resolution of RSV Lower Respiratory Tract Disease (LRTD) symptoms (cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) symptom scale through Day 33.

Secondary Endpoints

- Clinical efficacy:
 1. Time to resolution of each separate RSV LRTD symptom as assessed by RiiQ™ symptom scale score;
 2. Time to resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ symptom scale score;
 3. Time to resolution of all RSV symptoms as assessed by RiiQ™ symptom scale score;
 4. Change from Baseline in severity of RSV LRTD symptoms through Day 33 as assessed by RiiQ™ symptom scale score;
 5. Change from Baseline for RiiQ™ impact scale score through Day 33;
 6. Time to resolution of Upper Respiratory Tract Disease (sore throat and nasal congestion), LRTD, and 2 systemic symptoms through Day 33 as assessed by RiiQ™ symptom scale score;
 7. Time to no or mild impact of RSV disease on daily activities, emotions, and social relationships as assessed by RiiQ™ impact scale score;
 8. Percentage of participants with post-baseline RSV-related complications;
 9. Time to resolution of RSV infection symptoms as assessed by Patient Global Impression of Severity (PGI-S) scale score;
 10. Time to improvement in RSV disease as assessed by Patient Global Impression of Change (PGI-C) scale score;

11. Change from Baseline for Health-Related Quality of Life (HRQOL) through Day 33 as assessed by EuroQol 5 Dimensions 5 Levels (EQ--5D--5L) questionnaire;
 12. Time to return to usual health as assessed by 'Adult Return to Usual Health' question;
 13. Time to return to usual activities as assessed by the 'Adult Return to Usual Activities' question;
 14. Percentage of subjects with new antibiotic use, or new or increased use of bronchodilators, systemic or inhaled corticosteroids, or oxygen supplementation;
 15. Duration of treatment-emergent use of antibiotics;
 16. Duration of treatment-emergent new use or increased dose of bronchodilators or systemic or inhaled corticosteroids;
 17. Duration of new or increased oxygen supplementation;
 18. Percentage of subjects with unscheduled medically attended visits (i.e., outpatient clinic, urgent care center, or emergency room visits) for RSV infection or other causes;
 19. Percentage of subjects requiring hospitalization for RSV infection or other causes;
 20. Duration of hospitalization for RSV infection or other causes;
 21. Percentage of subjects requiring admission to intensive care unit (ICU) for RSV infection or other causes;
 22. Duration of ICU stay for RSV infection or other causes;
 23. Percentage of subjects requiring invasive or noninvasive mechanical ventilation;
 24. Duration of invasive or noninvasive mechanical ventilation;
 25. Duration of treatment-emergent new use or increased use of medications to treat CHF;
 26. All-cause mortality.
- Antiviral activity:
 1. RSV RNA viral load area under the curve (AUC) measured in nasopharyngeal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR) from Baseline at Days 3, 5, 9, and 14;
 2. Percentage of subjects with RSV RNA viral load Target Not Detected (TND) at any point during the study;
 3. Time to RSV RNA viral load below TND;

4. RSV RNA viral load change from Baseline at Days 3, 5, 9, and 14;
 5. Change in infectious RSV viral load over time by a quantitative cell-based infectivity assay.
- Pharmacokinetics:
 - Plasma concentrations of EDP-938 and its metabolites (EP-024766, EP-024636, EP-024594, and EP-024595);
 - Safety:
 - Safety endpoints include, but are not limited to, adverse events (AEs; including serious adverse events [SAEs], severe AEs, and AEs leading to discontinuation of the study drug), and clinically significant changes from baseline in vital sign measurements, pulse oximetry measurements, electrocardiograms (ECGs), and clinical laboratory test results (including chemistry and hematology).

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Study Design:

This is a Phase 2b, randomized, double-blind, placebo-controlled study of EDP-938 administered orally for the treatment of non-hospitalized adult subjects with confirmed RSV infection who are at high risk for complications after RSV infection.

For each subject, the duration of study participation will be approximately 33 days and will consist of 3 periods: Screening, Treatment, and Follow-up as follows:

Study Period	Duration
Screening (Day 1)	Occurs on Day 1
Treatment (Days 1 to 5)	5 days
Follow-up (Days 6 to 33)	28 days
Approximate total duration of participation	33 days

There are 6 scheduled visits as follows: Visit 1 on Day 1; Visit 2 on Day 3; Visit 3 or the End-of-Treatment (EOT) Visit on Day 5; Visit 4 on Day 9; Visit 5 on Day 14, and Visit 6 or the End-of-Study (EOS) Visit on Day 33. When possible, home nursing visits may replace all study site visits except Visit 1.

Screening Period on Day 1: At Screening, subjects will sign an initial informed consent form (ICF) for Rapid Viral Diagnostic Screening. Consented subjects will undergo a nucleic acid amplification test (NAAT) for RSV, SARS-CoV-2, and influenza virus using respiratory secretions obtained by nasal swab collection. Subjects whose swab sample tests are positive for RSV and negative for SARS-CoV-2 and influenza virus A/B may proceed for further screening and will sign a Study ICF prior to performing any further study-specific assessments. Subjects will be considered enrolled into the study at the time of signature of the Study ICF. After signing the Study ICF, subjects will undergo further screening procedures to determine study eligibility, including completing the RiiQ™ diary. Subjects meeting all study criteria and randomized into the study are considered enrolled.

Treatment Period (Days 1 to 5): 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 800 mg of EDP-938 or placebo QD. Subject randomization will be stratified by the number of high-risk factors (i.e., ≤ 2 vs. > 2) and the duration of respiratory symptoms (i.e., ≤ 48 hours vs. > 48 hours to ≤ 72 hours). The treatment duration is 5 days, during which 3 study visits are scheduled to be performed.

Randomized subjects must complete the Visit 1 (Day 1) sample collections (i.e., blood for hematology, blood chemistry, [REDACTED]; and nasopharyngeal swabs prior to receiving the first dose of EDP-938 or placebo. Visit 1 (Day 1) blood samples will be sent to both local (expedited testing and reporting) and central laboratories. Visit 1 (Day 1) nasopharyngeal swabs will be sent to the central laboratory only.

Randomized subjects will record RSV symptoms employing the RiiQ™ and health/functional status on an electronic device. The subject will be instructed on prohibited medications and the use of acetaminophen/paracetamol.

Subjects will receive the first dose of study drug while at the study site. After the first dose, subjects will be instructed to take or be administered study drug at approximately the same time every day (± 1 hour) on each of the 4 subsequent days. Because the subject is to take or be administered study drug at approximately the same time each day, study site visits and home nursing visits should be scheduled so that the dose is taken during the visit (e.g., the subject is to take the study drug in the presence of the study nurse during the home nursing visit). The subject will also receive instruction on the appropriate storage and transport of study drug.

The time and the number of tablets taken for each dosing day are to be recorded for each subject. For study site visits, the site will record the time the study drug was administered at the visit. At Visit 2 on Day 3 and Visit 3/EOT on Day 5 subjects are to bring their study drug with them to their study site visit for drug accountability and the time and number of tablets taken on Day 2 and Day 4 will be recorded per subject's recall of dosing.

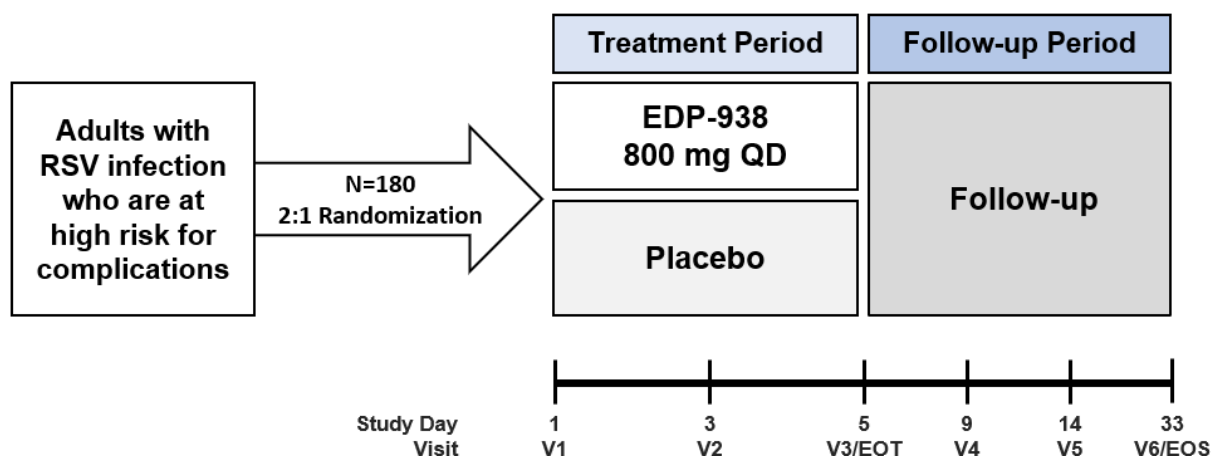
During the Treatment Period, subjects who discontinue the study drug prematurely (i.e., discontinue study drug prior to the last scheduled dose on Day 5) should be requested to return to the site within 24 hours and no more than 48 hours after the last dose later to complete the Visit 3/EOT Visit. Subjects who prematurely discontinue study drug should be requested to continue to participate in the safety monitoring through the Follow-up Period, until they complete the scheduled visits at Day 33. Subjects who withdraw or are withdrawn from the study at any time should be requested to return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.

Follow-up Period (Days 6 to 33): Subjects will have follow-up assessments from Day 6 through Day 33, with on-site study site visits on Visit 4 (Day 9), Visit 5 (Day 14), and Visit 6/EOS (Day 33) for post-treatment assessments.

Subjects who withdraw or are withdrawn from the study during the Follow-up Period should be requested to return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures. In such cases, the last study visit will include EOS assessments. Throughout the study, safety for each subject in each study period will be evaluated by assessment of AEs, clinical laboratory findings, physical examination findings (as applicable), vital sign measurements, and pulse oximetry measurements.

All study assessments for the Screening, Treatment, and Follow-Up Periods are detailed in the Schedule of Assessments.

Study Design Figure:



EOS = end of study; EOT = end of treatment; QD = once daily; RSV = respiratory syncytial virus; V = visit

The Day 3 and Day 5 visits have a window of ± 1 day.

Eligibility Criteria

Inclusion Criteria

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

1. The subject has signed and dated the ICFs.
2. The subject is a male or female adult at least 18 years of age, who has at least one of the following conditions that predispose them to complications after RSV infection:

- a. Age ≥ 65 years;
- b. CHF (NYHA Class I to IV)[[New York Heart Association Criteria Committee, 1994](#)];
- c. Asthma;
- d. COPD .

Note: Subjects with COPD and a diagnosis of alpha-1-anti-trypsin deficiency must have a transient elastography indicating no evidence of significant liver fibrosis (i.e., >7 kPa) or cirrhosis (i.e., >11 kPa).

3. The subject has a new onset of any of the following symptom(s) or worsening of pre-existing symptom(s) consistent with a respiratory tract infection no more than 72 hours prior to the administration of the first dose of study drug: feeling feverish, headache, neck pain, fatigue, loss of appetite, interrupted sleep, body aches, sore throat, nasal congestion, cough, cough with phlegm, wheezing, or short of breath.

Note: The duration of new onset of symptom(s) or worsening of pre-existing symptom(s) is to be measured from the estimated time of onset of the first symptom to the anticipated time of dosing with the study drug.

4. The subject reports at least 2 of the following symptoms, one of which must be reported as at least 'moderate' severity by the subject using the RiiQ™: cough, cough with phlegm, wheezing, or short of breath.
5. The subject has tested positive for RSV infection using a NAAT (polymerase chain reaction [PCR] or other) on a nasal swab sample.
6. The subject has a body mass index $\geq 18 \text{ kg/m}^2$ and $\leq 40 \text{ kg/m}^2$.
7. A heterosexually active female subject must agree to use 2 effective birth control methods for the duration of the study and for 30 days after the last dose of study drug, or be surgically sterile for at least 6 months or postmenopausal; subjects who are < 2 years postmenopausal will require a confirmatory serum follicle stimulating hormone (FSH) level $> 35 \text{ IU/mL}$.

Note: Effective birth control methods include male or female condom (may not be used together), intrauterine device (IUD), or systemic hormonal (i.e., oral, injectable, implantable, transdermal, or intravaginal) contraception associated with the inhibition of ovulation started a minimum of 2 weeks prior to signing the Study ICF:

- a. A heterosexually active female subject with a single male partner who has been vasectomized is not required to use another effective birth control method.
 - b. A female subject who practices sexual abstinence is not required to use another effective birth control method.
8. A heterosexually active male subject and their female partner(s) of childbearing potential must agree to use 2 effective birth control methods for the duration of the study and for 90 days after the last dose of study drug.

Note: Effective birth control methods include male or female condom (may not be used together), systemic hormonal contraception associated with the inhibition of ovulation started a minimum of 2 weeks prior to signing the Study ICF, or IUD.

- a. A vasectomized heterosexually active male subject with a single female partner is not required to use another effective birth control method;
 - b. Male subjects who practice sexual abstinence are not required to use another effective birth control method.
9. Male subject must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug.
 10. Female subject must agree to refrain from egg donation from the date of Screening until 30 days after their last dose of study drug.

11. Subject is willing and able to adhere to the assessments, visit schedule, prohibitions, and restrictions, as described in this protocol.

