Clinical Study Protocol

A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF EDP-938 ADMINISTERED ORALLY FOR THE TREATMENT OF ACUTE UPPER RESPIRATORY TRACT INFECTION WITH RESPIRATORY SYNCYTIAL VIRUS IN AMBULATORY ADULT SUBJECTS (RSVP)

Protocol Number: EDP 938-102

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Study Sponsor:	Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472
Sponsor Medical Monitor:	[redacted] Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472 [redacted]

CONFIDENTIAL

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SAE and Pregnancy Reporting	[redacted]	[redacted]

Protocol Approval – Sponsor Signatory

Study Title	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study of EDP-938 Administered Orally for the Treatment of Acute Upper Respiratory Tract Infection with Respiratory Syncytial Virus in Ambulatory Adult Subjects (RSVP)
Protocol Number	EDP 938-102
Protocol Date and Version	20 May 2020, Amendment 4.0 (Global); Version 5.0

Protocol accepted and approved by:

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

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Protocol Approval – Lead Statistician

Study Title	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study of EDP-938 Administered Orally for the Treatment of Acute Upper Respiratory Tract Infection with Respiratory Syncytial Virus in Ambulatory Adult Subjects (RSVP)
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Protocol accepted and approved by:

[redacted]

SIGNATURE PAGE

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

Principal Investigator:

_____

Signature: _____ Date: _____

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[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{0-24}	area under the curve from 0 to 24 hours
AUC_{0-inf}	area under the curve from 0 to infinity
ALRI	acute lower respiratory illness
ANCOVA	analysis of covariance
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence intervals
COPD	chronic obstructive pulmonary disease
C_{trough}	trough concentration
CYP	cytochrome P450
DSMB	Data Safety Monitoring Board
EC	ethics committee
EC_{50}	half-maximal effective concentration
EC_{90}	90% maximal effective concentration
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FIH	first-in-human
[redacted]	[redacted]
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HDPE	high-density polyethylene
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IWRS	Interactive Web Response System
LD	loading dose

LLN	lower limit of normal
mITT	Modified Intent-to-Treat
MCMC	Markov Chain Monte Carlo
N	nucleoprotein
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic(s)
PND	postnatal day
PP	Per Protocol
QTcF	QT interval corrected for heart rate according to Fridericia
RSV	respiratory syncytial virus
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	Safety (for the analysis population)
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Assessments
SPM	Study Procedures Manual
TEAE	treatment-emergent adverse event
TSS	total symptom score
ULN	upper limit of normal
URTI	upper respiratory tract infection
WHO	World Health Organization

PROTOCOL SUMMARY

Name of Sponsor/Company: Enanta Pharmaceuticals, Inc.
Name of Investigational Product: EDP-938
Study Title: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study of EDP-938 Administered Orally for the Treatment of Acute Upper Respiratory Tract Infection with Respiratory Syncytial Virus in Ambulatory Adult Subjects (RSVP)
Protocol Number: EDP 938-102
Phase of Development: 2b
Study Centers: This will be a multicenter global study and may include sites in North America, South America, Africa, Australia/New Zealand, and Europe.
Number of Subjects Planned: Approximately 70 subjects will be enrolled.
Planned Study Population: Ambulatory, nonhospitalized subjects (aged 18 to 75 years, inclusive) with up to 48 hours of upper respiratory tract infection (URTI) symptoms who test positive for respiratory syncytial virus (RSV) and negative for influenza virus by rapid testing (ie, Rapid Viral Screen). Subjects with stable asthma or chronic obstructive pulmonary disease (COPD) will be allowed in the study.
Investigational Product, Dosage, and Mode of Administration: EDP-938 will be supplied as tablets for oral administration [redacted]: [redacted] 200 mg. The total dose administered will be 800 mg of EDP-938 or placebo once daily for 5 days.
Duration of Treatment: 5 days
Study Objectives: **Primary Objective** • To evaluate the effect of EDP-938 on the progression of RSV infection by assessment of clinical symptoms **Secondary Objectives** • To evaluate the antiviral efficacy of EDP-938 • To evaluate the pharmacokinetics (PK) of EDP-938 • To evaluate the safety of EDP-938

Exploratory Objectives

- To evaluate EDP-938 in terms of emergence of viral resistance
- To evaluate the relationship between the PK of EDP-938 and antiviral activity and clinical symptoms
- To explore the progression of RSV infection using the [redacted]
- To evaluate the relationship between RSV subgroup A or B with antiviral and clinical efficacy of EDP-938

Criteria for Evaluation:

Primary Endpoint

- Effect of EDP-938 compared to placebo on RSV infection clinical symptoms measured as the total symptom score (TSS) area under the curve (AUC) from Day 1 through Day 14

Secondary Endpoints

- The AUC for RSV RNA viral load measured in nasopharyngeal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR)
- Percentage of subjects with RSV RNA viral load below the lower limit of quantitation in subjects receiving EDP-938 compared to placebo
- Plasma PK concentrations of EDP-938 [redacted]
- Safety endpoints include, but are not limited to, adverse events (AEs), vital sign measurements, pulse oximetry measurements, and clinical laboratory test results (including chemistry, hematology, and urinalysis)
- Time to RSV RNA viral load below the lower limit of quantitation in subjects receiving EDP-938 compared to placebo
- RSV RNA viral load change from Baseline

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Study Design:

This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study of EDP-938 administered orally for the treatment of acute URTI with confirmed RSV infection in ambulatory adult subjects.

For each subject, the duration of study participation will be approximately 2 weeks 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 14)	9 days after the last dose
Approximate total duration of participation	14 days

Screening Period on Day 1: At Screening (on Day 1), subjects will first review and sign the Rapid Viral Screen informed consent form (ICF) prior to RSV and influenza screening. Subjects will undergo a rapid diagnostic test for RSV and influenza virus using respiratory secretions obtained by nasal (or nasopharyngeal) swab collection. Subjects whose swab sample tests are positive for RSV and negative for influenza virus may proceed for further screening. Such subjects will be required to sign the full study ICF prior to performing any further study-specific assessments. After signing the full study ICF, subjects will undergo further screening procedures to determine study eligibility.

All study screening activities should be completed on Day 1. If any assessment is anticipated to fall outside of that window, then the Investigator should consult with the [redacted] Medical Monitor to determine if the subject can proceed. For subjects who sign the full study ICF and whose swab sample test results are positive for RSV and negative for influenza virus, the first screening activity should be to test subjects for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a rapid molecular diagnostic test. 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 electrocardiogram (ECG) and the screening urine pregnancy test. All screening procedures are detailed in the Schedule of Assessments (SoA).

Treatment Period (Days 1 to 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 1:1 to receive 800 mg of EDP-938 or placebo. Subject randomization will be stratified by the presence or absence of asthma/COPD.

Eligible subjects must complete the Day 1 biological sample collections (ie, blood, urine, and nasopharyngeal swab[s]) prior to receiving the first dose of EDP-938 or placebo. Day 1 blood and urine samples will be sent to both local (expedited testing and reporting) and central laboratories. Nasopharyngeal swab(s) will be sent to the central laboratory only.

Eligible subjects will receive an electronic data capture handheld device (ERT® electronic clinical outcome assessment [eCOA] Handheld eDiary) to use for the duration of the study. Subjects will use this device to complete the RSV symptom diary (twice daily at the same times each day ±2 hours) and the FLU-PRO questionnaire (once daily at the same time each day ±2 hours), to record when each dose of study drug is taken, and to record acetaminophen use. The device will also serve to alert the subject when it is time for study drug dosing. The subject will receive instruction on the proper use and care of the device, including the recording of the first

dose, and the device should be brought to each study site visit. In case the subject is unable to complete any assessments or recordings into the device for technical reasons, the subject will also be provided with a paper diary(ies) as a back-up.

The subject will be instructed on the use of concomitant medications during the study, including the use of acetaminophen as the study-specific analgesic/antipyretic (see Section 5.8 and Section 5.9).

Subjects will receive the first dose of study drug while at the study site. After the first dose, subjects will be instructed to take 800 mg of EDP-938 or placebo once daily 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.

On Day 3 and Day 5 (end-of-treatment), subjects should bring their study drug with them as part of their study site visit (in the provided cooler system) for drug accountability and for dosing of study drug on Day 5. 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, if feasible; refer to the Study Procedures Manual (SPM) for details.

Subjects who discontinue treatment early (ie, prior to completing 5 days of dosing) should return to the study site within 24 hours and no more than 48 hours later to complete the end-of-study (EOS) procedures.

All study assessments during the Treatment Period, including PK sample collection, are detailed in the SoA.

Follow-up Period (Days 6 to 14): Subjects should return to the study site for follow-up visits on Day 9 and Day 14 (EOS Visit) for post-treatment safety assessments. Visit assessments may be completed at the study site or by a study nurse via a home visit, if feasible; refer to the SPM for details.

Subjects who discontinue the study early (ie, prior to Day 14) should return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.

All study assessments during the Follow-up Period are detailed in the SoA.

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

Study Design Figure:

Abbreviations: d = day; FLU = influenza virus; RSV = respiratory syncytial virus.

Eligibility Criteria

Inclusion Criteria

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

1. A full ICF signed and dated by the subject. (Note: Prior to signing the full ICF, subjects will sign a Rapid Viral Screen ICF as described in inclusion criterion #4.)
2. Male or female individuals aged 18 to 75 years, inclusive.
3. Up to 48 hours of URTI symptoms with at least one of the following symptoms:

   Nasal discharge, nasal congestion, malaise/tiredness, headache, sinus congestion, sneezing, sore throat, hoarseness, cough, shortness of breath, respiratory wheeze, earache, and/or symptoms of fever.

   Note: The duration of symptoms (not more than 48 hours) is to be measured from the estimated time of onset of the first symptom.
4. After signing the Rapid Viral Screen ICF, positive for RSV infection and negative for influenza virus based on rapid diagnostic screen of nasal (or nasopharyngeal) swab samples.
5. Medically stable based on assessment of physical examination, medical history, vital sign measurements, pulse oximetry (only for subjects with asthma or COPD), and 12-lead ECG performed at Screening.
6. A body mass index $\geq$18 kg/m^2 and $\leq$40 kg/m^2.
7. Negative urine pregnancy test for women of childbearing potential as defined in inclusion criterion #8.

8. A woman of childbearing potential who is sexually active with a male must agree to use two effective methods of contraception from the date of Screening until 30 days after her last dose of study drug. Effective methods of contraception are defined as:

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

   a. Intrauterine device
   b. Occlusive cap (diaphragm or cervical/vault caps)
   c. Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive

   Note: The above does not apply to a female subject who has a vasectomized male as the sole partner or who is of nonchildbearing potential (ie, physiologically incapable of becoming pregnant) as defined below:

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

9. A male subject who has not had a vasectomy and is sexually active with a woman of childbearing potential must agree to use effective contraception from the date of Screening to 90 days after his last dose of study drug. Effective contraception is defined as a condom and at least one of the following for a female partner:

   a. Intrauterine device
   b. Occlusive cap (diaphragm or cervical/vault caps)
   c. Oral, injectable, implantable, transdermal, or intravaginal contraceptive

   Note: For a male subject who has had a vasectomy, use of a condom will still be required.

10. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after his last dose of study drug.
11. Must be willing and able to adhere to the study assessments, visit schedules, prohibitions, and restrictions, as described in this protocol.

Additional Inclusion Criteria for Subjects With Asthma

12. Physician-diagnosed asthma and currently receiving Global Initiative for Asthma (GINA) Step 2, 3, or 4 treatment, with stable dosing for at least 4 weeks prior to Screening.
13. Stable prebronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% of predicted within the prior 12 months of Screening based on historical spirometry medical records.

Additional Inclusion Criteria for Subjects With COPD

14. Physician-diagnosed COPD and currently receiving either short-acting bronchodilators (as required) or up to two maintenance therapies.
15. No change in the background COPD therapy for at least 4 weeks prior to Screening.
16. Stable postbronchodilator FEV_1 >50% of predicted and FEV_1:forced vital capacity (FVC) ratio <0.7 within the prior 12 months of Screening based on historical spirometry medical records.

Exclusion Criteria

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

1. Clinical evidence of a lower respiratory tract infection, as determined by the Investigator.
2. Anticipated need for hospitalization or emergency room care within 24 hours of Screening.
3. Receipt of systemic antiviral, antibacterial, antifungal, or antimycobacterial therapy within 7 days of Screening and for the duration of the study.
4. Awareness of concomitant respiratory infections that are viral (other than RSV), bacterial, or fungal, including systemic bacterial or fungal infections, within 7 days of Screening.
5. SARS-CoV-2 positive within 28 days of Screening or at Screening following signature of full ICF.
6. Frailty scale score ≥4 at Screening.
7. History of chronic liver disease (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, nonalcoholic steatohepatitis, and/or alcoholic liver disease); a history of biliary disease (eg, primary sclerosing cholangitis, cholecystitis, choledocholithiasis); or a history of portal hypertension. A diagnosis of hepatic steatosis (fatty liver) is not exclusionary.
8. Heart disease: any congenital heart disease, acute or chronic heart failure, ischemic heart disease, congenital long QT syndrome, or any clinical manifestation resulting in QT interval prolongation. Note: Subjects with controlled hypertension without cardiac compromise will be allowed to enroll. See exclusion criterion #18 for prohibited medications.
9. Neurological and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve, and muscle, eg, cerebral palsy, epilepsy [seizure disorders], stroke, muscular dystrophy, or spinal cord injury). Note: Minor neurological disorders (eg, past concussions, headaches, migraine) are allowed.
10. Malignant tumor or history of malignancy that may interfere with the aims of the study or a subject completing the study.
11. Prior receipt or the subject is waiting to receive a bone marrow, stem cell, or solid organ transplantation.

12. Diagnosis of cystic fibrosis.
13. Known positive human immunodeficiency virus, active hepatitis A virus infection, chronic hepatitis B virus infection, and/or current or treated hepatitis C virus infection.
14. Prior or planned ileal resection or bariatric surgery. Note: Subjects who have undergone gastric surgeries that do not affect drug absorption (eg, gastric band or gastric sleeve procedures) will be allowed to participate if they are stable for at least 1 year prior to Screening. Gastrectomy will be allowed if stable for at least 3 years prior to Screening.
15. Pregnant or nursing female subjects.
16. History of alcohol addiction or current heavy alcohol use defined as: >14 standard drinks per week and/or ≥4 standard drinks per occasion for males and >7 standard drinks per week and/or ≥3 standard drinks per occasion for females. A standard drink is 12 oz of beer (5% alcohol), 5 oz table wine (12% alcohol), or 1.5 oz of spirits (40% alcohol).
17. Known or suspected, in the opinion of the Investigator, renal disease or renal impairment.
18. Twelve-lead ECG demonstrating a QT interval corrected for heart rate according to Fridericia (QTcF) that is >500 msec or other clinically relevant abnormalities as judged by the Investigator at Screening.
19. Use of or intention to use excluded or contraindicated medication(s) or supplements, including any medication known to be a moderate or potent inducer or inhibitor of the cytochrome P450 3A4 enzyme, within 14 days prior to Screening and for the duration of the study.
20. Receipt of ≥14 days of systemic immunomodulator therapy (eg, oral corticosteroids) within 3 months of Screening.
21. Prior to the first dose of study drug and during study participation, the subject has received any vaccine, investigational agent, or biological product within 30 days or 5 times the half-life, whichever is longer. Note: Influenza vaccination within 7 days of Screening is not allowed.
22. Use of St John's wort within 28 days prior to the first dose of study drug and for the duration of the study.
23. History of or currently experiencing a medical condition or any other finding (including laboratory test results) that, in the opinion of the Investigator, might confound the results of the study; pose an additional risk in administering study drug to the subject; could prevent, limit, or confound the protocol-specified assessments; or deems the subject unsuitable for the study.

Additional Exclusion Criteria for Subjects With Asthma

24. Subjects must not have experienced a severe asthma exacerbation (defined as worsening asthma that requires treatment with oral corticosteroids for 3 or more days, or emergency room attendance) or deterioration in asthma requiring an increase in asthma treatment for at least 6 weeks prior to Screening.
25. Subject is receiving more than two maintenance asthma therapies or theophylline preparations for asthma treatment.
26. Pulse oximetry reading of <90% oxygen saturation measured at rest at Screening.

Additional Exclusion Criteria for Subjects With COPD

27. Receipt of theophylline, roflumilast, maintenance oral corticosteroids, or long-term oxygen therapy (defined as prescribed for 12 or more hours per day).
28. Exacerbation of COPD requiring treatment with systemic corticosteroids and/or antibiotics, or emergency room attendance or hospitalization within 6 weeks prior to Screening.
29. More than three COPD exacerbations with the past 12 months.
30. Pulse oximetry reading of <90% oxygen saturation measured at rest at Screening.

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

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

Sample Size Considerations: Using a ratio of 1:1, a sample size of 27 subjects per treatment group (54 subjects total) provides 80% power to detect a treatment reduction in TSS AUC of at least 55% from placebo (assuming TSS AUC from the previous Phase 2a clinical challenge study to: mean [standard deviation] of placebo: 500 [450] and EDP-938: 225 [200]) using a t-test with

[redacted]

Statistical Analysis: 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 subjects who receive at least one dose of study drug. Subjects will be analyzed as treated. The mITT Population is designated as the primary efficacy population.

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

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

Subject Disposition and Demographic Data: The number of subjects screened, randomized, and in the SAF, mITT, 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 the TSS AUC. The TSS AUC is measured twice daily (before or after treatment, morning/evening) using the 13-point symptom scale. The AUC will be calculated using the trapezoid rule. The TSS will be compared between EDP-938 and placebo using an analysis of covariance (ANCOVA) model with treatment group and stratification factor as fixed effects and the baseline TSS as a covariate. Treatment groups will be compared using a type III sum-of-squares. The least-squares means and two-sided 95% confidence intervals will be presented for individual groups and the difference between groups.

Sensitivity analysis of the primary endpoint will be performed using the Markov Chain Monte Carlo method of multiple imputation. Following imputation, the TSS AUC will be calculated and an ANCOVA model with treatment group and stratification factor as fixed effects, and the baseline TSS as a covariate will be performed. Treatment groups will be compared using a type III sum-of-squares. Other sensitivity analysis may include a mixed model repeated measures analysis on the change from Baseline over all visits.

The RSV RNA viral load AUC measured in nasopharyngeal swab samples by RT-qPCR will be measured on Days 1, 3, 5, 9, and 14. The trapezoid rule will be used to calculate the AUC of the RSV RNA viral load. An ANCOVA model with treatment group and stratification factor as fixed effects and the baseline RSV RNA viral load as a covariate will be performed. Treatment groups will be compared using a type III sum-of-squares. The proportion of subjects with RSV RNA below the lower limit of quantitation will be analyzed on Days 3, 5, 9, and 14. Treatment groups will be compared using a Cochran-Mantel-Haenszel test controlling for the stratification factor.

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

Pharmacokinetic Analyses: Summary of plasma concentration data will be descriptive in nature. 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.

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

[redacted]

Study Governance: Safety data from this study will be reviewed by a Data Safety Monitoring Board (DSMB) throughout the study. The DSMB will be headed by a DSMB Chair and will include physicians with expertise in RSV, consisting of a group of 3 experts independent from the Sponsor. Procedures for data review, including timing and potential outcomes, roles and responsibilities, and interactions with the Sponsor and PPD, will be governed by a separate DSMB charter.

1. INTRODUCTION

1.1 Overview

EDP-938 [redacted] is a novel orally administered non-fusion replication inhibitor of respiratory syncytial virus (RSV) that is being developed as a potential treatment for RSV infection. This Phase 2b study, EDP 938-102, is a randomized, double-blind, placebo-controlled, multicenter study designed to assess the efficacy and safety of EDP-938 compared to placebo in ambulatory adult subjects with RSV infection.