Exclusion Criteria

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

1. The subject has an anticipated need for hospitalization within 24 hours of signing the Study ICF.

Note: Emergency room or hospital observation status for an anticipated duration of less than <24 hours is not considered as hospitalization.
2. The subject has concomitant respiratory infections that are viral (other than RSV but including influenza), bacterial, or fungal, including systemic bacterial or fungal infections, within 7 days prior to signing the Study ICF.
3. The subject has a SARS-CoV-2 test result that is positive within 28 days prior to signing the Study ICF.
4. The subject is pregnant or nursing.
5. The subject has COPD GOLD Class IV [[Venkatesan P., 2022](#)];
6. The subject has a malignant tumor or history of malignancy that may interfere with the aims of the study or a subject completing the study.
7. The subject has prior receipt of or is waiting to receive a bone marrow, stem cell, or solid organ transplantation.
8. The subject has a known positive human immunodeficiency virus infection, active hepatitis A virus infection, chronic hepatitis B virus infection, and/or current hepatitis C virus (HCV) infection; subjects with a history of HCV infection who have achieved a documented sustained virologic response 12 weeks after completion of HCV therapy may be enrolled.
9. The subject has a history of chronic liver disease (e.g., hemochromatosis, Wilson's disease, cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis, and/or alcoholic liver disease); a history of active biliary disease (e.g., primary sclerosing cholangitis); or a history of portal hypertension. A diagnosis of hepatic steatosis (fatty liver) is not exclusionary.
10. The subject has any of the following cardiac conditions: any congenital heart disease, congenital long QT syndrome, or any clinical manifestation resulting in QT interval prolongation.
11. The subject has use of or intention to use excluded or contraindicated medication(s) or supplements, including any medication known to be a moderate or strong inducer or inhibitor of the cytochrome P450 3A4 enzyme (see [Section 5.8](#)) within 14 days prior to signing the Study ICF.
12. The subject has received an RSV vaccine within 12 months prior to signing the Study ICF.

13. The subject has received any investigational agent within 30 days (or 5 half-lives of that investigational agent, whichever is longer) prior to the first dose of study drug;
14. The subject has a history of or is 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.
15. Known hypersensitivity to the investigational product or any of its excipients.
16. Receiving dialysis or have known severe renal impairment (ie., eGFR <30 mL/min/1.73 m² within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula).

Statistical Methods: Detailed statistical analysis will be outlined in the Statistical Analysis Plan (SAP), which will be developed and finalized prior to database lock.

Sample Size Considerations: Using a randomization ratio of 2:1, a sample size of 180 subjects provides 80% power at 0.05 two-sided significance level under a log-rank test to detect a hazard ratio of 2.0 (note that a hazard ratio greater than 1.0 indicates a benefit) in time to resolution of RSV LRTD symptoms as assessed by the RiiQ™ symptom scale. This calculation assumes that 50% of subjects in the EDP-938 group and 30% of subjects in the placebo group will achieve a resolution of RSV LRTD symptom by Day 33, respectively, and up to 5% of subjects will discontinue the study drug early.

Subject Populations: The following analysis populations are planned:

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.

Modified Intent-to-Treat (mITT) Population: All randomized subjects positively diagnosed using the central RT-PCR quantification who receive at least one dose of assigned study drug will be included in the mITT population. The mITT population will be considered the efficacy population. Subjects will be analyzed as randomized.

Per Protocol (PP) Population: All subjects in the mITT population who completed 5-day Treatment Period and do not have major protocol deviations that may unduly influence RiiQ™ symptom scale scores. Subjects will be analyzed as randomized.

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

Statistical Analysis:

Subject Disposition and Demographic Data: The number of subjects screened, randomized, and in the SAF, mITT, PP, 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 primary efficacy analysis will be performed on time to resolution of RSV LRTD symptoms as assessed by RiiQ™ symptom scale through Day 33 using the stratified log-rank test for p-values and a Cox Proportional Hazards model including treatment group, stratification factors, and baseline RiiQ™ score to assess hazards ratio. Time to resolution (recorded in days) will be defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by RiiQ™ score is zero or 1. A Kaplan-Meier curve will display the probability estimates with resolution. Descriptive statistics on the graph will include the median and 95% confidence interval (CI) at a minimum. The change from baseline in RiiQ™ score will be compared between EDP-938 and placebo using mixed model for repeated measures (MMRM) with treatment group, Day (as class variable) and stratification factor as fixed effects, the baseline RiiQ™ as a covariate, treatment group by Day interaction, stratification factor by Day interaction, baseline RiiQ™ by Day interaction, as factors. Treatment groups will be compared at specified timepoints. The least-squares means and two-sided 95% CIs will be presented for individual groups and the difference between groups. Other continuous endpoints will be analyzed similarly with the MMRM model.

The categorical variables will be summarized and the between-group comparison will be analyzed using a Cochran-Mantel-Haenszel test controlling for the stratification factors.

Safety Analyses: Statistical methods for the safety analyses will be primarily descriptive in nature. Safety data, including AEs, vital sign measurements, pulse oximetry, ECGs, concomitant therapies, and clinically significant changes in laboratory measurements, 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.

Available plasma concentration-time data in the PK Population will be summarized by treatment group. Mean plasma concentration-time figures may be created for EDP-938 and its metabolites, as allowed by the data. Specific PK parameters will be listed in the SAP.

[REDACTED]

Study Governance: Safety data from this study will be reviewed by an independent Data Safety Monitoring Board (DSMB) throughout the study. The DSMB will be headed by a DSMB Chair and will include 3 experts independent from the Sponsor; 2 physicians with expertise in viral respiratory infections including RSV, and chronic health conditions included in this study, and 1 statistician. Procedures for data review, including timing

and potential outcomes, roles and responsibilities, and interactions with the Sponsor and contract research organization will be governed by a DSMB 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 patients with RSV infection. This Phase 2b study, EDP 938-104, is a randomized, double-blind, placebo-controlled, multicenter study designed to assess the efficacy and safety of EDP-938 compared to placebo in non-hospitalized adults with acute RSV infection who are at high risk for complications (age ≥ 65 years, congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD], or asthma).

1.2 Background

RSV is the leading cause of lower respiratory tract infection and presents a significant health challenge in small children, elderly, and immunocompromised patients [Falsey A.R. et al., 2005; Hall C.B. et al., 2009; Shook B.C. et al., 2017]. Although RSV was first recognized in 1957 as a cause of bronchiolitis in infants and is the most commonly identified cause of lower respiratory tract infection in young children [Hall C.B., 2001], RSV was not recognized as a potentially serious problem in older adults until the 1970s, when outbreaks of the virus occurred in long-term care facilities [Hart R., 1984; Sorvillo F.J. et al., 1984; Thompson W.W. et al., 2003; Vikerfors T. et al., 1987]. In fact, RSV is an important and often unrecognized cause of respiratory tract infection in adults, as well as an important cause of death in subjects older than 65 years and those with specific comorbidities (i.e., high-risk subjects), such as subjects with chronic cardiopulmonary disease [Falsey A.R. et al., 2000]. RSV is second only to influenza as a cause of medically significant respiratory tract illnesses in adults and is estimated to cause 177,000 hospitalizations and 14,000 annual deaths in US adults aged 65 years and older [CDC, 2020]. A statistical model by Thompson et. al. encompassing a 10-year period estimated more than 11,000 annual respiratory and circulatory deaths due to RSV in the US, with 78% in patients aged 65 years and older [Thompson W.W. et al., 2003]. Although RSV illness in healthy adults is typically self-limited and mild, illness in high-risk adults with chronic cardiopulmonary disease, particularly in patients with COPD and CHF, tends to be more severe, and is more likely to require medical attention. There is no specific treatment for RSV infection in adults.

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 was active against all RSV-A and RSV-B laboratory strains and clinical isolates tested *in vitro*. In primary human bronchial epithelial cells, EDP-938 had half-maximal effective concentration (EC₅₀) values of 21 nM, 23 nM, and 64 nM, against RSV-A Long, M37, and RSV-B Washington strains, respectively. 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 (N). An *in vitro* resistance study suggests that EDP-938 presents a higher barrier to resistance compared to 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 or synergistic antiviral effects *in vitro*. The *in vivo* efficacy of EDP-938 was demonstrated in the RSV-infected African Green Monkey model, with >4-log 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 (administered as a suspension in 0.5% methylcellulose) was 27.1% in dogs, 35.4% in mice, 35.7% in rats, and 39.5% in monkeys. An evaluation of membrane permeability of EDP-938 performed using Caco-2 cells showed a moderate *in vitro* permeability 3.6×10^{-6} cm/sec at 5 μ M. Based on the outcome of these absorption studies, EDP-938 is projected to have good oral absorption in humans.

Tissue distribution of EDP-938 was studied in rats. EDP-938 penetrated into the lung with a lung-to-plasma ratio of 0.7 to 2.5, with the lung being a critical target organ for RSV infection. [REDACTED]

The *in vitro* metabolite profile in liver microsomes showed that there are 5 potential metabolites formed across different species (human, monkey, dog, rat, and mouse). The structures of 4 of the 5 metabolites were confirmed, and authentic standards of the confirmed 4 metabolites [REDACTED] were synthesized. The human metabolites observed in *in vitro* liver microsomal incubations were also formed in mouse, rat, dog, and monkey, and no unique human metabolites were observed to date. Phenotyping with selective inhibitors and human complementary DNA-expressed isozymes suggests that cytochrome P450 (CYP) 3A4 is a major enzyme responsible for the formation of the 5 metabolites.

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 IC₅₀ values >20 µM for the NK1 and NK2 receptors. No secondary effects of toxicological concern were observed in the 28-day repeat-dose studies in mice, rats, or monkeys.

1.3.4 Nonclinical Toxicology

A battery of nonclinical toxicology studies with EDP-938 have been completed, including oral repeat-dose studies of up to 28 days duration in male and female rats, mice, and cynomolgus monkeys; *in vitro* and *in vivo* genotoxicity studies; *in vitro* mitochondrial toxicity studies; embryofetal development studies in time-mated rats and New Zealand white rabbits; and preliminary 2- and 4-week juvenile animal studies in rats.

In brief, EDP-938 was well tolerated in rodent and monkey repeat-dose toxicology studies. No adverse effects have been identified at the maximal exposures (area under the concentration-time curve [AUC]) obtained in mice (approximately 20 µg•hr/mL in both sexes), rats (approximately 35 µg•hr/mL in males and approximately 190 µg•hr/mL in females), or monkeys (approximately 40 µg•hr/mL in both sexes) in studies with up to a 28-day dosing duration. Non-adverse EDP-938-related microscopic findings have been limited to the liver with reversible minimal to mild hepatocellular hypertrophy and reversible minimal hepatocellular vacuolation observed in rats.

EDP-938 was negative in mutagenicity (Ames) and clastogenicity assays (*in vitro* chromosome aberration and *in vivo* micronucleus) and has shown no indication of mitotoxicity (Glucose/Galactose assay and mitobiogenesis).

EDP-938, administered over the course of organogenesis, was well tolerated in embryofetal development studies in time-mated rats and rabbits. No adverse effects on maternal or fetal parameters were observed at the highest doses administered in the definitive studies.

██████████. To date, preliminary 2- and 4-week tolerability and range-finding studies have been completed in juvenile rats with dosing initiated on postnatal day (PND) 4. EDP-938 at ≥ 200 mg/kg/day was not tolerated, and the liver and testes were identified as target organs at ≤ 100 mg/kg/day (AUC₀₋₂₄ up to 53.3 and 53.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and females, respectively, on PND 4 and up to 19.6 and 64.7 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and females, respectively, on PND 31).

1.4 Clinical Studies

Seven Phase 1 clinical studies have been completed:

- EDP-938-001: first-in-human (FIH) study in healthy adult subjects (n = 68 treated with EDP-938);
- EDP 938-002: drug-drug interaction (DDI) study in healthy adult subjects (n = 48 treated with EDP-938);
- EDP 938-003: DDI study in healthy adult subjects (n = 72 treated with EDP-938);
- EDP 938-004: bioavailability study in healthy adult subjects (n = 18 treated with EDP--938);
- EDP 938-006: DDI study in healthy adult subjects (n = 72 treated with EDP-938);
- EDP 983-007: DDI study in healthy adult subjects (n = 24 treated with EDP-938);
- EDP 938-009: mass balance, absorption, metabolism, and excretion study in healthy male subjects (n = 8 subjects treated with a single dose of 600 mg of [¹⁴C]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 Studies EDP-938-001, EDP 938-002, EDP 938-003, EDP 938-004, and EDP 938-009. EDP-938 was administered as a tablet formulation in Study EDP 938-004 (relative bioavailability study), EDP 938-006, and study EDP 938-007. In all the studies summarized in this section, EDP-938 was generally safe and well tolerated over a broad range of single and multiple doses.

In the FIH study (EDP-938-001), EDP-938 PK results indicated suitability for once daily (QD) or twice daily (BID) oral dosing regardless of food.

In Study EDP 938-002, the co-administration of the breast cancer resistance protein (BCRP)/P-gp inhibitor (and moderate CYP3A4 inhibitor) cyclosporine with EDP-938 had a weak effect on EDP-938 systemic exposures, measured by AUC from time 0 to infinity (AUC_{0-inf}), with an approximately 1.4-fold increase. The co-administration of the potential CYP3A4 inducer prednisone with EDP-938 showed no apparent effect on the EDP-938 AUC_{0-inf} (6.8% decrease).

In DDI Study EDP 938-003, when EDP-938 was co-administered with itraconazole (strong CYP3A4 inhibitor), EDP-938 AUC_{0-inf} increased by approximately 5.0-fold. When EDP-938 was co-administered with the strong CYP3A4 inducer rifampin, EDP-938 systemic exposures decreased by approximately 90%, while the co-administration of the P-gp inhibitor quinidine had no apparent effect on EDP-938 systemic exposures (1.06-fold increase in AUC_{0-inf}).

In DDI Study EDP 938-006, when EDP-938 was co-administered with dabigatran (P-gp substrate), dabigatran AUC_{0-inf} increased by 1.08-fold. When EDP-938 was coadministered with rosuvastatin (organic anion transporting polypeptide [OATP]1B1/B3 BCRP substrate), rosuvastatin AUC_{0-inf} increased by approximately 3.1-fold. When EDP-938 was coadministered with midazolam (CYP3A4 substrate), midazolam AUC_{0-inf}

decreased by approximately 44%. These results indicate that P-gp and CYP3A4 substrates may be coadministered with EDP-938 without dose adjustment. BCRP/OATP1B1/B3 substrates may be coadministered with EDP-938 without dose adjustment; however, BCRP/OATP1B1/B3 substrates should be monitored for safety due to possible increase in exposures of these substrates.

In DDI Study EDP 938-007, when EDP-938 was co-administered with fluconazole (moderate CYP3A4 inhibitor), EDP-938 AUC_{0-inf} increased by approximately 1.9-fold.

Based on results from completed DDI studies (Studies EDP 938-002, 003, 006 and 007), co-administration of EDP-938 with moderate or strong CYP3A4 inducers or inhibitors is not recommended. No dose adjustments of EDP-938 are required when it is co-administered with quinidine, other P-gp inhibitors/inducers, cyclosporine, or other BCRP inhibitors, or prednisone.

Study EDP 938-004 evaluated the PK of EDP-938 orally administered as a suspension formulation versus a tablet dosage form. The results suggest that EDP-938 can be administered without regard to food.

Study EDP 938-009 was conducted to determine the absorption, metabolism, and excretion of [¹⁴C]EDP-938 and to characterize and determine the metabolites present in plasma, urine, and feces in healthy male subjects following a single oral dose administration. The overall arithmetic mean recovery of total radioactivity was 98.1% of the administered radioactive dose in urine (6.85%) and feces (91.2%) through 240 hours postdose. Fecal excretion was the predominant route of elimination for EDP-938.

An RSV healthy subject challenge model study (EDP 938-101), has been completed and summarized below.

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 of study EDP 938-101, subjects were randomized to one of 3 treatment groups for 5 days of oral suspension dosing. 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 QD and BID 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.

In Part 2 of Study EDP 938-101, subjects were randomized into one of 3 treatment groups for 5 days of EDP-938 oral suspension. Both EDP-938 treatment regimens demonstrated robustly lower RSV RNA AUCs compared with placebo ($p < 0.001$), with no significant difference between the QD and BID 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 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, EDP 938-101, of healthy adults inoculated with RSV, all 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.

A Phase 2b study (EDP 938-102) has also been completed. This randomized, double blind, placebo-controlled study evaluated EDP-938 for the treatment of acute upper respiratory tract infection with RSV in ambulatory adults. Enrolled participants were randomly assigned 1:1 to receive 800 mg of EDP-938 or placebo once daily for 5 days. A total of 81 participants were randomized and dosed.

The study did not meet the primary endpoint of clinical symptom reduction. There was no statistical difference in the least square (LS) mean (SD) total symptom score (TSS) AUC from Day 1 through Day 14 between the EDP 938 treatment group (84.32 [83.560]) and the placebo group (69.24 [48.436]) ($p=0.246$). The secondary antiviral endpoints were not met; however, the percentage of subjects achieving undetectable RSV RNA viral load was numerically higher in the EDP-938 treatment group than in the placebo group at Days 3, 5, 9, and 14. The difference in the LS mean was statistically significant at Day 5 (end-of-treatment) between the 2 treatment groups ($p=0.033$).

EDP-938 was well tolerated in ambulatory adult subjects with RSV URTI. TEAEs occurred in 11 (27.5%) of the 40 subjects who received EDP-938 and 11 (26.8%) of the 41 subjects who received 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.

Potential risks to subjects receiving EDP-938 have been estimated based on safety data from the Phase 1 studies conducted in healthy subjects and the completed Phase 2a study (EDP 938-101) in healthy adult subjects infected with RSV-A Memphis 37b.

In the FIH EDP-938-001 study, overall, no safety concerns were reported in 68 healthy subjects dosed orally with EDP-938 in the single-ascending dose and multiple-ascending dose parts of the study. At single doses, EDP-938 was generally well tolerated with a total of 8 subjects reporting at least one adverse event (AE). Headache was the most frequently reported AE; all AEs were of mild intensity, and the majority were reported as not related or unlikely related to study drug. At multiple doses, EDP-938 was also generally well tolerated with a total of 9 subjects reporting at least one AE; headache being the most frequently reported AE. All AEs were of mild intensity, and the

majority of the AEs (i.e., headache) were reported as being possibly related to study drug, but ultimately with a similar distribution between EDP-938 (n = 3/30) and placebo (n = 2/10). All AEs resolved in follow-up. No serious AEs (SAEs) or AEs that led to study drug discontinuation were reported. There were no clinically significant, abnormal safety laboratory findings. Additionally, there were no clinically significant, abnormal electrocardiogram (ECG) or echocardiogram findings [[Ahmad A. et al., 2018](#)].

In the completed DDI studies EDP-938, AEs were generally mild and resolved in follow-up; there were no serious or severe AEs. In Study EDP 938-003, a subject discontinued from the study based on Principal Investigator decision; the subject had a transient, asymptomatic, and self-resolving nodal arrhythmia on ECG after a single dose of EDP-938.

Study EDP 938-004 evaluated the PK of EDP-938 orally administered as a suspension formulation versus a tablet dosage form. EDP-938 was generally well tolerated, with no severe or serious AEs, or discontinuations due to AEs.

Dosing is complete in Study EDP 938-006. Of the 72 subjects dosed in Part 2, 3, or 4, 10 subjects who received EDP-938 concomitantly either with rosuvastatin (3 subjects) or dabigatran (4 subjects) or EDP-938 alone (3 subjects) had maculopapular rash. Most of the rashes were moderate in severity, generalized, and associated with pruritus. All rash events resolved. Two subjects in Part 2 and one subject in Part 3 who had maculopapular rash with pruritus discontinued prematurely. Treatment-emergent adverse events (TEAEs) of rash (either localized or generalized) were not reported in Part 4. There were no other discontinuations due to TEAEs and SAEs.

In the Phase 2a EDP 938-101 study, all four EDP-938 regimens were generally well tolerated with safety profiles that were comparable to placebo. There were no severe AEs, no SAEs, and no TEAEs that led to study drug discontinuation. All TEAEs resolved in follow-up.

In Part 1, the only TEAEs reported for at least 5 (4.4%) subjects were headache, diarrhea, dizziness, nausea, and upper respiratory tract infection (URTI). Comparing the frequencies of these events in the EDP-938 QD, EDP-938 BID, and placebo arms, only headache (10.5%, 2.6%, 7.9%), dizziness (10.5%, 0%, 2.6%), and diarrhea (7.9%, 7.9%, 0%), respectively, were more common in one or both EDP-938 arms than in the placebo arm. Although more common in EDP-938 recipients, these events were infrequent, mild, and resolved. 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, the only TEAEs that were reported for at least 3 (4.8%) subjects were nausea, dizziness, headache, and URTI. Comparing the frequencies of these events in the EDP-938 and placebo arms, only nausea (4.8%, 14.3%, 0%), dizziness (0%, 9.5%, 4.8%), and URTI (4.8%, 9.5%, 4.8%), respectively, were more common in either EDP-938 arm than in the placebo arm. All TEAEs in EDP-938 recipients were mild except for a single event of vessel puncture site paresthesia that was considered moderate.

Among EDP-938 recipients, all events were reported as mild except for an event of moderate dyspepsia that was considered unrelated and resolved. No SAEs or AEs that led to study drug discontinuation were reported. Although the events of dizziness, headache, and diarrhea were numerically more common in EDP-938 recipients, these were infrequent, mild, and resolved.

In an *in vitro* photosafety assessment, EDP-938 was shown to have an absorption peak within the range of natural sunlight at 355 nm, suggesting that EDP-938 may be photoreactive. Therefore, precautions should be taken during the clinical trial to limit the subject's exposure to sunlight upon treatment with EDP-938.

It is possible that exposure to EDP-938 may lead to RSV resistance to EDP-938 as may occur with any 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.

2 OBJECTIVES AND ENDPOINTS

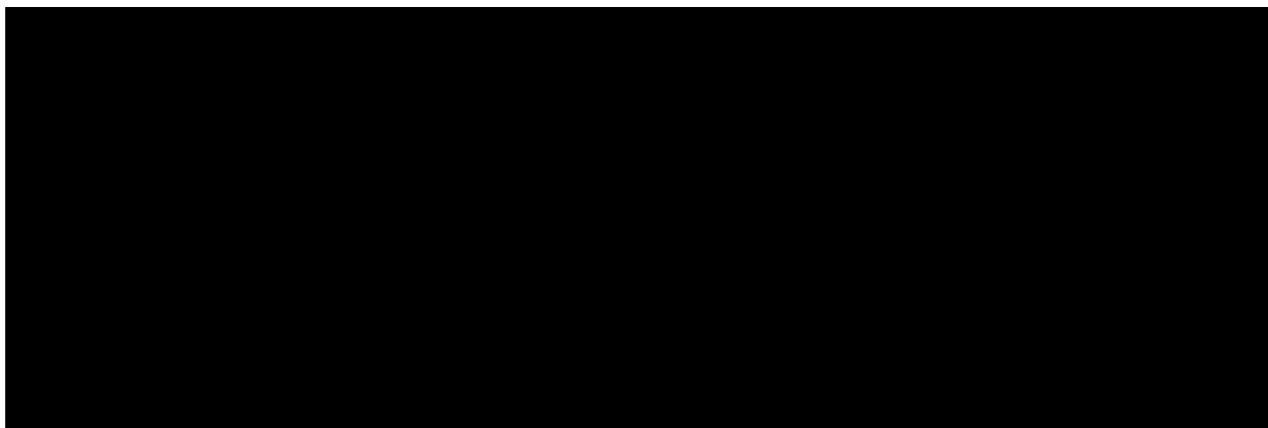
2.1 Objectives

2.1.1 Primary Objective

- To evaluate the effect of EDP-938 compared with placebo on the progression of RSV infection by assessment of clinical symptoms.

2.1.2 Secondary Objectives

- To evaluate the clinical efficacy of EDP-938 compared with placebo;
- To evaluate the antiviral activity of EDP-938 compared with placebo;
- To evaluate the PK of EDP-938;
- To evaluate the safety of EDP-938 compared with placebo.



2.2 Endpoints

2.2.1 Primary Endpoint

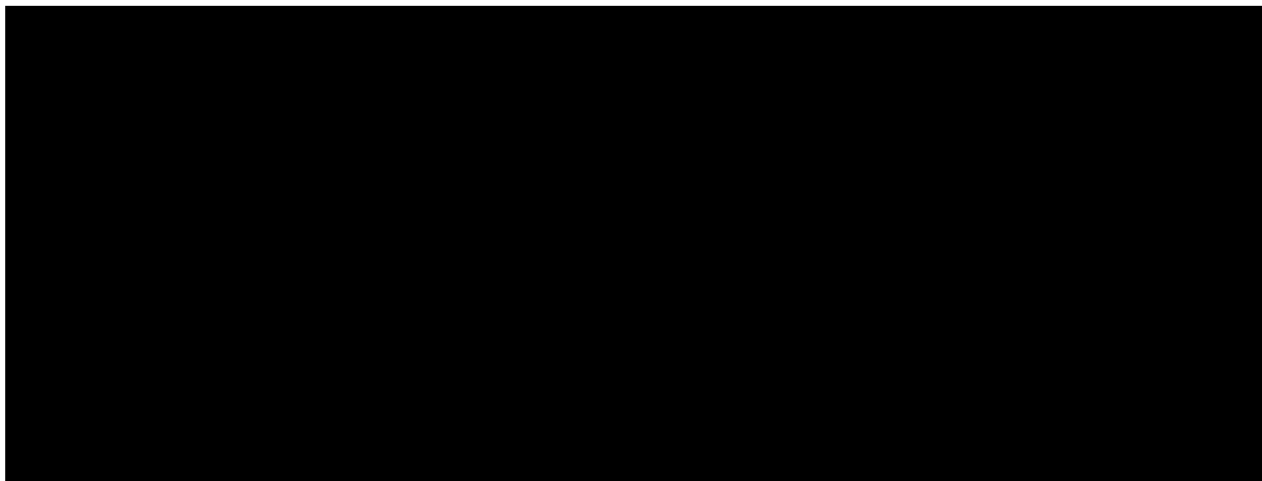
- Time to resolution of RSV Lower Respiratory Tract Disease (LRTD) symptoms (cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) symptom scale through Day 33.

2.2.2 Secondary Endpoints

- Clinical efficacy:
 1. Time to resolution of each separate RSV LRTD symptom as assessed by RiiQ™ symptom scale score;
 2. Time to resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ symptom scale score;

3. Time to resolution of all RSV symptoms as assessed by RiiQ™ symptom scale score;
4. Change from Baseline in severity of RSV LRTD symptoms through Day 33 as assessed by RiiQ™ symptom scale score;
5. Change from Baseline for RiiQ™ impact scale score through Day 33;
6. Time to resolution of Upper Respiratory Tract Disease (URTD, sore throat and nasal congestion), LRTD, and 2 systemic symptoms through Day 33 as assessed by RiiQ™ symptom scale score;
7. Time to no or mild impact of RSV disease on daily activities, emotions, and social relationships as assessed by RiiQ™ impact scale score;
8. Percentage of participants with post-baseline RSV-related complications;
9. Time to resolution of RSV infection symptoms as assessed by Patient Global Impression of Severity (PGI-S) scale score;
10. Time to improvement in RSV disease as assessed by Patient Global Impression of Change (PGI-C) scale score;
11. Change from Baseline for Health-Related Quality of Life (HRQOL) through Day 33 as assessed by EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire;
12. Time to return to usual health as assessed by 'Adult Return to Usual Health' question;
13. Time to return to usual activities as assessed by the 'Adult Return to Usual Activities' question;
14. Percentage of subjects with new antibiotic use, or new or increased use of bronchodilators, systemic or inhaled corticosteroids, or oxygen supplementation;
15. Duration of treatment-emergent use of antibiotics;
16. Duration of treatment-emergent new use or increased dose of bronchodilators or systemic or inhaled corticosteroids;
17. Duration of new or increased oxygen supplementation;
18. Percentage of subjects with unscheduled medically attended visits (i.e., outpatient clinic, urgent care center, or emergency room visits) for RSV infection or other causes;
19. Percentage of subjects requiring hospitalization for RSV infection or other causes;
20. Duration of hospitalization for RSV infection or other causes;
21. Percentage of subjects requiring admission to intensive care unit (ICU) for RSV infection or other causes;

- 22. Duration of ICU stay for RSV infection or other causes;
- 23. Percentage of subjects requiring invasive or noninvasive mechanical ventilation;
- 24. Duration of invasive or noninvasive mechanical ventilation;
- 25. Duration of treatment-emergent new use or increased use of medications to treat CHF;
- 26. All-cause mortality.
- Antiviral activity:
 - 1. RSV RNA viral load AUC measured in nasopharyngeal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR) from Baseline at Days 3, 5, 9, and 14;
 - 2. Percentage of subjects with RSV RNA viral load Target Not Detected (TND) at any point during the study;
 - 3. Time to RSV RNA viral load TND;
 - 4. RSV RNA viral load change from Baseline at Days 3, 5, 9, and 14;
 - 5. Change in infectious RSV viral load over time by a quantitative cell-based infectivity assay.
- Pharmacokinetics
 - Plasma concentrations of EDP-938 and its metabolites (EP-024766, EP-024636, EP-024594, and EP-024595).
- Safety
 - Safety endpoints include, but are not limited to AEs (including SAEs, severe AEs, and AEs leading to discontinuation of the study drug), and clinically significant changes from baseline in vital sign measurements, pulse oximetry measurements, ECGs, and clinical laboratory test results (including chemistry and hematology).