1.2 Background

Respiratory syncytial virus is the leading cause of lower respiratory tract infection and presents a significant health challenge in small children, elderly, and immunocompromised patients (*Falsey et al., 2005*; *Hall et al., 2009*; *Shook and Lin, 2017*). The incidence and mortality due to RSV-associated acute lower respiratory illness (ALRI) varies substantially from year to year in any given population. Recently, Shi et al reported that in 2015, globally, 33.1 million episodes of RSV-ALRI resulted in about 3.2 million hospital admissions, and 59,600 in-hospital deaths in children younger than 5 years (*Shi et al., 2017*). In children younger than 6 months, RSV-ALRI was also responsible for 1.4 million hospital admissions, and 27,300 in-hospital deaths. Overall RSV-ALRI mortality could be as high as 118,200 in young children (*Shi et al., 2017*). In the United States, RSV infection is the most common cause of hospitalization in infants (*Hall et al., 2009*; *Nair et al., 2010*).

[redacted]

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

1.3 Nonclinical Studies

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

1.3.1 Nonclinical Pharmacology

EDP-938 is a novel non-fusion replication inhibitor of RSV. [redacted]

[redacted]

1.3.2 Nonclinical Pharmacokinetics

[redacted]

1.3.3 Safety Pharmacology

No safety pharmacology concerns have been identified following EDP-938 administration. [redacted]

[redacted]

1.3.4 Nonclinical Toxicology

[redacted]

1.4 Clinical Studies

Four Phase 1 clinical studies, including a first-in-human (FIH) study in healthy subjects, two drug-drug interaction studies, and a bioavailability study, as well as one Phase 2a study are ongoing as shown in Table 1.

Table 1: List of Clinical Studies With EDP-938

Study Number	Study Title	Study Phase	Status
EDP-938-001	A Randomized, Double-Blind, Placebo-Controlled, First-In-Human Study of Orally Administered EDP-938 to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (SAD), Multiple Ascending Doses (MAD) and the Effect of Food on EDP-938 Pharmacokinetics in Healthy Subjects	1	[redacted]
EDP 938-002	A Non-Randomized, Open-Label, Two-Part, Drug-Drug Interaction Study to Evaluate the Effects of Cyclosporine and Prednisone on the Pharmacokinetics and Safety of EDP-938 in Healthy Adult Subjects	1	[redacted]
EDP 938-003	A Non-Randomized, Open-Label, Three-Part, Drug-Drug Interaction Study to Evaluate the Effects of Itraconazole, Rifampin, and Quinidine on the Pharmacokinetics and Safety of EDP-938 in Healthy Subjects	1	[redacted]
EDP 938-004	A Randomized, Single-Dose, Open-Label, 3-Way, 3-Period Crossover, 6-Sequence Bioavailability Study Comparing the Pharmacokinetics of EDP-938 Suspension (Reference) to Tablet (Test) in Healthy Human Subjects under Fed and Fasted Conditions	1	[redacted]
EDP 938-101	A Randomized, Phase 2a, Double-Blind, Placebo-Controlled study to Evaluate the Safety, Pharmacokinetics and Antiviral Activity of Multiple Doses of Orally Administered EDP-938 Against Respiratory Syncytial Virus Infection in the Virus Challenge Model	2a	[redacted]

1.5 Potential Risks and Benefits

Potential risks to subjects receiving EDP-938 have been estimated based on safety data from the ongoing Phase 1 studies (EDP-938-001, EDP 938-002, EDP 938-003, and EDP 938-004) conducted in healthy subjects and the ongoing Phase 2a study (EDP 938-101) in healthy adult subjects infected with RSV A Memphis 37b.

[redacted]

In the Phase 2a EDP 938-101 study, both EDP-938 regimens (600 mg once daily or a 500 mg loading dose [LD] followed by 300 mg twice daily for 5 days) were generally well tolerated with safety profiles that were comparable to placebo. 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.

Across these studies, EDP-938 has been observed to be safe and generally well tolerated with AEs being infrequent, generally mild, and resolving in follow-up. No definitive pattern of AEs has been observed to date. There have been no SAEs or severe AEs, with a single subject discontinuing study drug as noted above.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

- To evaluate the antiviral efficacy of EDP-938
- To evaluate the PK of EDP-938
- To evaluate the safety of EDP-938

[redacted]

2.2 Endpoints

2.2.1 Primary Endpoint

- Effect of EDP-938 compared to placebo on RSV infection clinical symptoms measured as the total symptom score (TSS) AUC from Day 1 through Day 14

2.2.2 Secondary Endpoints

- The AUC for RSV RNA viral load measured in nasopharyngeal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR)
- Percentage of subjects with RSV RNA viral load below the lower limit of quantitation in subjects receiving EDP-938 compared to placebo

- Plasma PK concentrations of EDP-938 and its major metabolites (EP-024636, EP-024594, and EP-024595)
- Safety endpoints include, but are not limited to, AEs, vital sign measurements, pulse oximetry measurements, and clinical laboratory test results (including chemistry, hematology, and urinalysis)
- Time to RSV RNA viral load below the lower limit of quantitation in subjects receiving EDP-938 compared to placebo
- RSV RNA viral load change from baseline

3. SELECTION OF SUBJECTS

A total of approximately 70 subjects are planned to be enrolled into this study.

3.1 Subject Inclusion Criteria

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

1. A full informed consent form (ICF) signed and dated by the subject. (Note: Prior to signing the full ICF, subjects will sign a Rapid Viral Screen ICF as described in inclusion criterion #4.)
2. Male or female individuals aged 18 to 75 years, inclusive.
3. Up to 48 hours of upper respiratory tract infection (URTI) symptoms with at least one of the following symptoms:

   Nasal discharge, nasal congestion, malaise/tiredness, headache, sinus congestion, sneezing, sore throat, hoarseness, cough, shortness of breath, respiratory wheeze, earache, and/or symptoms of fever.

   Note: The duration of symptoms (not more than 48 hours) is to be measured from the estimated time of onset of the first symptom.
4. After signing the Rapid Viral Screen ICF, positive for RSV infection and negative for influenza virus based on rapid diagnostic screen of nasal (or nasopharyngeal) swab samples.
5. Medically stable based on assessment of physical examination, medical history, vital sign measurements, pulse oximetry (only for subjects with asthma or chronic obstructive pulmonary disease [COPD]), and 12-lead ECG performed at Screening.
6. A body mass index (BMI) $\geq$18 kg/m^2 and $\leq$40 kg/m^2.
7. Negative urine pregnancy test for women of childbearing potential as defined in inclusion criterion #8.
8. A woman of childbearing potential who is sexually active with a male must agree to use two effective methods of contraception from the date of Screening until 30 days after her last dose of study drug. Effective methods of contraception are defined as:

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

   a. Intrauterine device
   b. Occlusive cap (diaphragm or cervical/vault caps)
   c. Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive

Note: The above does not apply to a female subject who has a vasectomized male as the sole partner or who is of nonchildbearing potential (ie, physiologically incapable of becoming pregnant) as defined below:

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

9. A male subject who has not had a vasectomy and is sexually active with a woman of childbearing potential must agree to use effective contraception from the date of Screening to 90 days after his last dose of study drug. Effective contraception is defined as a condom and at least one of the following for a female partner:
   a. Intrauterine device
   b. Occlusive cap (diaphragm or cervical/vault caps)
   c. Oral, injectable, implantable, transdermal, or intravaginal contraceptive

   Note: For a male subject who has had a vasectomy, use of a condom will still be required.
10. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after his last dose of study drug.
11. Must be willing and able to adhere to the study assessments, visit schedules, prohibitions, and restrictions, as described in this protocol.

Additional Inclusion Criteria for Subjects With Asthma

12. Physician-diagnosed asthma and currently receiving Global Initiative for Asthma (GINA) Step 2, 3, or 4 treatment, with stable dosing for at least 4 weeks prior to Screening.
13. Stable prebronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% of predicted within the prior 12 months of Screening based on historical spirometry medical records.

Additional Inclusion Criteria for Subjects With COPD

14. Physician-diagnosed COPD and currently receiving either short-acting bronchodilators (as required) or up to two maintenance therapies.
15. No change in the background COPD therapy for at least 4 weeks prior to Screening.
16. Stable postbronchodilator FEV_1 >50% of predicted and FEV_1:forced vital capacity (FVC) ratio <0.7 within the prior 12 months of Screening based on historical spirometry medical records.

3.2 Subject Exclusion Criteria

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

1. Clinical evidence of a lower respiratory tract infection, as determined by the Investigator.
2. Anticipated need for hospitalization or emergency room care within 24 hours of Screening.
3. Receipt of systemic antiviral, antibacterial, antifungal, or antimycobacterial therapy within 7 days of Screening and for the duration of the study.
4. Awareness of concomitant respiratory infections that are viral (other than RSV), bacterial, or fungal, including systemic bacterial or fungal infections, within 7 days of Screening.
5. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive within 28 days of Screening or at Screening following signature of full ICF.
6. Frailty scale score ≥4 at Screening.
7. History of chronic liver disease (eg, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, nonalcoholic steatohepatitis, and/or alcoholic liver disease); a history of biliary disease (eg, primary sclerosing cholangitis, cholecystitis, choledocholithiasis); or a history of portal hypertension. A diagnosis of hepatic steatosis (fatty liver) is not exclusionary.
8. Heart disease: any congenital heart disease, acute or chronic heart failure, ischemic heart disease, congenital long QT syndrome, or any clinical manifestation resulting in QT interval prolongation. Note: Subjects with controlled hypertension without cardiac compromise will be allowed to enroll. See exclusion criterion #18 for prohibited medications.
9. Neurological and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve, and muscle, eg, cerebral palsy, epilepsy [seizure disorders], stroke, muscular dystrophy, or spinal cord injury). Note: Minor neurological disorders (eg, past concussions, headaches, migraine) are allowed.
10. Malignant tumor or history of malignancy that may interfere with the aims of the study or a subject completing the study.
11. Prior receipt or the subject is waiting to receive a bone marrow, stem cell, or solid organ transplantation.
12. Diagnosis of cystic fibrosis.
13. Known positive human immunodeficiency virus, active hepatitis A virus infection, chronic hepatitis B virus infection, and/or current or treated hepatitis C virus infection.

14. Prior or planned ileal resection or bariatric surgery. Note: Subjects who have undergone gastric surgeries that do not affect drug absorption (eg, gastric band or gastric sleeve procedures) will be allowed to participate if they are stable for at least 1 year prior to Screening. Gastrectomy will be allowed if stable for at least 3 years prior to Screening.
15. Pregnant or nursing female subjects.
16. History of alcohol addiction or current heavy alcohol use defined as: >14 standard drinks per week and/or ≥4 standard drinks per occasion for males and >7 standard drinks per week and/or ≥3 standard drinks per occasion for females. A standard drink is 12 oz of beer (5% alcohol), 5 oz table wine (12% alcohol), or 1.5 oz of spirits (40% alcohol).
17. Known or suspected, in the opinion of the Investigator, renal disease or renal impairment.
18. Twelve-lead ECG demonstrating a QT interval corrected for heart rate according to Fridericia (QTcF) that is >500 msec or other clinically relevant abnormalities as judged by the Investigator at Screening.
19. Use of or intention to use excluded or contraindicated medication(s) or supplements, including any medication known to be a moderate or potent inducer or inhibitor of CYP3A4 enzyme, within 14 days prior to Screening and for the duration of the study.
20. Receipt of ≥14 days of systemic immunomodulator therapy (eg, oral corticosteroids) within 3 months of Screening.
21. Prior to the first dose of study drug and during study participation, the subject has received any vaccine, investigational agent, or biological product within 30 days or 5 times the half-life, whichever is longer. Note: Influenza vaccination within 7 days of Screening is not allowed.
22. Use of St John's wort within 28 days prior to the first dose of study drug and for the duration of the study.
23. History of or currently experiencing a medical condition or any other finding (including laboratory test results) that, in the opinion of the Investigator, might confound the results of the study; pose an additional risk in administering study drug to the subject; could prevent, limit, or confound the protocol-specified assessments; or deems the subject unsuitable for the study.

Additional Exclusion Criteria for Subjects With Asthma

24. Subjects must not have experienced a severe asthma exacerbation (defined as worsening asthma that requires treatment with oral corticosteroids for 3 or more days, or emergency room attendance) or deterioration in asthma requiring an increase in asthma treatment for at least 6 weeks prior to Screening.
25. Subject is receiving more than two maintenance asthma therapies or theophylline preparations for asthma treatment.
26. Pulse oximetry reading of <90% oxygen saturation measured at rest at Screening.

Additional Exclusion Criteria for Subjects With COPD

27. Receipt of theophylline, roflumilast, maintenance oral corticosteroids, or long-term oxygen therapy (defined as prescribed for 12 or more hours per day).
28. Exacerbation of COPD requiring treatment with systemic corticosteroids and/or antibiotics, or emergency room attendance or hospitalization within 6 weeks prior to Screening.
29. More than three COPD exacerbations with the past 12 months.
30. Pulse oximetry reading of <90% oxygen saturation measured at rest at Screening.

4. STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study of EDP-938 administered orally for the treatment of acute URTI with confirmed RSV infection in ambulatory adult subjects.

The study is composed of 3 periods:

- Screening Period will occur on Day 1. During this period, subjects will review and sign the Rapid Viral Screen ICF. Subjects will undergo a rapid diagnostic screen for RSV and influenza virus using respiratory secretions obtained by nasal (or nasopharyngeal) swab collection. Subjects whose swab sample tests positive for RSV and negative for influenza virus will review and sign the full study ICF and may proceed for further screening procedures. RSV positive and influenza negative subjects will be tested for SARS-CoV-2 at Screening and subjects who have positive test results for SARS-CoV-2 will be excluded from the study.
- Treatment Period will begin with the first dose of study drug on Day 1 and will conclude with the end-of-treatment (EOT) Visit on Day 5.
- Follow-up Period for safety will begin following the last dose of study drug and will conclude at the end-of-study (EOS) Visit on Day 14, 9 days following the last dose of study drug.

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 1:1 to receive 800 mg of EDP-938 or placebo once daily 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

Abbreviations: d = day; FLU = influenza virus; RSV = respiratory syncytial virus.

4.2 Rationale for Study Design

This proposed study will evaluate EDP-938 in adult subjects with confirmed RSV, who will be randomized to receive either 800 mg of EDP-938 or placebo in a 1:1 ratio.

4.2.1 Justification of Study Design, Endpoints, and Subject Population

Despite the significant medical need, there is no vaccine or highly effective treatment currently available for RSV. At present, there are only two agents approved for the prevention or treatment of RSV lower respiratory tract disease, a prophylactic agent (palivizumab) and a therapeutic agent (aerosolized ribavirin); each having indications for use that are limited to the pediatric population. Analyses performed subsequent to the approval of aerosolized ribavirin suggest that it failed to impart any clinically significant benefits (*Randolph and Wang, 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.

This Phase 2b study aims to evaluate the efficacy and safety of EDP-938 in an adult population with early detection of RSV infection as well as early initiation of EDP-938. In order to more fully investigate the efficacy of EDP-938, and noting the lack of a highly effective RSV therapy, 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 1:1 fashion. The study endpoints include efficacy and safety assessments. The primary endpoint is based on the subject's twice daily assessment of defined, RSV-related, clinical symptoms over the course of the 14-day study. These data will enable the calculation of the AUC for the TSS as was used in the Phase 2a EDP 938-101 study. The antiviral efficacy will be assessed as the AUC for RSV RNA quantitation by nasopharyngeal swab over the course of the 14-day study. 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.

The eligible population comprises non-hospitalized individuals who have RSV infection and who may have permissible comorbidities. This includes subjects who are otherwise healthy, aged up to 75 years, have a BMI up to 40 kg/m^2, and those with asthma or COPD that is stable and less severe by established guidelines. Individuals with asthma or COPD are at risk for more significant RSV disease. These individuals may be more sensitive to early onset of URTI symptoms and thus may be more likely to present for RSV screening. At this stage of development, subjects with more severe or unstable asthma or COPD are excluded from study participation. Similarly, 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 liver, kidney, heart and/or neurologic disease, and those who are frail.

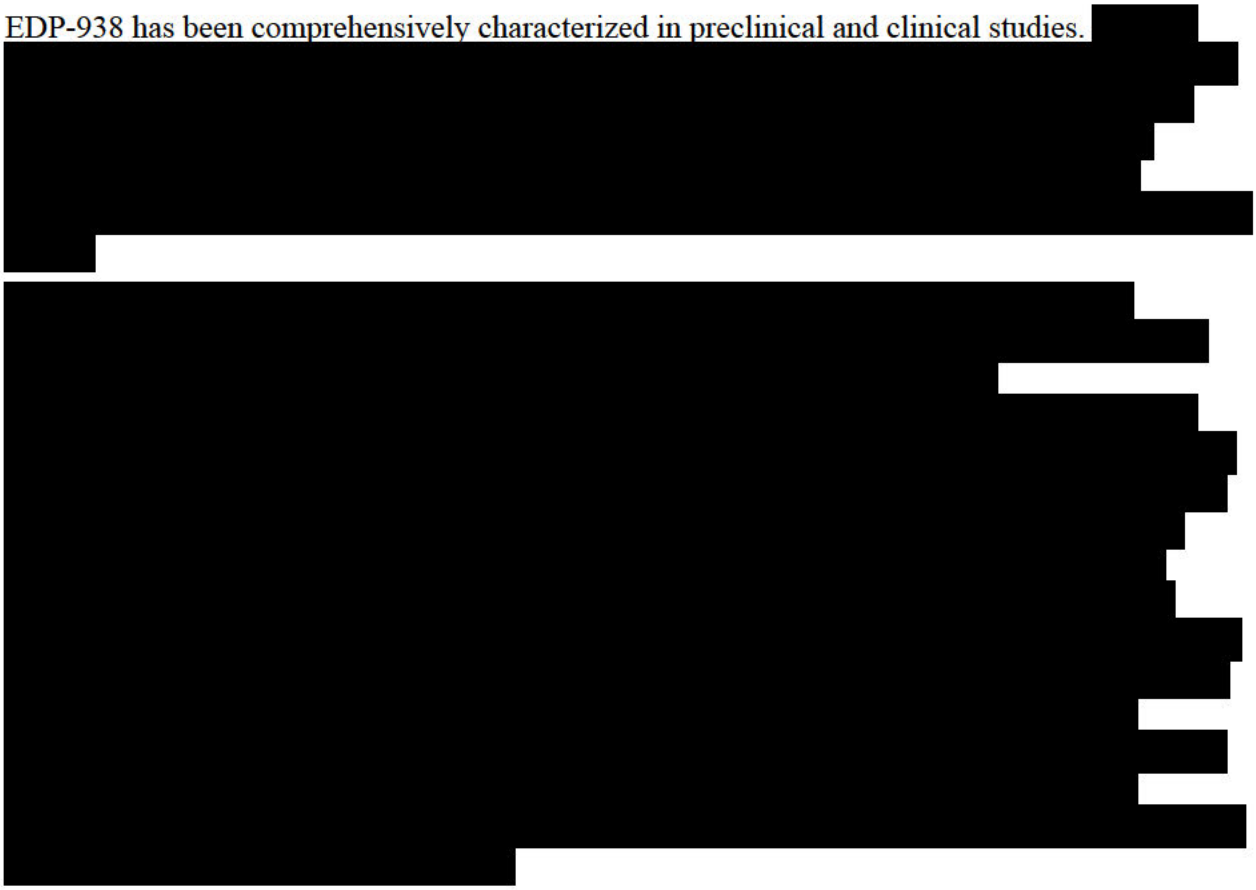
Because the window for optimal intervention for RSV infection may be discrete, the screening process is optimized to allow rapid identification of subjects with RSV (but who do not have influenza virus) and who are otherwise appropriate for the study so that EDP-938 (or placebo)

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 (see Section 1.4 and Section 1.5), in which healthy adult subjects were inoculated with RSV and received EDP-938 either once daily or twice daily 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 (see Section 1.4 and Section 1.5).