3 SELECTION OF SUBJECTS

A total of approximately 180 subjects are planned to be randomized into this study.

3.1 Subject Inclusion Criteria

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

1. The subject has signed and dated the informed consent forms (ICFs).
2. The subject is a male or female adult at least 18 years of age, who has at least one of the following conditions that predispose them to complications after RSV infection:
 - a. Age ≥ 65 years;
 - b. CHF (New York Heart Association [NYHA] Class I to IV) [[New York Heart Association Criteria Committee, 1994](#)];
 - c. Asthma;
 - d. COPD.

Note: Subjects with COPD and a diagnosis of alpha-1 anti-trypsin deficiency must have a transient elastography indicating no evidence of significant liver fibrosis (i.e., >7 kPa) or cirrhosis (i.e., >11 kPa).

3. The subject has a new onset of any of the following symptom(s) or worsening of pre-existing symptom(s) consistent with a respiratory tract infection no more than 72 hours prior to the administration of the first dose of study drug: feeling feverish, headache, neck pain, fatigue, loss of appetite, interrupted sleep, body aches, sore throat, nasal congestion, cough, cough with phlegm, wheezing, or short of breath.

Note: The duration of new onset of symptom(s) or worsening of pre-existing symptom(s) is to be measured from the estimated time of onset of the first symptom to the anticipated time of dosing with investigational drug.

4. The subject reports at least 2 of the following symptoms, one of which must be reported as at least 'moderate' severity by the subject using the RiiQ: cough, cough with phlegm, wheezing, or short of breath.
5. The subject has tested positive for RSV infection using a nucleic acid amplification test (NAAT; polymerase chain reaction [PCR] or other) on a nasal swab sample.
6. The subject has a body mass index ≥ 18 kg/m² and ≤ 40 kg/m².

7. A heterosexually active female subject must agree to use 2 effective birth control methods for the duration of the study and for 30 days after the last dose of study drug or be surgically sterile for at least 6 months or postmenopausal; subjects who are <2 years postmenopausal will require a confirmatory serum follicle -stimulating hormone (FSH) levels >35 IU/mL.

Note: Effective birth control methods include male or female condom (may not be used together), intrauterine device (IUD), or systemic hormonal (i.e., oral, injectable, implantable, transdermal, or intravaginal) contraception associated with the inhibition of ovulation started a minimum of 2 weeks prior to signing the Study ICF:

- a. A heterosexually active female subject with a single male partner who has been vasectomized is not required to use another effective birth control method.
 - b. A female subject who practices sexual abstinence is not required to use another effective birth control method.
8. A heterosexually active male subject and their female partner(s) of childbearing potential must agree to use 2 effective birth control methods for the duration of the study and for 90 days after the last dose of study drug.

Note: Effective birth control methods include male or female condom (may not be used together), systemic hormonal contraception associated with the inhibition of ovulation started a minimum of 2 weeks prior to signing the Study ICF, or IUD:

 - a. A vasectomized heterosexually active male subject with a single female partner is not required to use another effective birth control method;
 - b. Male subjects who practice sexual abstinence are not required to use another effective birth control method.
9. Male subject must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug.
10. Female subject must agree to refrain from egg donation from the date of Screening until 30 days after their last dose of study drug.
11. Subject is willing and able to adhere to the assessments, visit schedule, prohibitions, and restrictions, as described in this protocol.

3.2 Subject Exclusion Criteria

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

1. The subject has an anticipated need for hospitalization within 24 hours of signing the Study ICF.

Note: Emergency room or hospital observation status for an anticipated duration of less than <24 hours is not considered as hospitalization.

2. The subject has concomitant respiratory infections that are viral (other than RSV but including influenza), bacterial, or fungal, including systemic bacterial or fungal infections, within 7 days prior to signing the Study ICF.
3. The subject has a SARS-CoV-2 test result that is positive within 28 days prior to signing the Study ICF.
4. The subject is pregnant or nursing;
5. The subject has COPD GOLD Class IV [[Venkatesan P., 2022](#)];
6. The subject has a malignant tumor or history of malignancy that may interfere with the aims of the study or a subject completing the study.
7. The subject has prior receipt of or is waiting to receive a bone marrow, stem cell, or solid organ transplantation.
8. The subject has a known positive human immunodeficiency virus infection, active hepatitis A virus infection, chronic hepatitis B virus infection, and/or current hepatitis C virus (HCV) infection; subjects with a history of HCV infection who have achieved a documented sustained virologic response 12 weeks after completion of HCV therapy may be enrolled.
9. The subject has a history of chronic liver disease (e.g., hemochromatosis, Wilson's disease, cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis, and/or alcoholic liver disease); a history of active biliary disease (e.g., primary sclerosing cholangitis); or a history of portal hypertension. A diagnosis of hepatic steatosis (fatty liver) is not exclusionary.
10. The subject has any of the following cardiac conditions: any congenital heart disease, congenital long QT syndrome, or any clinical manifestation resulting in QT interval prolongation.
11. The subject has use of or intention to use excluded or contraindicated medication(s) or supplements, including any medication known to be a moderate or strong inducer or inhibitor of the CYP450 3A4 enzyme (see [Section 5.8](#)), within 14 days prior to signing the Study ICF.
12. The subject has received an RSV vaccine within 12 months prior to signing the Study ICF.
13. The subject has received any investigational agent within 30 days (or 5 half-lives of that investigational agent, whichever is longer) prior to the first dose of study drug.
14. The subject has a history of or is 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.
15. Known hypersensitivity to the investigational product or any of its excipients.

16. Receiving dialysis or have known severe renal impairment (ie., eGFR <30 mL/min/1.73 m² within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula).

4 STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled study of EDP-938 administered orally for the treatment of non-hospitalized adult subjects with confirmed RSV infection who are at high risk for complications after RSV infection.

For each subject, the duration of study participation will be approximately 33 days and will consist of 3 periods: Screening, Treatment, and Follow-up as shown in [Table 1](#):

Table 1: Timing and Duration of Study Periods

Study Period	Duration
Screening (Day 1)	Occurs on Day 1
Treatment (Days 1 to 5)	5 days
Follow-up (Days 6 to 33)	28 days
Approximate total duration of participation	33 days

There are 6 scheduled visits as follows: Visit 1 on Day 1; Visit 2 on Day 3; Visit 3 or the End-of-Treatment (EOT) Visit on Day 5; Visit 4 on Day 9; Visit 5 on Day 14, and Visit 6 or the End-of-Study (EOS) Visit on Day 33. When possible, home nursing visits may replace all study site visits except Visit 1.

- **Screening Period on Day 1:** At Screening, subjects will sign an initial ICF for Rapid Viral Diagnostic Screening. Consented subjects will undergo NAAT for RSV, SARS-CoV-2, and influenza virus using respiratory secretions obtained by nasal swab collection. Subjects whose swab sample tests are positive for RSV and negative for SARS-CoV-2 and influenza virus may proceed for further screening and will sign a Study ICF prior to performing any further study-specific assessments. After signing the Study ICF, subjects will undergo further screening procedures to determine study eligibility, including completing the RiiQ™ diary. Subjects meeting all study criteria and randomized into the study are considered enrolled.
- **Treatment Period (Days 1 to 5):** 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 800 mg of EDP-938 or placebo. Subject randomization will be stratified by the number of high-risk factors (i.e., ≤2 vs. >2) and the duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours). The treatment duration is 5 days, during which 3 study visits are scheduled to be performed.

Randomized subjects must complete the Visit 1 (Day 1) sample collections (i.e., blood for hematology, blood chemistry, [REDACTED] and nasopharyngeal swabs) prior to receiving the first dose of EDP-938 or placebo.

Visit 1 (Day 1) blood samples will be sent to both local (expedited testing and reporting) and central laboratories. Visit 1 (Day 1) nasopharyngeal swabs will be sent to the central laboratory only.

Randomized subjects will record RSV symptoms and health/functional status on an electronic device. The subject will be instructed on prohibited medications and the use of acetaminophen/paracetamol.

Subjects will receive the first dose of study drug while at the study site. After the first dose, subjects will be instructed to take or be administered study drug at approximately the same time every day (± 1 hour) on each of the 4 subsequent days. Because the subject is to take or be administered study drug at approximately the same time each day, study site visits and home nursing visits should be scheduled so that the dose is taken during the visit (e.g., the subject is to take the study drug in the presence of the study nurse during the home nursing visit). The subject will also receive instruction on the appropriate storage and transport of study drug.

The time and the number of tablets taken for each dosing day are to be recorded for each subject. For study site visits, the site will record the time the study drug was administered at the visit. At Visit 2 on Day 3 (± 1 day) and Visit 3/EOT on Day 5 (± 1 day) subjects are to bring their study drug with them to their study site visit for drug accountability and the time and number of tablets taken on Day 2 and Day 4 will be recorded per subject's recall of dosing.

During the Treatment Period, subjects who discontinue the study drug prematurely (i.e., discontinue study drug prior to the last scheduled dose on Day 5) are requested to return to the site within 24 hours and no more than 48 hours after the last dose later to complete the Visit 3/EOT Visit. Subjects who prematurely discontinue the study drug should be requested to continue to participate in the safety monitoring through the Follow-up Period, until they complete the scheduled visits at Day 33. Subjects who withdraw or are withdrawn from the study at any time should be requested to return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.

- **Follow-up Period (Days 6 to 33):** Subjects will have follow-up assessments from Day 6 through Day 33, with on-site study site visits on Visit 4 (Day 9), Visit 5 (Day 14), and Visit 6/EOS (Day 33) for post-treatment assessments.

Subjects who withdraw or are withdrawn from the study during the Follow-up Period should be requested to return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures. In such cases, the last study visit will include EOS assessments.

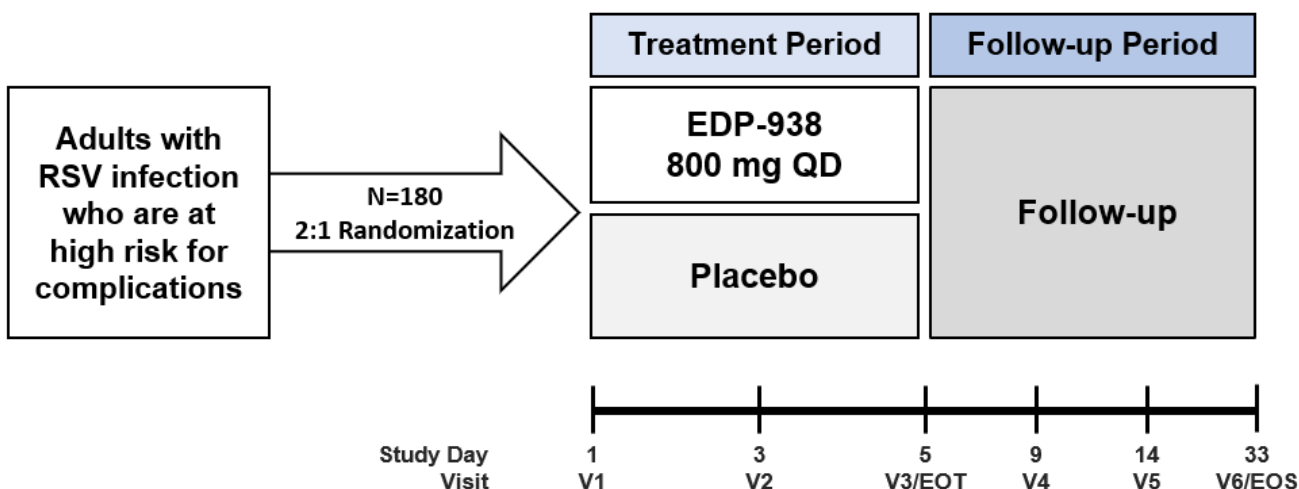
Throughout the study, safety for each subject in each study period will be evaluated by assessment of AEs, clinical laboratory findings, physical examination findings (as applicable), vital sign measurements, and pulse oximetry measurements.

All study assessments for the Screening, Treatment and Follow-Up Periods are detailed in the Schedule of Assessments ([Appendix 1](#)).

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 randomized 2:1 to receive 800 mg of EDP-938 or placebo QD for a total of 5 days. An overview of the study design is shown in [Figure 1](#). Study site visits and assessments are detailed in the Schedule of assessments (SoA; [Appendix 1](#)).

Figure 1: Study Design



EOS = end of study; EOT = end of treatment; QD = once daily; RSV = respiratory syncytial virus; V = visit

The Day 3 and Day 5 visits have a window of ± 1 day.

4.2 Rationale for Study Design

This proposed study will evaluate EDP-938 in non-hospitalized adults with acute RSV infection who are at high risk for complications (age ≥ 65 years and high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma). Eligible subjects will be randomized to receive either 800 mg of EDP-938 or placebo in a 2:1 ratio.

4.2.1 Justification of Study Design, Endpoints, and Subject Population

Despite the significant medical need, there is no highly effective treatment currently available for RSV. Analyses performed subsequent to the approval of aerosolized ribavirin suggest that it failed to impart any clinically significant benefits [[Randolph A.G. et al., 1996](#)]. Consequently, physicians have no safe and highly effective treatment for RSV infection. This is an issue of significant concern for those providing medical care for patients at risk of severe RSV disease, including the elderly, those with chronic lung

and/or heart diseases, immunosuppressed individuals, and pediatric patients. In these populations, RSV infection may be associated with significant morbidity and even mortality.

RSV is an important and often unrecognized cause of respiratory tract infection in adults, as well as an important cause of death in subjects older than 65 years and those with specific comorbidities (i.e., high-risk adults), such as adults with chronic cardiopulmonary disease. RSV is second only to influenza as a cause of medically significant respiratory tract illnesses in adults and is estimated to cause 177,000 hospitalizations and 14,000 annual deaths in US adults aged 65 years and older [CDC, 2020]. A statistical model encompassing a 10-year period estimated more than 11,000 annual respiratory and circulatory deaths due to RSV in the US with 78% in patients aged 65 years and older [Thompson W.W. et al., 2003].

This Phase 2b study aims to evaluate the efficacy, safety, and PK of EDP-938 in a population of non-hospitalized adults with acute RSV infection who are at high risk for complications (age ≥ 65 years and high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma), with early detection of RSV infection as well as early initiation of EDP-938. The total proportion of subjects either ≥ 65 to ≤ 74 years of age or patients with asthma combined will be capped at 20%. To more fully investigate the efficacy of EDP-938, a double-blind, placebo-controlled study design was selected, where subjects will be randomized to receive either 800 mg of EDP-938 or placebo in a 2:1 ratio. The study endpoints include efficacy, safety, and PK assessments. The primary endpoint is based on the subject's once daily assessment of RSV-related clinical symptoms over the course of the 33-day study using the RiiQTM patient-reported outcome (PRO) questionnaire. These data will enable the determination of the time to resolution of RSV LRTD symptoms. The antiviral activity will be assessed as the AUC for RSV RNA quantitation by nasopharyngeal swab over the course of the 33-day study, among other endpoints. The RSV RNA AUC assessment was similarly employed in the Phase 2a EDP 938-101 study. Safety and PK assessments will also be summarized in relation to study treatment group.

These eligible populations may be more sensitive to early onset of URTI symptoms and thus may be more likely to present for RSV screening. The study also excludes subjects who are not considered to be medically stable or who require urgent, emergency medical care, or hospitalization. Also excluded are subjects with known concomitant infections, and liver, kidney, and/or heart disease.

Because the window for optimal intervention for RSV infection may be discrete, the screening process is optimized to allow rapid identification of subjects infected with RSV (but who are not infected with SARS-CoV-2 or the influenza virus) and who are otherwise appropriate for the study so that EDP-938 (or placebo) can be initiated at the earliest possible timepoint. A dosing duration of 5 days has been selected as EDP-938 was demonstrated to be generally safe and efficacious in the Phase 2a EDP 938-101 study (Section 1.4 and Section 1.5), in which healthy adult subjects were inoculated with RSV and received EDP-938 either QD or BID for up to 5 days. Additionally, 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 (Section 1.4 and Section 1.5).

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 an independent Data Safety Monitoring Board (DSMB) whose activities will be defined in a separate DSMB charter.

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 470 subjects exposed to single or multiple doses of EDP-938 for up to 21 days.

Study EDP-938-001, the FIH study, evaluated EDP-938 administered as a suspension in 68 healthy subjects dosed orally with EDP-938 up to 800 mg (single-ascending dose part) and with multiple doses up to 600 mg QD or 300 mg BID for 7 days (multiple-ascending dose part). In this study, EDP-938 was observed to be generally safe and well tolerated with no SAEs or severe AEs and no discontinuations of EDP-938 due to AEs (Section 1.4).

In Study EDP 938-101, EDP-938 (administered as a suspension) was rapidly absorbed and had an elimination half-life ($t_{1/2}$) that supports QD or BID dosing. Based on predose concentrations, steady state appeared to be reached after approximately 2 doses of EDP-938. Following 5 days of dosing, the geometric mean plasma C₂₄ was approximately 14.5- and 25-fold higher than the *in vitro* 90% maximal effective concentration (EC₉₀) of RSV M37 for the 300 mg QD group and the 600 mg QD group, respectively. Similarly, the geometric mean plasma C₁₂ was approximately 25- and 40-fold higher than the *in vitro* EC₉₀ of RSV M37 for the 400 mg loading dose (LD)/200 mg BID group and the 500 mg LD/300 mg BID group, respectively. All EDP-938 regimens were superior to placebo with respect to efficacy endpoints (viral load AUC and TSS AUC). All 4 dose regimens of EDP-938 were well tolerated. There were no serious or severe TEAEs and no TEAEs led to withdrawal from the study or to discontinuation of study drug. TEAEs were also generally mild, with events of moderate intensity being very infrequent among EDP-938 recipients. There were no clinically significant laboratory abnormalities or ECG findings.

Study EDP 938-004, a relative bioavailability study comparing the suspension formulation (used in Study EDP-938-001 and Study EDP 938-101) to the Phase 2b formulation (tablet), provided information on the relative peak and systemic exposures of 600 mg administered as a tablet (in fasted and fed states) or as a suspension. PK results from this study showed that in the fasted state, the tablet formulation had slightly lower systemic exposures (16% lower) compared with the suspension formulation. Further, following a high-fat meal, the tablet formulation had higher peak and systemic exposures than the tablet formulation administered in the fasted state; the geometric mean maximum concentration and AUC_{0-inf} were approximately 2.4- and 1.4-fold higher, respectively, in the fed state versus the fasted state. The geometric mean half-life was generally similar in both states (approximately 13 to 15 hours), suggesting that it was

not affected by formulation or food. The mean concentration at 24 hours postdose was generally comparable across treatment groups and was approximately 400 ng/mL, which is approximately 20-fold higher than the *in vitro* EC₉₀ for RSV M37 (20 ng/mL). Taken together, these results suggest that EDP-938 tablets can be administered regardless of food. Based on the PK data from Studies EDP 938-001, -004, and -101, and accounting for the formulation difference and modest food effect observed in Study EDP 938-004, an EDP-938 dose of 800 mg can be administered without regard to food and is expected to provide exposures similar to the 600 mg 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 contain a formulated blend of EDP-938 solid dispersion intermediate [REDACTED] and pharmaceutically acceptable generally recognized as safe and/or excipients that are listed in the Food and Drug Administration (FDA) inactive ingredient database. These excipients include microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, and sodium stearyl fumarate. Placebo tablets contain microcrystalline cellulose, mannitol, and sodium stearyl fumarate. Both active and matching placebo tablets are coated using Opadry White, a hydroxypropyl methylcellulose-based coating used for aesthetic (nonfunctional) purposes.

5.2 Packaging and Labeling

EDP-938 drug product tablets and the corresponding placebo tablets are supplied as 22 count (200 mg) tablets in white 60-cc high-density polyethylene (HDPE) bottles closed with a child-resistant polypropylene closure. Each HDPE bottle is induction sealed and contains a 1-g silica gel desiccant and a low moisture polyester coil.

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 15°C to 30°C (59°F to 86°F). Additional information can be found in the Pharmacy Manual.

Subjects will be instructed to store study drug in the original bottle at 15°C to 30°C (59°F to 86°F).

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.

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. Dosing administered by subject including date, time, and number of tablets should be recorded in source based on subject recall.

5.5 Handling and Disposal

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 designee until monitored by the Study Monitor. Full accountability of all study drug distributed to subjects will be documented per Section 5.4.

At the end of the study, 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 Response Technology (IRT). Subjects will be randomized in a 2:1 ratio to the EDP-938 or placebo treatment group as shown below:

- Group 1 (approximately 120 subjects): 800 mg of EDP-938 orally QD for 5 days
- Group 2 (approximately 60 subjects): Placebo orally QD for 5 days

In addition, subject randomization will be stratified by the number of high-risk factors (i.e., ≤ 2 vs. > 2) and the duration of respiratory symptoms (i.e., ≤ 48 hours vs. > 48 hours to ≤ 72 hours).

The randomization code will be produced by Enanta Pharmaceuticals, Inc. (or designee). The Enanta Pharmaceuticals, Inc. unblinded biostatistician or designee will review and approve the final randomization list.

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).

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 800 mg EDP-938 or placebo orally while at the study site. After the first dose, subjects will be instructed to take or be administered the study drug orally at approximately the same time every day (± 1 hour) on each of the 4 subsequent days.

Note: Site staff will record the time and date of all study drug doses taken at the site.

For any day dosing is self-administered by subject, the site will request the subject to report the date and time of the administration based on recall. The dosing date and time of dosing administered by subject will be recorded in source.

On Day 3 and Day 5, subjects should bring their study drug with them as part of their study site visit for drug accountability and for dosing of study drug, as described below. If the subject is unable to attend Visit 2 (Day 3) and/or Visit 3/EOT (Day 5) at the study site, a home visit by a study nurse may be arranged.

On Day 3 and Day 5, the study site visit should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site. If the study site visit occurs up to 4 hours after the time scheduled for dosing of study drug, then the subject should take the study drug at the site during the visit (refer to the SoA [Appendix 1]). If the study site visit occurs more than 4 hours after the time scheduled for dosing of study drug, then the subject should take the study drug at the scheduled time.

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 1 dose should be taken on any calendar day;
- There must be a minimum of 16 hours between doses.

5.7.1 Dispensing of Study Drug

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

5.7.2 Treatment Compliance

The subject will be instructed to bring all study drug (including empty bottles) to the site on Visit 2 (Day 3), Visit 3 (Day 5), or the EOT/EOS Visit for subjects who discontinue the study drug or withdraw from the study early. 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 the time they took their dose on the previous day and 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 nurse via a home visit, if feasible.

For any subject considered to demonstrate continued noncompliance of study drug dosing despite continued educational efforts, the Investigator should contact the contract research organization's (CRO) or the Sponsor's Medical Monitor to discuss possible withdrawal of the subject from the study.

5.8 Prohibited Medications

Participants may continue taking chronic, scheduled medications during the study, except for medications that are moderate or strong inhibitors or inducers of CYP3A4 (see below).

New use of the following drugs and over-the-counter medications with equivalent efficacy will be prohibited from the first dose of study drug on Day 1 through Day 33 or early discontinuation of the study drug:

- Systemic antiviral (except study drug), antimicrobial* and antifungal drugs*;
- Antipyretics/analgesics (except acetaminophen/paracetamol)†;
- Antitussives/expectorants;
- Combination cold remedies;
- Antihistamines‡;
- Immunomodulators;
- Traditional medicines used for respiratory infection (e.g., Maoutou);
- Ribavirin;
- Other investigational drugs.

* Except for the treatment of complications of RSV infection suspected to be a bacterial infection after Day 1.

† If RSV symptoms occur, such as fever or headache, that require symptomatic relief during the study, then subjects may take acetaminophen/paracetamol at a dose of 3000 mg/day or less. Acetaminophen/paracetamol will be permitted only for the relief of fever or pain. If a subject plans to take acetaminophen/paracetamol within 2 hours of a scheduled time to record RSV symptoms in the electronic device, then the RSV symptom record should be completed immediately before the subject takes acetaminophen/paracetamol or 4 hours after taking acetaminophen/paracetamol.

‡ Dermal preparations are permitted, but systemic use or topical application to the eyes or nose are prohibited.

Additionally, moderate or strong inhibitors and inducers of CYP3A4 are prohibited within 14 days prior to the first dose of study drug and throughout study duration.

Note: A comprehensive list of CYP3A4 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>

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/CRO statistician for the 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 DSMB charter;
- Unblinded members of the independent DSMB for purposes of unblinded data review;
- Unblinded Drug Supply Chain personnel for the purpose of monitoring drug supplies;
- Enanta/CRO Pharmacovigilance Group 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, 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 IRT process.

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.

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

(Table 2). Information relating to unblinding (e.g., the reason, date) should be clearly recorded in the participant's study file.

Table 2: [REDACTED] Medical Monitor 24-Hour Safety Hotline for Protocol Inquiries

Region	Phone Number
Europe, Middle East, and Africa (EMEA) and Asia-Pacific (APAC)	+44 122 337 4240
United States	+1 888 483 7729
Latin America	+55 11 4504 4801

Information relating to unblinding (e.g., 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] Medical Safety Services 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.

Note: Investigative sites will be provided country-specific toll-free telephone and fax numbers.

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.

Throughout the study, safety for each subject in each study period will be evaluated by assessment of AEs, clinical laboratory findings, physical examination findings (as applicable), vital sign measurements, and pulse oximetry measurements. Any subject with ongoing AEs/SAEs at the EOS Visit should be followed up until resolution of their AE/SAE, until the Investigator has determined that the event has stabilized, or until a pre-defined outcome is reached as discussed in Section 9.3.

7.1.1 Screening Period

Screening procedures will occur after the subject signs and dates Institutional Review Board (IRB)- or Ethics Committee (EC)-approved ICFs and provides authorization to use protected health information (Section 12.1.3). The ICFs will be completed prior to conduct of any study specific- assessments.