To date, EDP-938 has demonstrated a favorable safety profile with dosing in approximately 300 subjects exposed to single or multiple doses of EDP-938 for up to 7 days. The double-blind design utilizing a matched placebo for EDP-938 will allow for the most unbiased assessment of the clinical safety profile of EDP-938. Subject safety will be monitored through regularly scheduled assessments of AEs, safety laboratory tests, and the inclusion of a 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.



Study EDP 938-101 is an ongoing Phase 2a study evaluating the safety, PK, and antiviral activity of multiple doses of orally administered EDP-938 against RSV infection in the healthy volunteer virus-challenge model (see Section 1.5). The study is composed of two parts and final data analyses are available for Part 1, in which a total of 115 subjects were randomized (1 subject

randomized was not dosed) to receive placebo (n=38), 600 mg once daily (n=39), or a single 500 mg LD followed by 300 mg twice daily (n=38) for 5 days.

Data from Part 1 of the EDP 938-101 study demonstrated proof-of-concept in adults inoculated with RSV. The primary and key secondary efficacy endpoints were achieved with high statistical significance at both dose levels, 600 mg once daily and a 500 mg LD followed by 300 mg twice daily. Both EDP-938 treatment regimens demonstrated robustly lower RSV RNA AUC values compared to placebo ($p<0.001$) with no significant difference between the once daily and twice daily treatment groups. Additional study findings were as follows:

- Both EDP-938 treatment regimens demonstrated robustly lower 10-point TSS AUC values compared to placebo ($p<0.001$) with no significant difference between once daily and twice daily treatment groups.
- Both EDP-938 regimens were observed to be generally safe and well tolerated with no SAEs, severe AEs, or discontinuations of EDP-938 due to AEs (see Section 1.5).

The mean EDP-938 trough concentrations (C_{trough}) were maintained at 22- to 42-fold above the *in vitro* 90% maximal effective concentration (EC_{90}) for RSV M37. The mean (coefficient of variation) total daily EDP-938 AUC after the last dose was approximately 24,700 (38.4) ng·hr/mL and 26,300 (29.0) ng·hr/mL for the 600 mg once daily group and the 500 mg LD followed by 300 mg twice daily group, respectively. The systemic exposures in this study were generally comparable to those observed in Study EDP-938-001 at similar doses.

[redacted]

The dose selected for the present Phase 2b EDP 938-102 study is 800 mg of EDP-938 (or placebo) administered as a tablet formulation once daily for 5 days. [redacted]

[redacted] 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 [redacted]

5.2 Packaging and Labeling

EDP-938 drug product tablets [redacted]

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

5.3 Storage

EDP-938 and placebo tablets [redacted]

5.4 Accountability

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

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

Unused study drug must not be discarded or used for any purpose other than for administration to subjects enrolled into this clinical 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.

[redacted]

5.5 Handling and Disposal

Study drug must not be used for any purpose other than for administration to subjects enrolled into this clinical study. All study drug bottles that are opened and returned by subjects as well as those that are not opened or assigned to subjects will be retained at the site according to instructions provided by Enanta Pharmaceuticals, Inc. or 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 Web Response System (IWRS). Subjects will be randomized in a 1:1 ratio to the EDP-938 or placebo treatment group as shown below:

- Treatment Group 1 (approximately 35 subjects): 800 mg of EDP-938 orally once daily for 5 days
- Treatment Group 2 (approximately 35 subjects): Placebo orally once daily for 5 days

In addition, subject randomization will be stratified based on the presence or absence of asthma/COPD.

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.

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

5.7 Study Drug Dose and Administration

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

Following randomization on Day 1, subjects will receive the first dose of 800 mg EDP-938 or placebo orally while at the study site. After the first dose, subjects will be instructed to take the study drug once daily on each of the 4 subsequent days. Subjects will be instructed to take the study drug orally at approximately the same time every day (±1 hour). From Day 1, subjects will electronically record the time and date that each dose is taken.

On Day 3 and Day 5, subjects should bring their study drug with them as part of their study site visit [redacted] for drug accountability and for dosing of study drug on Day 5 as described below. If the 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, if feasible; refer to the Study Procedures Manual (SPM) for details.

On 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 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 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.

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 and
- There must be a minimum of 16 hours between doses.

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

Stopping rules for study drug administration are provided in Section 10.1.

5.7.1 Dispensing of Study Drug

EDP-938 and placebo must be dispensed by a licensed investigational pharmacist or other authorized site staff with appropriate training. [redacted]

5.7.2 Treatment Compliance

The subject will be instructed to bring all study drug (including empty bottles) to the site on Day 3, Day 5, and EOS Visit (for subjects who discontinue study drug or the study early). Both accountability and study drug compliance, including tablet counts and the electronic dosing record (or back-up paper diary as applicable) completed by the subjects, will be reviewed at each study site visit as indicated in the SoA (Appendix 1). The number of tablets will be counted, and

the site staff will ask the subjects why any doses were missed, if applicable. Any potential reasons for lack of compliance with dosing will be monitored and followed up by the site staff. Compliance assessment may be completed at the study site or by a study nurse via a home visit, if feasible; refer to the SPM for details.

The time and date of doses of study drug taken at the study site should be recorded by site staff. From Day 1, subjects will electronically record the time and date that each dose is taken. In case the subject is unable to complete any assessments or recordings into the device for technical reasons, the subject will also be provided with a paper diary(ies) as a back-up.

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

5.8 Concomitant Medications

All subjects enrolled in the study must abstain from taking any prohibited medications through the end of the study (see Section 5.9).

If RSV symptoms occur, such as fever or headache that require symptomatic relief during the study, then subjects may take acetaminophen at a dose of 3000 mg/day or less. Acetaminophen will be permitted only for the relief of fever or pain. From Day 1, subjects will electronically record the date and time of any acetaminophen use. In case the subject is unable to complete any recordings into the device for technical reasons, the back-up paper diary may be completed by subjects [redacted]

For subjects with physician-diagnosed asthma, current GINA Steps 2, 3, or 4 treatment will be allowed as long as the dose is stable for at least 4 weeks prior to Screening. The GINA treatment guidelines (ie, main report and pocket guide) may be accessed at: https://ginasthma.org/reports/. Administration of more than two maintenance asthma therapies or theophylline preparations will not be allowed for study participation.

For subjects with physician-diagnosed COPD, short-acting bronchodilators (as required) are permitted. No more than two maintenance therapies are permitted. Receipt of theophylline, roflumilast, maintenance oral corticosteroids, or long-term oxygen therapy (defined as prescribed for 12 or more hours per day) will not be allowed for study participation.

Details of prior and concomitant medication use will be recorded in the source documentation and the electronic case report form (eCRF) as indicated in the SoA (Appendix 1).

5.9 Prohibited Medications

Receipt of systemic antiviral, antibacterial, antifungal, or antimycobacterial therapy within 7 days of Screening and for the duration of the study are prohibited. The 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 14 or early termination:

- Systemic antiviral (except study drug), antimicrobial*, and antifungal drugs**
- Antipyretics/analgesics (except acetaminophen)
- Antitussives/expectorants
- Combination cold remedies
- Antihistamines**
- Corticosteroids**
- Immunomodulators
- Traditional medicines used for respiratory infection (eg, Maoutou)
- Other investigational drugs

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

**Dermal preparations permitted, but systemic use or topical application to the eyes, nose, or ears, or by inhalation are prohibited. However, inhaled corticosteroids used for treatment of COPD or asthma are permitted.

The use of St John's wort within 28 days prior to first dose of study drug and for the duration of the study is prohibited.

Additional prohibited medications are presented in Section 3.2.

6. BLINDING

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

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

6.1 Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will use the IWRS process.

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 such cases, the Investigator must first attempt to contact the [redacted] Medical Monitor to discuss and agree to the need for unblinding. In situations which the Investigator has attempted and failed to contact the [redacted] Medical Monitor and/or 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.

For unblinding, in the event that the local [redacted] Medical Monitor cannot be reached, sites at all locations should call the following 24/7 global medical coverage hotline: [redacted]

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the [redacted] Medical Monitor and study coordinator should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (eg, the reason, date) should be clearly recorded in the subject's study file. In addition, the Investigator should consider whether the clinical event that prompted unblinding should be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report as described in Section 9.2.

The [redacted] 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). Also refer to the SPM. Study sites will be responsible for following up with subjects for any missed study site visits.

7.1.1 Screening Period on Day 1

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

At Screening (on Day 1), subjects will first review and sign the Rapid Viral Screen ICF prior to RSV and influenza screening. Subjects will undergo a rapid diagnostic screen for RSV and influenza virus using respiratory secretions obtained by nasal (or nasopharyngeal) swab collection; refer to the Laboratory Manual for details. Subjects whose swab sample test results positive for RSV and negative for influenza virus may proceed for further screening. Such subjects will be required to sign the full study ICF prior to performing any further study-specific assessments. After signing the full study ICF, subjects will undergo further screening procedures to determine study eligibility.

All study screening activities should be completed on Day 1. If any assessment is anticipated to fall outside of that window, then the Investigator should consult with the [redacted] Medical Monitor to determine if the subject can proceed. For subjects who sign the full study ICF and whose swab sample test results are positive for RSV and negative for influenza virus, the first screening activity should be to test subjects for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a rapid molecular diagnostic test. 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 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 1:1 to receive 800 mg of EDP-938 or placebo. Subject randomization will be stratified by the presence or absence of asthma/COPD.