At Screening, subjects will first review and sign the ICF for Rapid Viral Diagnostic Screening prior to RSV, SARS-CoV-2, and influenza screening. Once subjects have been assigned a unique participant number, they will undergo Rapid Viral Diagnostic Screening for RSV, SARS-CoV-2, and influenza virus using respiratory secretions obtained by nasal swab collection. Subjects whose swab sample test results are

positive for RSV and negative for SARS-CoV-2 and influenza virus A/B may proceed with further screening. Such subjects will be required to review and sign the second, Study ICF prior to performing any further study-specific assessments. After signing the Study ICF, subjects will undergo further screening procedures to determine study eligibility, including recording RSV symptoms using the RiiQ™ PRO questionnaire on an electronic device.

All study screening activities should be completed on Day 1 prior to randomization. If any assessment is anticipated to fall outside of that window, then the Investigator should consult with the CRO Medical Monitor to determine if the subject can proceed. Subjects will not be randomized until all screening activities that allow assessment of inclusion/exclusion criteria have been completed to the satisfaction of the Investigator, including the screening ECG and the screening urine pregnancy test.

All screening procedures are detailed in the SoA ([Appendix 1](#)).

7.1.2 Screen Failure/Rescreening

Individuals who do not meet the inclusion/exclusion criteria for participation in this study (screen failure) may be rescreened after a period of wellness and a new onset of symptoms. However, subjects who have completed the RiiQ™ one time may not rescreen.

7.1.3 Treatment Period (Days 1 to 5)

Study Site Visits (Days 1, 3, and 5):

Subjects who meet all inclusion criteria and none of the exclusion criteria to the satisfaction of the Investigator will be eligible to enter the study and will be randomized 2:1 to receive 800 mg of EDP-938 or placebo.

Randomized subjects must complete the Day 1 biological sample collections (i.e., blood for hematology, blood chemistry, [REDACTED] and nasopharyngeal swabs) prior to receiving the first dose of EDP-938 or placebo. Day 1 blood samples will be sent to both local (expedited testing and reporting) and central laboratories. Nasopharyngeal swabs will be sent to the central laboratory only. Swabs are to be collected as close to the time of administration of the dose as possible.

On Day 1, after randomization but before the first dose of IP, subjects will record baseline RSV symptoms and health status using RiiQ™, PGI-C, PGI-S, EQ-5D-5L, and Return to Usual Health/Activities questions on an electronic device. The subject is to bring the electronic device to each study site visit.

The subject will be instructed on prohibited medications and the use of acetaminophen/paracetamol (Section [5.8](#)).

Subjects will receive the first dose of study drug while at the study site. After the first dose, subjects will be instructed to take or be administered 800 mg of EDP-938 or placebo QD at approximately the same time every day (± 1 hour) on each of the

4 subsequent days. The subject will also receive instruction on the appropriate storage and transport of study drug (Section 5.3).

On Day 3 (± 1 day) and Day 5 (± 1 day) (EOT), subjects should bring their study drug with them as part of their study site visit for drug accountability and for dosing of study drug as described in Section 5.7. If a subject is unable to attend the Day 3 and/or Day 5 study site visit, a home visit by a study nurse may be arranged. It is anticipated that every reasonable effort will be made to ensure that subjects return to the site for the Day 3 and Day 5 visits. If the Day 3 visit occurs on Day 4 due to the visit window, the Day 5 visit should occur on Day 5 or Day 6.

All study assessments during the Treatment Period are detailed in the SoA (Appendix 1). At visits, study drug is to be taken after other visit activities have been completed, except for the collection of the post-dose PK sample at Visit 1.

7.1.4 Follow-up Period (Days 6 to 33)

Study Site Visits (Days 9, 14, and 33):

Subjects should return to the study site for follow-up visits on Day 9, Day 14, and Day 33 (EOS Visit) for post-treatment assessments. Visit assessments may be completed at the study site or by a study nurse via a home visit, if feasible.

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

7.2 Early Withdrawal from the Study/Early Discontinuation of Treatment

Subjects may withdraw from the study or discontinue the study drug at any time at their own request, or subjects may be withdrawn or have the study drug discontinued at any time at the discretion of the Investigator or Enanta Pharmaceuticals, Inc. for safety, behavioral, or administrative reasons. However, the Investigator should consult with the CRO Medical Monitor whenever possible before prematurely withdrawing a subject from the study or discontinuing the study drug. For any subject who decides to withdraw from the study, the Investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject returns for a final study site visit, if applicable, and follow up with the subject regarding any unresolved AEs. Although a subject may discontinue the study drug or withdraw from the study early, every effort must be made to request the subject to return to the site within 24 hours and no more than 48 hours later to complete any follow-up visits/procedures as necessary (Section 7.2.2).

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. The subject is considered completing treatment if the subject completed the

treatment period and did not permanently discontinue the study during the duration of the treatment or follow-up periods.

7.2.1 Withdrawal Criteria

Subjects may be withdrawn from the study at any time if the subject, Investigator, or Sponsor determines that it is not in the best interest of the subject to continue participation. Reasons for discontinuation include the following:

- AE;
- 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 of Study Drug or Withdrawal from the Study

During the Treatment Period, subjects who discontinue study drug prior to the last scheduled dose on Day 5 but remain in the study to complete the follow up-period are requested to return to the site within 24 hours and no more than 48 hours after the last dose to complete the Visit 3/EOT Visit. Subjects who prematurely discontinue study drug should be requested to continue to participate in the safety monitoring through the Follow-up Period, until they complete the scheduled visits at Day 33. Subjects who withdraw from the study at any time (including during the treatment period) should be requested to return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures per the SoA ([Appendix 1](#)). Any subject who withdraws from the study with ongoing AEs/SAEs should be followed up until resolution of their AE(s), until the Investigator has determined that the AE(s) has stabilized, or until a predetermined outcome has been reached.

Site staff will make at least 3 attempts to contact a subject who does not return to the site for the EOS Visit, using the subject's preferred method of communication. If the 3 attempts are unsuccessful, the site staff will send a letter to the subject in a way that requires delivery notification. Subjects 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 from the Study, Early Discontinuation of the Study Drug, and Lost to Follow Up

The reason for early withdrawal from the study, discontinuation of the study drug, and being classified as lost to follow up must be documented on the subject's appropriate electronic case report form (eCRF).

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, at a minimum, the year of birth and age, sex, race (if available), ethnicity (if available), medical, disease, and smoking history will be obtained from each subject and entered in the eCRF as reported at Screening.

Medical history is to include history regarding the diagnosis and status of CHF, COPD, and asthma.

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 the 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 Medications and Therapies

Prior therapies will include medications and other therapies (including diagnostics, surgeries, and other interventions) that end prior to the first dose of study drug. Concomitant therapies include medications, diagnostic tests and procedures such as antibiotics, bronchodilators, systemic or inhaled corticosteroids, supplemental oxygen, and mechanical ventilation ongoing at the time of 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 will be recorded with indication, dosage, route of administration, and start and stop dates of administration, as applicable. 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

in the study will also be documented in source documents 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 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.

8.3.2 Electrocardiograms

A resting 12-lead ECG will be performed locally and recorded at Screening on Day 1 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 QT interval corrected for heart rate according to the Fridericia formula (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 (i.e., clinically significant or not clinically significant).

An ECG will be repeated on Day 5 and Day 33, and may be repeated at the discretion of the Investigator to address suspected errors in performance. Prior to dosing, the screening ECG must be reviewed to confirm that no clinically significant cardiac abnormalities are present.

8.3.3 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 the previous status. Only clinically significant abnormalities should be recorded in the eCRF as AEs.

8.3.4 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. Body mass index (BMI) will be calculated at Screening (to assess eligibility) according to the following equation:

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

These measurements will be obtained as specified in the SoA ([Appendix 1](#)).

8.3.5 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 to manage the AEs are performed and documented in the subject source notes and eCRF.

8.3.6 Pulse Oximetry

At Screening, subjects will have pulse oximetry performed to measure oxygen saturation and to ensure study exclusion criteria are not met (Section 3.2). Subsequent pulse oximetry measurements will be performed as indicated in the SoA (Appendix 1).

8.3.7 Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) Symptom Scale

At Screening and at timepoints indicated in the SoA (Appendix 1), subjects will assess the severity of RSV-related signs and symptoms and record the 13-item RiiQ™ symptom scores in the electronic device.

The RSV symptoms will be recorded at the same time of day ± 1 hour in the electronic device.

The 13-item diary uses a 4-point scale that consists of grading symptoms on a scale of 0 to 3, where Grade 0 is None, Grade 1 is Mild, Grade 2 is Moderate, and Grade 3 is Severe.

The 13 RSV symptoms assessed will comprise 3 domains:

- LRTD; cough, wheezing, shortness of breath, and coughing up phlegm/sputum;
- URTD; nasal congestion and sore throat);
- Systemic symptoms (headache, feeling feverish, neck pain, body aches and pain, fatigue/tiredness, interrupted sleep, and loss of appetite).

If a subject plans to take acetaminophen/paracetamol within 2 hours of the scheduled RSV symptom diary completion, then the RSV symptom diary should be completed immediately before the subject takes acetaminophen/paracetamol or 4 hours after taking acetaminophen/paracetamol.

The RiiQ™ also consists of 3 additional impact scales that records the impact of RSV disease:

1. Daily activities on a 4-point scale (0 = No difficulty, 1 = Some difficulty, 2 = Moderate difficulty, 3 = Great difficulty);
2. Emotions on a 4-point scale (0 = Not at all, 1 = Somewhat, 2 = Moderately, 3 = Extremely);
3. Social relationships on a 4-point scale (0 = Not at all concerned, 1 = Somewhat concerned, 2 = Moderately concerned, 3 = Extremely concerned).

8.3.8 Patient Global Impression of Severity and Patient Global Impression of Change Scales

At timepoints indicated in the SoA ([Appendix 1](#)), subjects will assess the severity of RSV infection symptoms at their worst that day using the PGI-S scale, and also, assess the subject's perceptions of improvement or deterioration in the severity of RSV symptoms compared to before the subject started taking the study drug using the PGI-C scale.

The PGI-S scale is a single item PRO measured on a 4-point scale asking the subject to assess the severity of symptoms of RSV infection (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe).

The PGI-C scale is a single item PRO measured on a 5-point scale asking the subject to describe overall change in RSV symptoms since beginning study medication (2 = Much better, 1 = A little better, 0 = No change, -1 = A little worse, and -2 = Much worse).

The PGI-S and PGI-C will be recorded at the same time of day ± 1 hour in the electronic device.

8.3.9 EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) Health-Related Quality of Life (HRQOL) Questionnaire

At timepoints indicated in the SoA ([Appendix 1](#)), subjects will assess HRQOL as measured by the EQ-5D-5L questionnaire. The EQ-5D-5L consists of 2 scoring systems to measure self-reported health: the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the patient's self-rated health on 'how good or bad your health is today' on a vertical VAS, in which the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine.'

8.3.10 Adult RSV Return to Usual Health and Adult RSV Return to Usual Activities Question

At timepoints indicated in the SoA ([Appendix 1](#)), subjects will assess return to usual health and activities with 2 Yes/No questions below:

- Have you returned to your usual health today?

- Have you returned to your usual activities today?

8.3.11 Collection of Nasal or Nasopharyngeal Swabs and Blood Samples

Refer to Section 8.5 for samples that will be collected for virology assessments. The RSV-specific tests are indicated in Table 3. Refer to the Laboratory Manual for additional details.

8.4 Laboratory and Diagnostic Procedures

At Screening, the Rapid Viral Diagnostic Screening will be performed on site, using a nasal swab sample obtained before randomization. Subsequent virology assessments will be performed at the central laboratory(ies), using nasopharyngeal swab samples post randomization.

On Day 1, enrolled subjects will undergo the clinical laboratory evaluations of blood samples specified in Table 3, which will be performed at the local site laboratory (expedited testing and reporting) and the central laboratory(ies). Subsequent clinical laboratory evaluations will be performed by the central laboratory(ies).

The Day 1 collection of blood and nasopharyngeal swab samples will be completed prior to but as close to the administration of study drug as possible.

A Laboratory Manual will be provided to the site detailing kit contents, reordering supplies, sample collection, handling, storage, and shipment instructions. All blinded 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) (Section 9.1).

Table 3: Clinical and Respiratory Syncytial Virus Laboratory Evaluations

CHEMISTRY PANEL Alanine aminotransferase* Albumin, serum* Alkaline phosphatase, serum* Amylase* Aspartate aminotransferase* Bilirubin, total and direct* BUN* BUN/creatinine ratio (calculation) Calcium, serum Creatine kinase Creatinine, serum* Estimated glomerular filtration rate (eGFR) Uric acid Electrolyte panel (sodium, potassium, chloride, bicarbonate)* Phosphorus Gamma glutamyltransferase Globulin, total Glucose, serum* Cholesterol Triglycerides Lactate dehydrogenase Lipase Protein, total, serum	HEMATOLOGY/COAGULATION PANEL Hemoglobin* Hematocrit* White blood cell count* Differential white blood cell count, percentage and absolute cell counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils)* Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count* Red blood cell count International normalized ratio* Prothrombin time* Activated thromboplastin time* RSV-SPECIFIC AND OTHER VIROLOGY TESTS RSV, SARS-CoV-2 and influenza virus A/B diagnostic test (nasal secretions) Respiratory pathogen panel RSV RNA quantitation of viral load (nasopharyngeal secretions) RSV infectious viral titer (nasopharyngeal secretions) Viral resistance (nasopharyngeal secretions) RSV serology (neutralizing antibodies, serum) PREGNANCY AND OTHER TESTS Urine pregnancy test (Screening and the EOS Visit) Serum pregnancy test (only Day 1 and to the central laboratory) Follicle-stimulating hormone (if needed)
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Abbreviations: BUN = blood urea nitrogen; EOS = end of study; RSV = respiratory syncytial virus; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2.

*On Day 1, blood samples should be taken from all eligible subjects and sent to the local laboratory for these identified tests, which should be assayed and reported in an expedited manner. In parallel, blood samples for complete hematology and chemistry panels should be sent to the central laboratory with the other Day 1 samples.

8.4.1 Routine Laboratory Panels

Blood samples will be collected for analysis of the analytes as shown in [Table 3](#). Samples will be collected from all subjects enrolled into the study.

Blood and urine samples for clinical laboratory assessments will be collected according to the SoA ([Appendix 1](#)). Samples to be analyzed at the central laboratory will be processed as indicated in the Laboratory Manual. Samples to be analyzed at the local laboratory will be processed according to local laboratory procedures. The eGFR

will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

8.4.2 Pregnancy and Menopausal Laboratory Testing

All female subjects of childbearing potential will undergo a urine pregnancy test at Screening and at the EOS Visit. In addition, on Day 1, blood will be collected from all female subjects of childbearing potential 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 up to 2 years, documentation of serum FSH levels >35 IU/mL will be required. When 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.

8.5 Virology Assessments

Virology assessments and tests ([Table 3](#)) will be performed using nasal or nasopharyngeal swabs and serology samples collected at Screening and at timepoints indicated in the SoA ([Appendix 1](#)) and as further described in the Laboratory Manual, including swab collection, sampling, and handling procedures. Multiple nasopharyngeal swab samples may be collected at each timepoint; refer to the Laboratory Manual for details. With the exception of the Rapid Viral Diagnostic Screening (for RSV, SARS-CoV-2, and influenza virus A/B) 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, Influenza, and SARS-CoV-2 Rapid Molecular Diagnostic Tests

After a subject reviews and signs the Rapid Viral Diagnostic Screening ICF, the subject will undergo a rapid molecular diagnostic screen for RSV, SARS-CoV-2, and influenza virus A/B at the local site. A nasal swab sample will be collected to obtain respiratory secretions. Subjects whose swab sample tests positive for RSV and negative for SARS-CoV-2 and influenza virus A/B and who agree to proceed, will be required to read and sign the Study ICF and may proceed with further screening assessments. Results will be recorded in the source documents.

8.5.2 Respiratory Pathogen Panel

The respiratory pathogen panel will be performed to identify other nasopharyngeal co-pathogens that may include adenovirus, coronavirus, human metapneumovirus, human rhinovirus/enterovirus, parainfluenza virus, *Chlamydophila pneumoniae*, and/or *Mycoplasma pneumoniae*, that may impact the course of a subject's illness.

8.5.3 Respiratory Syncytial Virus RNA Quantification of Viral Load

The RSV RNA viral load will be measured in nasopharyngeal swabs by RT-qPCR assay at the timepoints specified in the SoA ([Appendix 1](#)). The RT-qPCR will also be used to determine viral dynamics (e.g., peak viral load and time to peak).

8.5.4 Respiratory Syncytial Virus Subgroup (A or B) Determination

Nasopharyngeal swab sample(s) will be analyzed to determine whether the virus belongs to RSV subgroup A or B.

8.5.5 Respiratory Syncytial Virus Infectious Viral Titer

Nasopharyngeal swab sample(s) will be analyzed to determine infectious titer of RSV.

8.5.6 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 an RSV gene to monitor for treatment-emergent resistance mutations.

8.5.7 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.

8.6 Pharmacokinetic Samples

Blood (plasma) samples for PK analysis will be collected on Day 1 (postdose; at least 1 hour after dosing or right before the subject leaves the site, whichever is later), Day 3 and Day 5 (predose, at the same approximate time as that of the nasopharyngeal swab collection).

If the Day 3 or Day 5 study site visit occurs up to 4 hours after the time scheduled for dosing of study drug, then the subject should take the study drug at the site during the visit (refer to the SoA [[Appendix 1](#)]). If the Day 3 or Day 5 study site visit occurs more than 4 hours after the time scheduled for dosing of study drug, then the subject should take the study drug at the scheduled time at home. On Day 3 or Day 5, if the subject takes the study drug prior to the study site visit (Section [5.7](#)), the PK sample should be taken at the same approximate time as that of the nasopharyngeal swab collection.

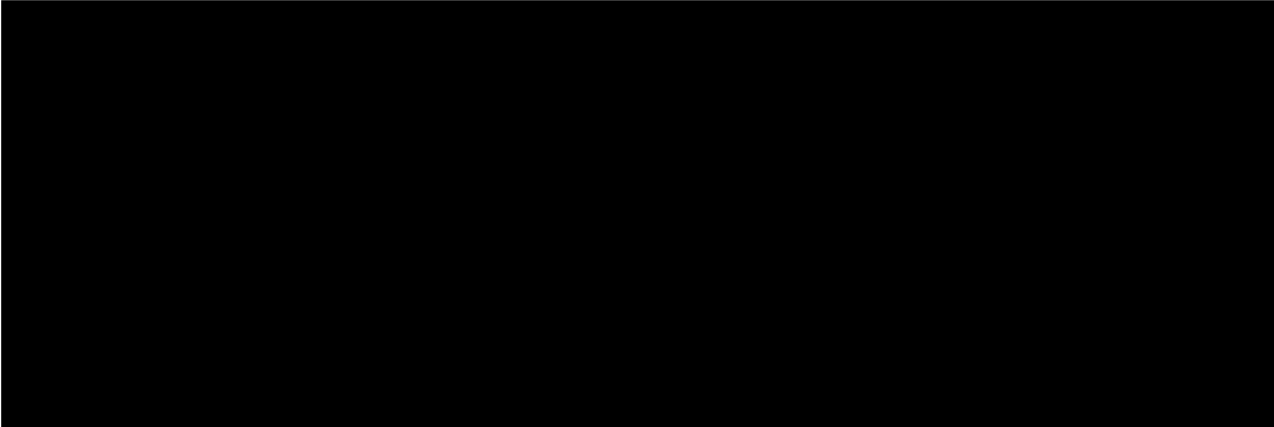
For subjects who discontinue the study drug early, a PK sample should be collected at the first visit after the last dose of study drug is taken. The PK sample should be collected at the same approximate time as that of the nasopharyngeal swab collection.

Blood samples will be collected and processed to measure plasma concentrations of EDP-938 and its metabolites according to the procedures provided and/or approved by

Enanta Pharmaceuticals, Inc. Pharmacokinetic samples will be collected as specified in the SoA ([Appendix 1](#)). Additional details will be provided in the Laboratory Manual.

Actual date and time of PK sample collection will be recorded on the laboratory requisition and in the eCRF. It is important that the date and time of each PK blood sample are accurately recorded in the source documents.

Pharmacokinetic samples may be stored and used for future metabolite 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).



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 first Rapid Viral Diagnostic Screening 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. Therefore, an AE can 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. AEs 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 (e.g., 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 (e.g., 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:
 - o RSV disease progression;
 - o Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
 - o Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the Study ICF;
 - o Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission;
 - o 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, may still be 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)

AEs 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 signing the Rapid Viral Diagnostic Screening ICF to the EOS Visit for each subject will be recorded in the subject's source documents. For subjects who do not receive study drug (i.e., screen failures), AEs will only be recorded in the source documents. For subjects randomized into the study, 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. The date and time of the AE are to be recorded in the source if the AE starts on Day 1.

Adverse events (serious and nonserious) will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5, 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 (e.g., 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:

- 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, prior to 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:

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition;
- Pre-planned medical or surgical procedures (e.g., 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 prior to 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 AE. 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 AE to be related to the study drug and causes other than the study drug have been ruled out, and/or the AE reappeared on re-exposure to the study drug;
- **Possibly related:** There is an association between the AE and the administration of the study drug and there is a plausible mechanism for the AE 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 AE is unlikely to be related to the study drug and likely to be related to factors other than study drug;
- **Not related:** The AE 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 based upon the Investigator's assessment that can be taken with study drug are defined in [Table 4](#).

Table 4: Options for Action Taken With Study Drug as a Result of an AE

Action	Definition
Dose Not Changed	Study drug dose not changed in response to the adverse event
Drug Interrupted	Study drug administration was interrupted in response to the adverse event.
Drug Withdrawn	Study drug administration permanently discontinued in response to the 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 discontinue 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 and the definitions are shown in [Table 5](#). The outcome must be entered into the appropriate field on the AE eCRF and (if appropriate) SAE Form for each event.

Table 5: 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 (specify sequelae)
Recovering/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 the death is at least possibly related to the adverse event
Unknown	Outcome of an adverse event is not known (e.g., a subject is 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 (i.e., signing the Study ICF) through the EOS Visit, regardless of causality, must be reported by the Investigator or designee to [REDACTED] Medical Safety Services 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] Medical Safety Services and Enanta Pharmaceuticals, Inc. within 24 hours of learning of its occurrence. Additional details are provided in the Safety Management Plan. Contact information is shown in Table 6.

Table 6: Contacts for Serious Adverse Event and Pregnancy Reporting

[REDACTED] Medical Safety Services	
24-hour Global Safety Hotline	Phone: +1 800 722 2215
North/South America	Fax: +1 888 772 6919 or +1 434 951 3482 Email: CHOSafety@prahs.com
Europe/Asia-Pacific	Fax: +44 1792 525720 Email: MHGSafety@prahs.com

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. For the purposes of study analysis, if an SAE 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] Medical Safety Services the CRO Project Manager, 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 designees, as study Sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions involving the study drug to all regulatory authorities, and participating investigators, in accordance with FDA, International Council for Harmonisation (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 the period of study drug administration 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 immediately be permanently discontinued. The Investigator or designee must notify [REDACTED] Medical Safety Services, the Sponsor's Medical Monitor, and the [REDACTED] Medical

Safety Services Project Manager within 1 business day after any member of the site staff first becomes aware of the pregnancy, using 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 ([Table 5](#)), 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.

AEs will be captured in the eCRF if the event started prior to or at the time of the EOS Visit. AE outcomes are determined based on the status at the end of the subject's participation in the study and at the time of database lock.

9.4 Sponsor's Review of Adverse Events and Serious Adverse Events

Enanta Pharmaceuticals, Inc. will maintain an ongoing review of all AEs and SAEs.

9.5 Independent Data Safety Monitoring Board

Safety data from this study will be reviewed by an independent DSMB throughout the study. The DSMB will be headed by a DSMB Chair and will include 3 experts independent from the Sponsor; 2 physicians with expertise in viral respiratory infections including RSV, and chronic health conditions included in this study, and 1 statistician. Procedures for data review, including timing and potential outcomes, roles and responsibilities, and interactions with the Sponsor and the CRO, will be governed by a DSMB charter.

10 TERMINATION OF THE STUDY OR TERMINATION OF A STUDY SITE

10.1 Termination of the Study

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:

- The 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;
- A 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 Termination of a Study Site

A single site may warrant termination from participation in the study 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.

10.3 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

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a separate Statistical Analysis Plan (SAP). The SAP of this study will be dated and maintained by the Sponsor, Enanta Pharmaceuticals, Inc. or its designee. This documentation may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Time-to-event variables will be analyzed using the Kaplan-Meier method. This method will be applied to derive the median event time and a CI for the median for each treatment arm. The CI will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods. The p-values will be derived by stratified log-rank test where the comparison of 2 treatment groups is needed. Cox proportional hazard models will be used to explore the potential influences of the baseline stratification factors on the primary endpoint. The estimated hazard ratio and 2-sided 95% CI will be provided. Additionally for each treatment arm, the median event time and a 2-sided 95% CI will be provided for each level of the stratification factors or baseline characteristics.

Continuous variables will be summarized using n, mean, standard deviation, median, 25th quartile, 75th quartile, minimum, and maximum values. Categorical variables 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.

11.2 Sample Size Considerations

Using a randomization ratio of 2:1, a sample size of 180 subjects provides 80% power at 0.05 two-sided significance level under a log-rank test to detect a hazard ratio of 2.0 (note that a hazard ratio greater than 1.0 indicates a benefit) in time to resolution of RSV LRTD symptoms as assessed by the RiiQ™ symptom scale. This calculation assumes that 50% of subjects in the EDP-938 group and 30% of subjects in placebo group will achieve a resolution of RSV LRTD symptoms by Day 33, respectively, and up to 5% of subjects will discontinue the study treatment early.

11.3 Analysis Populations

The following analysis populations are planned:

- **Safety (SAF) Population:** All subjects who receive at least one dose of study drug will be included in the SAF. Subjects will be analyzed in the treatment group that corresponds to the study drug received during the study;
- **Modified Intent-to-Treat (mITT) Population:** All randomized subjects positively diagnosed with RSV using the central RT-qPCR quantification who receive at least one dose of assigned study drug will be included in the mITT population. The mITT population will be considered the efficacy population. Subjects will be analyzed as randomized;
- **Per Protocol (PP) Population:** All subjects in the mITT population who completed 5-day Treatment Period and do not have major protocol deviations that may unduly influence RiiQ™ symptom scale scores will be included in the PP population. Subjects will be analyzed as randomized;
- **PK Population:** All subjects receiving active study drug and having any measurable plasma concentration of study drug at any timepoint will be included in the PK population.

11.4 Subject Disposition and Demographic Data

The number of subjects screened, randomized, and in the SAF, mITT, PP, and PK Populations will be summarized using frequencies and percentages. The denominator for the calculation of percentages will be 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;
- Withdrew from the study early and the reason for withdrawal.

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 inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized on Day 1 in a 2:1 ratio to 800 mg of EDP-938 or placebo. Assignment to treatment groups will be determined by a computer-generated random sequence using an IRT. The IRT will be used to assign investigational product to each subject. To achieve between-group comparability, the randomization will be stratified by the number of high-risk factors (i.e., ≤ 2 vs. > 2) and

the duration of respiratory symptoms (i.e., ≤ 48 hours vs. > 48 hours to ≤ 72 hours). The treatment duration is 5 days.

11.6 Efficacy Analyses

11.6.1 Primary Efficacy Analyses

The primary efficacy endpoint is described in Section 2.2.1.