Eligible subjects must complete the Day 1 biological sample collections (ie, blood, urine, and nasopharyngeal swab[s]) prior to receiving the first dose of EDP-938 or placebo. Day 1 blood

and urine samples will be sent to both local (expedited testing and reporting) and central laboratories. Nasopharyngeal swab(s) will be sent to the central laboratory only.

Eligible subjects will receive an electronic data capture handheld device (ERT® electronic clinical outcome assessment [eCOA] Handheld eDiary) to use for the duration of the study. [redacted] The device will also serve to alert the subject when it is time for study drug dosing. The subject will receive instruction on the proper use and care of the device, including the recording of the first dose, and the device should be brought to each study site visit. In case the subject is unable to complete any assessments or recordings into the device for technical reasons, the subject will also be provided with a paper diary(ies) as a back-up.

The subject will be instructed on the use of concomitant medications during the study, including the use of acetaminophen as the study-specific analgesic/antipyretic (see Section 5.8 and Section 5.9).

Subjects will receive the first dose of study drug while at the study site. After the first dose, subjects will be instructed to take 800 mg of EDP-938 or placebo once daily 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 (see Section 5.3).

On Day 3 and Day 5 (EOT), subjects should bring their study drug with them as part of their study site visit [redacted] for drug accountability and for dosing of study drug on Day 5 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, if feasible; refer to the SPM for details. 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.

Subjects who discontinue treatment early (ie, prior to completing 5 days of dosing) should return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.

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

7.1.3 Follow-up Period (Days 6 to 14)

Study Site Visits (Days 9 and 14):

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

Subjects who discontinue the study early (ie, prior to Day 14) should return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.

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

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

7.2 Subject Withdrawal/Early Termination

Subjects may withdraw from the study at any time at their own request, or subjects may be withdrawn 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 [redacted] Medical Monitor where possible before prematurely removing a subject. For any subject who decides to withdraw from the study, the Investigator should inquire about the reason for withdrawal, request that the subject returns 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 the study early, every effort must be made for the subject to return to the site within 24 hours and no more than 48 hours later to complete the EOS procedures.

If a subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Enanta Pharmaceuticals, Inc. may retain and continue to use any data collected before such withdrawal of consent.

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

7.2.1 Withdrawal Criteria

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

7.2.2 Procedures for Early Discontinuation or Early Termination of Treatment

Subjects who prematurely discontinue treatment early and have received at least one dose of study drug should return to the site within 24 hours and no more than 48 hours later and undergo the EOS procedures per the SoA (Appendix 1). Any subject who withdraws with ongoing AEs/SAEs should be followed up until resolution of their AE(s) or until the Investigator has determined that the AE(s) has stabilized.

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

7.2.3 Documentation of Withdrawal of Subjects

The reason for early withdrawal/termination/lost to follow-up of any subject from the study must be documented on the appropriate eCRF. If the reason for early withdrawal is an AE or an abnormal laboratory value, the specific event or test result, if available, should be recorded on the AE eCRF and the subject should be monitored until the event is resolved or deemed stable by the Investigator.

8. STUDY PROCEDURES/EVALUATIONS

8.1 Timing of Assessments

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

8.2 Demographics and Medical History

Demographics and baseline characteristics including date of birth or age, gender or sex, race, ethnicity, medical history, and smoking history will be obtained from each subject and entered in the eCRF as reported during Screening. Significant medical history will be obtained by consulting with the subject. As a general rule, all medical events occurring within the last 6 months should be recorded. For events that occurred more than 6 months ago (and that are not ongoing), only significant or relevant events should be entered on 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

Any medication taken during the course of the study through the end of the study will be recorded with indication, dosage, route of administration, and start and stop dates of administration. All subjects will be questioned about concomitant medication 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 QTcF intervals will be utilized.

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

An ECG may be repeated at the discretion of the Investigator to address suspected errors in performance. 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 previous status. Only clinically significant abnormalities should be recorded in the eCRF (eg, use of contact lenses does not need to be recorded).

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 will be calculated at Screening (to assess eligibility) according to the following equation:

BMI = weight (kg)/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 are performed and documented in the subject source notes and eCRF.

8.3.6 Pulse Oximetry

At Screening, subjects diagnosed with asthma or COPD will have pulse oximetry performed to measure oxygen saturation and to ensure study exclusion criteria are not met (see Section 3.2).

Subsequent pulse oximetry measurements will be performed for subjects with asthma or COPD as indicated in the SoA (Appendix 1).

8.3.7 Frailty Scale Score

At Screening, all subjects will have a frailty scale score documented by the Investigator or site staff based on subject interview and medical history to ensure that study exclusion criteria are not met (see Section 3.2). Frailty will be assessed by a validated 9-point scale (*Rockwood et al., 2005*) or as otherwise indicated in the SPM.

8.3.8 Respiratory Syncytial Virus Symptom Diary

At Screening and at timepoints indicated in the SoA (Appendix 1), subjects will assess the severity of RSV-related signs and symptoms and self-complete the 13-point RSV symptom diary. The 13-item diary will consist of grading symptoms on a scale of 0 to 3, where Grade 0 is absence, Grade 1 is just noticeable, Grade 2 is bothersome but does not prevent participation in activities, and Grade 3 is bothersome and interferes with activities. The 13 RSV symptoms assessed will comprise nasal discharge, nasal congestion, malaise/tiredness, headache, sinus congestion, sneezing, sore throat, hoarseness, cough, shortness of breath, respiratory wheeze, earache, and/or symptoms of fever. The RSV symptom diary will be completed twice daily at the same times each day ±2 hours as an eCOA. In case the subject is unable to complete the RSV symptom diary assessment for technical reasons, the subject will also be provided with a paper diary(ies) as a back-up. If a subject plans to take acetaminophen within 2 hours of the scheduled RSV symptom diary completion, then the RSV symptom diary should be completed immediately before the subject takes acetaminophen or 4 hours after taking acetaminophen.

8.3.10 Collection of Nasal and 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 2.

8.4 Laboratory and Diagnostic Procedures

At Screening, the rapid viral diagnostic screen will be performed on site. Subsequent virology assessments will be sent to the central laboratory(ies).

On Day 1, enrolled subjects will undergo the clinical laboratory evaluations of blood and urine samples specified Table 2, 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, urine, and nasopharyngeal swab samples will be completed prior to administration of study drug.

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

8.4.1 Routine Laboratory Panels

Blood samples will be collected for analysis of the analytes as shown in Table 2. 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) and processed as indicated in the Laboratory Manual. Estimated creatinine clearance will be calculated using the Cockcroft-Gault equation using actual body weight.

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 for a serum pregnancy test to be performed by the central laboratory. The screening urine pregnancy test results will be used to qualify subjects at study entry.

To confirm nonsurgical postmenopausal status for women stating that they are amenorrhoeic for 1 to 2 years, documentation of FSH levels >35 mIU/mL will be required. Where such documentation is not available, then 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.

Table 2: Clinical and Respiratory Syncytial Virus Laboratory Evaluations

CHEMISTRY PANEL Alanine aminotransferase[a] Albumin, serum[a] Alkaline phosphatase, serum[a] Amylase[a] Aspartate aminotransferase[a] Bilirubin, total and direct[a] BUN[a] BUN/Creatinine ratio (calculation) Calcium, serum Creatine kinase Creatinine, serum[a] Creatinine clearance, estimated Uric acid Electrolyte panel (sodium, potassium, chloride, bicarbonate) [a] Phosphorus Gamma glutamyl transferase Globulin, total Glucose, serum[a] Cholesterol Triglycerides Lactate dehydrogenase Lipase Protein, total, serum	**HEMATOLOGY PANEL** Hemoglobin[a] Hematocrit[a] Differential white blood cell count, percentage and absolute (basophils, eosinophils, lymphocytes, monocytes, neutrophils)[a] Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count[a] Red blood cell count White blood cell count[a] International normalized ratio[a] Prothrombin time[a] Activated thromboplastin time[a] **RSV-SPECIFIC AND OTHER VIROLOGY TESTS** RSV and influenza A/B diagnostic test (nasal or nasopharyngeal secretions) SARS-CoV-2 diagnostic test (nasopharyngeal or oropharyngeal secretions) Confirmatory respiratory pathogen panel RSV RNA quantitation of viral load (nasopharyngeal secretions) [redacted] RSV serology (neutralizing antibodies, serum, archived)
URINALYSIS Routine urinalysis to include: Color and appearance, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, protein, urobilinogen, microscopic examination (including red blood cells and white blood cells)[a]	**PREGNANCY AND OTHER TESTS** Urine pregnancy test Serum pregnancy test (only Day 1 and to the central laboratory) Follicle-stimulating hormone

Abbreviations: BUN = blood urea nitrogen; RSV = respiratory syncytial virus.
[a] On Day 1, blood and urine 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, complete hematology, chemistry, and urine panels should be sent to the central laboratory with the other Day 1 samples.

8.5 Virology Assessments

Virology assessments and tests (see Table 2) will be performed using nasal (or nasopharyngeal) swab (rapid diagnostic screen) or nasopharyngeal swab samples (other virology assessments) and serology samples collected at Screening and at timepoints indicated in the SoA (Appendix 1) and as further described in the Laboratory Manual, including swab collection, sampling, and handling procedures. Note: Multiple nasopharyngeal swab samples may be collected at each timepoint; refer to the Laboratory Manual for details. With the exception of the rapid diagnostic test (for RSV and influenza 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 Screen ICF, the subject will undergo a rapid molecular diagnostic screen for RSV and influenza A/B at the local site. Refer to the Laboratory Manual for details. A nasal (or nasopharyngeal) swab sample will be collected to obtain respiratory secretions. Subjects whose swab sample tests positive for RSV and negative for influenza virus and who agree to proceed, will be required to read and sign the full study ICF and may proceed for further screening assessments. Results will be recorded in the source documents.

In the event that the rapid molecular diagnostic test is unavailable for technical reasons, then rapid antigen tests for RSV and influenza virus may be used as a back-up. The use of such tests and the results must be recorded in the source documents.

Subjects, who sign the full study ICF and whose swab sample test results are positive for RSV and negative for influenza, will be screened for SARS-CoV-2 using a rapid molecular diagnostic test.

8.5.2 Confirmatory Respiratory Pathogen Panel

Following randomization on Day 1, as specified in the SoA (Appendix 1), eligible subjects will have additional nasopharyngeal swab sample(s) taken prior to taking the first dose of EDP-938 or placebo for central laboratory analysis and confirmation of respiratory pathogens recovered. This testing will be performed to identify other nasopharyngeal co-pathogens that may include adenovirus, coronavirus, human metapneumovirus, human rhinovirus/enterovirus, parainfluenza virus, *Bordetella pertussis*, *Chlamydophila pneumoniae*, and/or *Mycoplasma pneumoniae*, which may impact the course of a subject's illness. Refer to the Laboratory Manual for further details.

8.5.3 Respiratory Syncytial Virus 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 (eg, peak viral load and time to peak). Refer to the Laboratory Manual for further details.

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. Refer to the Laboratory Manual for further details.

8.5.5 Viral Resistance

Nasopharyngeal swab sample(s) may be analyzed for potential viral resistance monitoring assessment. Resistance monitoring assessment, if performed, will be conducted by population and/or deep sequencing of the RSV gene to monitor for treatment-emergent resistance mutations. Refer to the Laboratory Manual for further details.

8.5.6 Respiratory Syncytial Virus Serology

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

8.6 Pharmacokinetic Samples

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

If the 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 5 study site visit occurs more than 4 hours after the time scheduled for dosing of study drug, then subject should take the study drug at the scheduled time. On Day 5 if the subject takes the study drug prior to the study site visit (see Section 5.7), a PK sample should be taken at the same approximate time as that of the nasopharyngeal swab collection.

At the EOS Visit, a PK sample is only required for subjects who discontinue the study before 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 [redacted] 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 in the eCRF. In addition, the site should record the date and time of last dose taken prior to the PK sample collection. It is important that the date and time of each of PK blood sample are accurately recorded in the source documents.

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

[redacted]

[redacted]

9. SAFETY MONITORING AND REPORTING

9.1 Definitions

9.1.1 Pretreatment Events

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

9.1.2 Adverse Events

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

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

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

9.1.3 Serious Adverse Events

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

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

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

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

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

Adverse events will be evaluated and documented using the grading scales contained in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

9.2.1 Documenting and Reporting Adverse Events

All AEs reported from the time of informed consent to the EOS Visit for each subject will be recorded in the subject's source documents. For subjects who do not receive study drug (ie, alternates or screen failures), AEs will only be recorded in the source documents. For subjects enrolled into the study (ie, randomized), all AEs will be recorded in the subject's AE eCRF and the SAE Form (if applicable). The AE eCRF will indicate if the event occurred prior to the first dose of study drug, during treatment, or during the postdose Follow-up Period. The site should record all AEs regardless of the intensity, seriousness, or relationship to study drug.

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

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

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

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

An AE includes the following:

- Progression or exacerbation of the subject's underlying disease. Clinical sequelae that result from disease progression, such as pleural effusion or small bowel obstruction, are reportable as AEs
- Pre-existing event that increases in frequency or intensity
- Condition detected or diagnosed during the study period, even though it may have been present, in retrospect, 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
- An overdose of the study drug without any signs or symptoms will be considered an AE. A calculated dose that exceeds its correct dose by 10% or more and is administered to the subject will be considered an overdose and documented as an AE

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

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, etc); however, the condition (the "triggering event") that leads to the procedure may be an AE
- Pre-existing conditions present or detected 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 event. Every effort will be made by the Investigator to assess the relationship of each AE to study drug. To ensure consistency of AE/SAE causality assessments, the Investigator should apply the following guidelines:

- **Related:** There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than

the study drug have been ruled out, and/or the event reappeared on re-exposure to the study drug.

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

9.2.3 Classifying Action Taken With Study Drug

In the case of an AE, the actions that can be taken with study drug are defined in Table 3.

Table 3: Options for Action Taken With Study Drug

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

9.2.4 Classifying Adverse Event Outcome

For every AE/SAE, the possible outcomes of the event and the definition of the outcome are shown in Table 4. One outcome must be entered into the appropriate field on the AE and (if appropriate) SAE Form for each event as discussed in the eCRF instructions.

Table 4: Classification and Definition of Adverse Event Outcomes

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

9.2.5 Documenting and Reporting Serious Pretreatment Events and Serious Adverse Events

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

The SAE Form should be sent to [redacted]

All SAEs will be recorded on the SAE Form using a recognized medical term or diagnosis that accurately reflects the event. All SAEs will be assessed by the Investigator for severity, relationship to the investigational study drug, and possible etiologies. On the SAE Form, relationship to study drug will be assessed only as related or not related. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the Investigator is required to follow up the event to resolution and report the outcome of the event to [redacted] 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 (ie, SUSARs) 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 study drug and for 90 days after the last dose of study drug.

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. The Investigator or designee must notify [redacted], the Sponsor's Medical Monitor, and the [redacted] within 1 business day of the sites' knowledge of the subject's (or partner's) pregnancy, by utilizing the study-specified pregnancy report form. If confirmed to be on active drug, the subject or partner will be followed up until the end of the pregnancy and the infant will be followed up for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

9.3 Follow-up of Adverse Events and Serious Adverse Events

All AEs (serious and nonserious) will be followed up until resolution or otherwise explained (see Table 4), the subject dies, the event stabilizes and is not expected to further resolve with the maximum time limit for stabilization defined as 30 days after the occurrence of the event, or when alternative therapy is instituted, whichever occurs first. If alternative therapy is instituted, it should be documented. Enanta Pharmaceuticals, Inc. may request that the Investigator perform or arrange for supplemental measurements or evaluations to further clarify the nature of the event.

9.4 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 Data Safety Monitoring Board

Safety data from this study will be reviewed by a DSMB throughout the study. The DSMB will be headed by a DSMB Chair and will include physicians with expertise in RSV, consisting of a group of 3 experts independent from the Sponsor. Procedures for data review, including timing and potential outcomes, roles and responsibilities, and interactions with the Sponsor and PPD, will be governed by a separate DSMB charter.

10. SUBJECT SAFETY MANAGEMENT/ STUDY STOPPING RULES

10.1 Study Stopping Rules

If any of these events occur, dosing will be placed on hold pending a full review of all available clinical safety data and discussion with the investigators and the DSMB.

- Two or more subjects receiving EDP-938 experience a similar Grade 3 study drug-related AE, including a confirmed treatment-emergent Grade 3 laboratory abnormality
- One or more subjects receiving EDP-938 experience a study drug-related SAE
- One or more subjects receiving EDP-938 experience Grade 4 or higher AE or a confirmed treatment-emergent laboratory abnormality regardless of causality attribution to study drug

10.2 Site or Study Discontinuation

10.2.1 Study Discontinuation

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

- 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.

10.2.2 Site Termination

A single site may warrant termination under the following conditions:

- Failure of the site to enroll subjects into the study at an acceptable rate

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

10.2.3 Study Termination Procedures

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

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

11. STATISTICAL CONSIDERATIONS

11.1 General Considerations

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

Continuous endpoints will be summarized using n, mean, standard deviation, median, 25^{th} quartile, 75^{th} quartile, minimum, and maximum values. Categorical endpoints will be summarized by the number of subjects meeting the endpoint and the percentage of subjects out of the appropriate population. The denominator will be displayed when needed. Statistical inference will be performed as appropriate. Inferential testing will be conducted using a two-sided alpha of 0.05, unless stated otherwise.

Any change to the data analysis methods described in the protocol will require an amendment if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report or SAP. Changes may only be made in the SAP prior to unblinding.

11.2 Sample Size Considerations

Using a ratio of 1:1, a sample size of 27 subjects per treatment group (54 subjects total) provides 80% power to detect a treatment reduction in TSS AUC of at least 55% from placebo (assuming TSS AUC from the previous Phase 2a clinical challenge study to: mean [standard deviation]) of placebo: 500 [450] and EDP-938: 225 [200]) using a t-test with unequal variance. Assuming a 20% dropout rate, approximately 35 subjects per treatment group (approximately 70 subjects total) are needed.

11.3 Analysis 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 subjects who receive at least one dose of study drug. Subjects will be analyzed as treated. The mITT Population is designated as the primary efficacy population.
- *Per Protocol (PP) Population*: All subjects who are randomized and receive all planned doses of study drug and do not have major protocol deviations that may unduly influence outcome. Subjects will be analyzed in the treatment group that corresponds to the study drug received during the study.

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

11.4 Subject Disposition and Demographic Data

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

The following categories will also be summarized for subject disposition:

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

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

11.5 Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized to blinded treatment on Day 1 in a 1:1 ratio to 800 mg of EDP-938 or placebo. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign investigational product to each subject. To achieve between-group comparability, the randomization will be stratified by asthma/COPD status.

11.6 Efficacy Analyses

11.6.1 Primary Efficacy Analyses

The primary efficacy analysis will be performed on the TSS AUC. The TSS AUC is measured twice daily (before or after treatment, morning/evening) using the 13-point symptom scale. Date and time of completion and symptom severity (graded 0 to 3) will be recorded. The TSS will be derived for each from the last nonmissing measurement (Baseline) collected prior to dosing to the final on Day 14. The average daily TSS will be computed as part of the primary efficacy endpoint. The AUC will be calculated using the trapezoid rule (*Matthews et al., 1990*). The TSS will be compared between EDP-938 and placebo using an analysis of covariance (ANCOVA) model with treatment group and stratification factor as fixed effects and the baseline TSS as a covariate. Treatment groups will be compared using a type III sum-of-squares. The least-squares means and two-sided 95% confidence intervals (CI) will be presented for individual groups and

the difference between groups. Descriptive statistics will include at a minimum the number of nonmissing measurements, mean, median, minimum, maximum, and 95% CI for the mean.