The primary efficacy analysis will be based on mITT population and performed on time to resolution of RSV LRTD symptoms as assessed by RiiQ™ symptom scale through Day 33 using the stratified log-rank test for p-values and a Cox Proportional Hazards model including treatment group, stratification factors, and baseline RiiQ™ score to assess hazards ratio. The estimated hazard ratio and 2-sided 95% CI will be provided.

Time to resolution (recorded in days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by RiiQ™ score is zero or 1. The resolution of RSV LRTD symptoms is assessed by the RiiQ™ symptom scale through Day 33. Subjects without resolution prior to Day 33 will be censored at Day 33.

The Kaplan-Meier method will be applied to time to resolution of RSV LRTD symptoms to derive the median event time and a CI for the median for each treatment arm. A Kaplan-Meier curve will display the probability estimates with resolution. Descriptive statistics on the graph will include the median and 95% CI at a minimum. For subjects who withdraw or are withdrawn early from the study, the reason for withdrawal will be considered. If a subject withdraws or is withdrawn due to an AE, that subject will be set as a failure in the analysis. Subjects who withdraw from the study due to other reasons will be censored.

Additionally for each treatment arm, the median event time and a 2-sided 95% CI will be provided for each level of the stratification factors or baseline characteristics.

11.6.2 Secondary Efficacy Analyses

The secondary efficacy endpoints are described in Section 2.2.2.

The Kaplan-Meier method will be applied to time-to-event variables to derive the median event time and a CI for the median for each treatment arm. The CI will be 2-sided, have a stated coverage probability of 95%, and be calculated using normal approximation methods. Descriptive statistics on the Kaplan-Meier curve will at least include the median and 95% CI.

The categorical variables will be summarized and the between-group comparison will be analyzed using a Cochran-Mantel-Haenszel test controlling for the stratification factors.

The continuous variables will be compared between EDP-938 and placebo using mixed model for repeated measures (MMRM) with treatment group, Day (as class variable) and stratification factor as fixed effects, the baseline RiiQ™ as a covariate, treatment group by Day interaction, stratification factor by Day interaction, baseline RiiQ by Day

interaction, as factors. Treatment groups will be compared at specified timepoints. The least-squares means and two-sided 95% CIs will be presented for individual groups and the difference between groups.

11.6.3 Multiplicity Testing Procedure

There is no planned multiplicity of testing for the primary endpoint.

11.6.4 Handling of Missing Data

The assessment of missing data for the resolution of RSV LRTD symptoms and sensitivity analyses to assess the impact of missing data for the primary endpoint will be performed.

If the amount of missing data is not significant (i.e., less than 5% in any given treatment group), then the assessment of missing data will not include multiple imputation techniques. If there is a significant amount of missing data, then a more thorough investigation will be conducted and the multiple imputation techniques will be applied to the primary analysis model.

Further details regarding the statistical strategy for assessing missing data will be provided in the SAP.

11.7 Safety Analyses

Statistical methods for the safety analyses will be primarily descriptive in nature. Safety data, including AEs, vital sign measurements, pulse oximetry, ECGs, concomitant therapies, and clinically significant changes in laboratory measurements, 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

AEs 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. TEAEs are defined as reported AEs that first occurred after first treatment or worsened during the post-Baseline period compared to 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 AE is considered treatment-emergent. No statistical testing will be performed.

Summaries of AEs will include at a minimum an overall summary of AEs with a line for each of the categories provided below:

- TEAEs;
- Study treatment-related TEAEs;

- Maximum severity TEAE according to NCI-CTCAE scale;
- TEAEs by severity;
- TEAEs leading to study drug discontinuation;
- SAEs, including fatal SAEs;
- Study treatment-related treatment-emergent SAEs.

11.7.2 Clinical Laboratory Data

Laboratory assessments (including chemistry and hematology) 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 variables: Treatment-emergent abnormal is defined as a change from normal at Baseline to abnormal at any post-Baseline visit.

For continuous variables:

- 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 signs observed, change, and percentage change will be summarized by treatment over visits.

11.7.4 Electrocardiograms

ECG data will be provided in data listings.

11.7.5 Pulse Oximetry

Pulse oximetry measurements will be summarized by visit and treatment group.

11.7.6 Prior and Concomitant Medications and Therapies

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. Concomitant medications will be summarized by treatment group in the SAF Population. The prior medication and therapies will be presented in the listings.

11.7.7 Physical Examinations

Physical examination data will be provided in data listings.

11.8 Pharmacokinetic Analyses

Summary of plasma concentration data will be descriptive in nature. Available plasma concentration-time data in the PK Population will be summarized by treatment group. Mean plasma concentration-time figures may be created for EDP-938 and its metabolites, as allowed by the data. Specific PK parameters will be listed in the SAP.

11.9 Subgroup and Covariate Analyses

Subgroup analyses will be performed on the primary and secondary efficacy endpoints. A logistic regression model will be performed for categorical endpoints. The model will include treatment group and stratification factor as fixed effects, with subgroup, and subgroup -by -treatment interaction as well. Odds ratios and 95% CI will be reported. For continuous endpoints, an MMRM model with treatment group and stratification factor as fixed effects in the model, with subgroup and subgroup-by-treatment interaction as well. mITT study population may be used. Forest plots will be provided to visually describe the association.

Subgroup analyses for the primary endpoint and key secondary endpoints may be considered for the following baseline variables, if there are enough subjects in the subgroups to support the planned analyses:

- Sex (female vs male);
- Number of high-risk factors (≤ 2 vs > 2);
- Presence of individual risk factors:
 - o Age (< 65 years of age vs 65 to ≤ 74 years of age vs > 74 years of age);
 - o CHF (yes vs no);
 - o COPD (yes vs no);
 - o Asthma (yes vs no).
- Duration of respiratory symptoms (≤ 48 hours vs > 48 hours to ≤ 72 hours);
- RSV subset (RSV-A vs RSV-B).

11.11 Interim Analyses

An interim analysis may be performed when at least 30% of the subjects complete the study.

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 ICFs, 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 ICFs 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 AEs, and all other elements of consent as defined in 21 CFR Part 50, and other applicable national and local regulations governing informed consent.

For this study, there will be 2 ICFs to participate:

1. Rapid Viral Diagnostic Screening ICF: an ICF to provide consent for Rapid Viral Diagnostic Screening for RSV, SARS-CoV-2, and influenza;
2. Study ICF: eligible subjects after Rapid Viral Diagnostic Screening will sign a second ICF to participate further in the study.

Details on these are provided in Section 7.1.1.

Each subject must provide signed and dated ICFs prior to 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 prior to 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 designees, 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 prior to 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 (i.e., efficacy assessments) will require IRB/EC notification prior to 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 prior to 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 for each randomized subject will be entered into an eCRF by site staff. Subjects who did not randomize will not be entered into the eCRF. Limited screen failure information including reasons for screen failure will be collected in the IRT

system. In addition, specific criteria for confirming RSV eligibility will be collected in the IRT system.

It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF 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 from scheduled visits in the source (e.g., Missed visit).

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.

Assessments that occur due to standard of care are not required to be collected as unscheduled data in the eCRF. In addition, it is recommended unscheduled data be entered if associated with an AE during study conduct before the participant completes the EOS Visit. The completion date of the study is associated with the last required assessment conducted for the EOS Visit.

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 designee 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 designee, 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 ICFs authorizing the use of protected health information.

12.4 Quality Assurance

At its discretion, Enanta Pharmaceuticals, Inc. or its designee 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 and CRO 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 will remain confidential and will not be supplied to Enanta Pharmaceuticals, Inc. or its designee. Limited demographic information and eligibility criteria will be collected in IRT as local regulations allow. If the subject name or other identifying protected health information appears on any other document collected (e.g., unit discharge summary), it must be obliterated before the document is transmitted to Enanta Pharmaceuticals, Inc. or its designee. All study findings will be stored in electronic databases. As indicated in the ICFs, 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. Enanta Pharmaceuticals, Inc. reserves the right, among other things, to:

- 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 for a sufficient time to allow Enanta Pharmaceuticals, Inc. to seek patent protection of any invention contained therein.

13 REFERENCES

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14 APPENDICES

Appendix 1: Schedule of Assessments

Period	Screening	Treatment					Follow-up				
Day	1	1	2	3 (±1d) ^a	4	5 (±1d) ^a	6-8	9 (±1d)	10-13	14 (±1d)	33 (±1d)
Visit	Screening	Rand. V1		V2		V3 EOT		V4		V5	V6 EOS
Study site visit ^b	X	X		X		X		X		X	X
ICF for Rapid Viral Diagnostic Screening	X										
Nasal swab for Rapid Viral Diagnostic Screening	X										
ICF for Study participation	X										
Inclusion/Exclusion criteria	X	X									
Demographics	X										
Medical, smoking and disease history ^c	X										
Prior therapies	X										
Concomitant therapies ^d	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs and SpO ₂	X ^e	X ^e		X		X		X		X	X
12-Lead ECG (resting)	X					X					X
Physical examination ^f	X										
Weight, height ^g , and BMI	X			X		X		X		X	X
FSH (if needed)		X									

Period	Screening	Treatment					Follow-up				
Day	1	1	2	3 (±1d) ^a	4	5 (±1d) ^a	6-8	9 (±1d)	10-13	14 (±1d)	33 (±1d)
Visit	Screening	Rand. V1		V2		V3 EOT		V4		V5	V6 EOS
Randomization		X									
Study drug dosing ^h		X	X	X	X	X					
Study drug accountability		X		X ⁱ		X ⁱ					X
Clinical laboratory tests ^j		X		X		X		X		X	X
Pregnancy test ^k	X	X									X
PK sample collection ^{l,m}		X		X		X					X ^m
NP swab sample ⁿ		X		X		X ^o		X		X	X ^o
RSV serology sample		X									X
Electronic device dispensation/return		X									X
RiiQ TM ^q	X ^e	X ^e	X	X	X	X	X	X	X	X	X
PGI-C ^q		X	X	X	X	X	X	X	X	X	X
PGI-S ^q		X	X	X	X	X	X	X	X	X	X
EQ-5D-5L		X				X		X		X	X
Return to Usual Health/ Activities questions ^q		X	X	X	X	X	X	X	X	X	X
Assess ICU admissions, hospitalization, and medically attended visits	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; d = day; ECG = electrocardiogram; EOS = end-of-study; EOT = end-of-treatment; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; FSH = follicle-stimulating hormone; ICF = informed consent form; NP = nasopharyngeal; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; Rand = randomization; RiiQTM = Respiratory Infection Intensity and Impact Questionnaire; RSV = respiratory syncytial virus; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; SpO₂ = oxygen saturation.

Note: Refer to the Laboratory Manual for sample collection and processing details.

- ^a If the Day 3 visit occurs on Day 4 due to the visit window, the Day 5 visit should occur on Day 5 or Day 6.
- ^b Home nursing visits, when possible, may replace all visits to the study site except for Visit 1. For visits done at home, blood draws for chemistry, PK, or optional biomarker samples that require special sample processing with equipment not available for home visits (e.g., centrifugation) may be omitted.
- ^c Data for medical history includes additional disease history regarding the diagnosis and status of CHF, COPD, and asthma.
- ^d Concomitant therapies include medications, diagnostic tests and procedures, such as antibiotics, bronchodilators, systemic or inhaled corticosteroids, supplemental oxygen, and mechanical ventilation.
- ^e If Screening and Randomization occur on the same calendar day, this assessment does not need to be repeated on Day 1.
- ^f A full 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.
- ^g Height will be measured only at Screening.
- ^h Study Drug (EDP-938 or placebo) is to be administered at the study site on days when visits occur. Study drug is to be administered after the completion of other scheduled visit activities, except for the collection of postdose plasma PK sample at Visit 1. Whenever possible, the study site visit should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site.
- ⁱ If a participant discontinues treatment prior to Day 5, but remains in the study, the participant should return study drug for accountability at the EOT visit. If a participant withdraws from the study before Day 5, the participant should return study drug for accountability at the EOS visit.
- ^j Clinical laboratory tests include chemistry and hematology/coagulation. Collect samples for clinical laboratory tests prior to the administration of study drug but after randomization.
- ^k Pregnancy testing will be performed in female subjects of childbearing potential. A urine pregnancy test will be performed at Screening and at the EOS Visit. In addition, on Visit 1 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.
- ^l Collect 1 plasma PK sample at each Visit 1, Visit 2, and Visit 3/EOT for randomized subjects. At Visit 1, collect 1 postdose plasma PK sample, at least 1 hour after dosing or right before the subject leaves the site, whichever is later. At Visit 2 and 3/EOT, collect 1 predose plasma PK sample at the same approximate time as the NP swabs. Note for Visit 2 and Visit 3/EOT: if the subject takes the study drug prior to attending study site visit, the Visit 3 PK sample should be taken at the same approximate time as that of the NP swab collection.
- ^m If a participant discontinues treatment prior to Day 5 but remains in the study, a PK sample should be taken at the approximate time as the NP swab at the EOT Visit. The EOT visit should occur within 24 hours following the last dose of study drug. If the subject discontinues treatment prior to Day 5 and does not remain in the study, a PK sample should be taken at the approximate time as the NP swab at the EOS visit. The EOS visit should occur within 24 to 48 hours after discontinuation.
- ⁿ At Visit 1, NP swabs are to be collected after randomization and prior to first study drug dose administration. At Visit 2 and Visit 3, NP swabs are to be collected prior to the administration of the dose. Swabs are to be collected as close to the administration of dose as possible. At each visit, 2 swabs are to be collected: a primary swab and a backup swab.
- ^o If a participant discontinues treatment prior to Day 5, but remains in the study, an NP swab sample should be taken at the EOT Visit. If the subject withdraws or is withdrawn from the study prior to Day 14 and does not have an EOT visit prior to discontinuing the study, an NP swab sample should be taken at the EOS visit.
- ^p [REDACTED]
- ^q RiIQ, PGI-C, PGI-S, and Return to Usual Health/Activities questions are to be completed once daily each at approximately the same time of day ($\pm$ 1 hour) by subjects, from Day 1 after randomization, predose through to the EOS.