11.6.2 Secondary Efficacy Analyses

Sensitivity analysis of the primary endpoint will be performed using the Markov Chain Monte Carlo (MCMC) method of multiple imputation (*Dong and Peng, 2013*). Following imputation using MCMC methods, the TSS AUC will be calculated and an ANCOVA model with treatment group and stratification factor as fixed effects, and the baseline TSS as a covariate will be performed. Treatment groups will be compared using a type III sum-of-squares. Other sensitivity analysis may include a mixed model repeated measures analysis on the change from Baseline over all visits.

The RSV RNA viral load AUC measured in nasopharyngeal swab samples by RT-qPCR will be measured on Days 1, 3, 5, 9, and 14. The trapezoid rule will be used to calculate the AUC of the RSV RNA viral load. An ANCOVA model with treatment group and stratification factor as fixed effects and the baseline RSV RNA viral load as a covariate will be performed. Treatment groups will be compared using a type III sum-of-squares. The proportion of subjects with RSV RNA below the lower limit of quantitation will be analyzed on Days 3, 5, 9, and 14. Treatment groups will be compared using a Cochran-Mantel-Haenszel test controlling for the stratification factor.

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 (only for subjects with asthma or COPD), concomitant medications, and laboratory values, will be summarized separately by treatment group. Change from Baseline will be included in summary tables for vital sign measurements and laboratory parameters. Shift tables will also be generated by laboratory analyte. All laboratory data will be included in the data listings, and all test values outside the normal range will be flagged.

11.7.1 Treatment Compliance

Listing of the randomization schedule and study drug dispensed with lot number will be provided. Treatment compliance for each subject will be calculated as the number of subjects receiving the amount of drug taken divided by the amount prescribed multiplied by 100.

11.7.2 Adverse Events

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

Summaries of AEs will include the following at a minimum:

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

11.7.3 Clinical Laboratory Data

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

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

For continuous tests:

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

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

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

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

11.7.4 Vital Sign Measurements

The incidence rate of subjects with treatment-emergent vital sign changes at any post-Baseline visit will be summarized. Specific criteria for the classification of treatment emergent will be

documented in the SAP. Vital sign observed, change, and percentage change will be summarized by treatment over visits.

11.7.5 Electrocardiograms

Screening ECG data will be provided in data listings.

11.7.6 Pulse Oximetry

Pulse oximetry measurements will be summarized by visit and treatment.

11.7.7 Concomitant Medications

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

11.7.8 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 [redacted], as allowed by the data. Additional details will be provided in the SAP.

11.9 Subgroup and Covariate Analyses

Subgroup analyses will be performed on the primary and secondary endpoints, primarily. A logistic regression model will be planned when categorical endpoints are analyzed. 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 ANCOVA model with treatment group and stratification factor as fixed effects in the model, with subgroup and subgroup-by-treatment interaction as well.

Various study populations may be used. Forest plots will be provided to visually describe the association.

[redacted]

11.11 Interim Analyses

No interim analysis will be performed in this 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 ICF, any other written documentation provided to the subject, and all advertisements that may be used for study-specific recruitment to the IRB/EC for review and approval before commencing study-specific assessments. If it is necessary to amend the protocol during the study, then it is the responsibility of the Investigator to ensure that IRB/EC approval is obtained before implementation of the amended procedures. It is also the responsibility of the Investigator to provide the IRB/EC with any SAE or Investigational New Drug safety reports. A copy of the ICF approved by the IRB/EC must be forwarded to Enanta Pharmaceuticals, Inc. for regulatory purposes.

12.1.3 Written Informed Consent

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

For this study, there will be two ICFs. Details on these are provided in Section 7.1.1. Each subject must provide a signed and dated ICF 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 (ie, 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. 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.

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

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

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 designated agent, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or study site records of all subjects enrolled into this study. A statement to this effect will be included in the ICF authorizing the use of protected health information.

12.4 Quality Assurance

At its discretion, Enanta Pharmaceuticals, Inc. or its 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 [redacted] and will allow the inspector direct access to all source documents, eCRFs, and other study documentation for source data check and/or on-site audit inspection.

12.5 Retention of Records

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

12.6 Information Disclosure

12.6.1 Confidentiality

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

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

12.6.2 Publication Policy

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

All information generated from this study is the proprietary property of Enanta Pharmaceuticals, Inc. 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 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 Screening	1 Eligible Subjects[a]	2	3	4	5 (+1 d) EOT	6-8	9 (±1 d)	10-13	14 (±1 d) EOS[b]
Study site visit	X			X[c]		X[c]		X[c]		X[c]
Informed consent form[d]	X									
RSV/influenza rapid diagnostic test[e]	X									
Inclusion/Exclusion criteria	X									
SARS-CoV-2 rapid diagnostic test[f]	X									
Demographics	X									
Medical history	X									
Smoking history	X									
Prior medications	X									
Vital sign measurements[g]	X					X				X
12-Lead ECG (resting)	X									
Physical examination[h]	X									
Weight, height, and BMI[i]	X									X
Pulse oximetry[j]	X					X				X
Frailty scale score (see SPM)	X									
Pregnancy test[k]	X (urine)	X (serum)								X (urine)
FSH[l]		X								
Clinical laboratory tests[m]		X				X				X
Randomization[n]		X								
eCOA Handheld eDiary[o]		X								X
RSV symptom diary eCOA[p]		X	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X	X
NP swab collection: confirmatory respiratory pathogen panel		X								
NP swab collection: RSV RNA quantitation of viral load		X		X		X		X		X
[redacted]		X		X		X		X		X
RSV serology collection		X								X
[redacted]		X								X
Study drug dosing[s]		X[s]	X	X	X	X[s]				
Study drug accountability[t]				X		X				X
PK sample collection		X[u]		X[u]		X[u]				X[v]
Concomitant medications[w]		X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; d = day; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; EOS = end-of-study; EOT = end-of-treatment; [redacted] FSH = follicle-stimulating hormone; ICF = informed consent form; NP = nasopharyngeal; PK = pharmacokinetic; RSV = respiratory syncytial virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SPM = Study Procedures Manual. Note: Refer to the Laboratory Manual for sample collection and processing details.

[a] Day 1 assessments to be performed in randomized subjects.
[b] Subjects who discontinue treatment early (ie, prior to completing 5 days of dosing) or the study early (ie, prior to Day 14) should return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.
[c] Visit assessments may be completed at the study site or by a study nurse via a home visit, if feasible; refer to the SPM for details. 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.
[d] Informed consent must be obtained prior to conducting any study-specific assessments. For this study, there will be two ICFs. Subjects will review and sign the Rapid Viral Screen ICF prior to RSV and influenza screening. Subjects whose swab sample tests positive for RSV and negative for influenza virus may proceed for further screening. Such subjects will be required to sign the full study ICF prior to performing any further study-specific assessments. After signing the full study ICF, subjects will undergo further screening procedures to determine study eligibility.
[e] A nasal (or NP) swab sample will be collected to obtain respiratory secretions for a rapid diagnostic screen for RSV and influenza A/B.
[f] Subjects who sign the full study ICF and whose swab sample test results are positive for RSV and negative for influenza will be screened for SARS-CoV-2, using a rapid diagnostic test.
[g] Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Vital signs will be measured after the subject has been supine for a minimum of 5 minutes.
[h] 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.
[i] Height will be documented at Screening only. Body mass index will be calculated at Screening (to assess eligibility) according to the following equation: BMI = weight (kg)/height $(m)^2$.
[j] Pulse oximetry measurements should only be performed in subjects with asthma or COPD.
[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 Day 1, blood will be collected for a serum pregnancy test to be performed by the central laboratory. The screening urine pregnancy test results will be used to qualify subjects at study entry. Refer to Section 8.4.2 for pregnancy testing requirements for postmenopausal females.
[l] Follicle-stimulating hormone should be tested in postmenopausal females. Refer to Section 8.4.2.
[m] Clinical laboratory tests include chemistry, hematology, and urinalysis. See Section 8.4 and Table 2 for details regarding Day 1 sample collection and evaluations for the local and central laboratory(ies).
[n] Subjects who meet all inclusion criteria and none of the exclusion criteria to the satisfaction of the Investigator, including the screening ECG and the screening urine pregnancy test, will be eligible to enter the study and will be randomized 1:1 to receive 800 mg of EDP-938 or placebo. Subject randomization will be stratified by the presence or absence of asthma/COPD.
[o] Eligible subjects will receive an electronic data capture handheld device (ERT® eCOA Handheld eDiary) on Day 1 and will return the device to the study site at the EOS Visit. Refer to Section 7.1.2 for additional details.
[p] The RSV symptom diary will be self-completed by subjects twice daily at the same times each day ±2 hours as an eCOA. If a subject plans to take acetaminophen within 2 hours of the scheduled RSV symptom diary completion, then the RSV symptom diary should be completed immediately before the subject takes acetaminophen or 4 hours after taking acetaminophen.
[redacted]
[s] Study drug (EDP-938 or placebo) should be administered at the study site on Days 1 and 5. On 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. From Day 1, subjects will electronically record the time and date that each dose is taken. See Section 5.7 for additional dosing details.
[t] Study drug accountability by tablet count and review of the electronic dosing record completed by the subjects.
[u] On Day 1, collect one postdose plasma PK sample, at least 1 hour after dosing or right before the subject leaves the site, whichever is later. On Day 3, collect one plasma PK sample at the same approximate time as that of the NP swab collection. On Day 5, collect one predose PK sample. If the subject takes the study drug prior to the study site visit, a PK sample should be taken at the same approximate time as that of the NP swab collection. See Section 5.7 and Section 8.6 for additional details.
[v] At the EOS Visit, a PK sample is only required for subjects who discontinue the study before the last dose of study drug is taken. The PK sample should be collected at the same approximate time as that of the NP swab collection.
[w] Acetaminophen use will be permitted only for the relief of fever or pain. Subjects will electronically record the date and time of any acetaminophen use. See Section 5.8 for additional details on acetaminophen use.