Clinical Study Protocol

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 2-PART STUDY TO EVALUATE EDP-938 REGIMENS IN SUBJECTS AGED 28 DAYS TO 36 MONTHS INFECTED WITH RESPIRATORY SYNCYTIAL VIRUS (RSV)

Protocol Number: EDP 938-201

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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

Protocol Document History

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Protocol Approval – Sponsor Signatory

Study Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 2-Part Study to Evaluate EDP-938 Regimens in Subjects Aged 28 Days to 36 Months Infected With Respiratory Syncytial Virus (RSV)
Protocol Number	EDP 938-201
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Protocol accepted and approved by:

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Signature

7/11/2024

Date

SIGNATURE PAGE

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

Principal Investigator:

_____

Signature: _____ Date: _____

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LIST OF ABBREVIATIONS

AE	adverse event
ALRI	associated acute lower respiratory illness
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{0-24}	area under the curve from time zero to 24 hour
BID	twice daily
BiPAP	bilevel positive airway pressure
C_{12}	plasma concentration 24 hours after dosing
C_{24}	plasma concentration 12 hours after dosing
C_{max}	maximum observed concentration, occurring at T_{max}
CPAP	continuous positive airway pressure
CYP	cytochrome P450
EC	ethics committee
EC_{50}	50% 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
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IRB	institutional review board
IRT	interactive response technology
IV	Intravenous
JAS	juvenile animal study
LD	loading dose
LLN	lower limit of normal
LOD	limit of detection
MAARI	medically attended acute respiratory infection
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
PE	physical examination
PK	pharmacokinetic(s)
PND	postnatal day
PT	post-treatment day
QD	once daily
RSV	respiratory syncytial virus

RT-qPCR	reverse transcription-quantitative polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Assessments
SpO_2	oxygen saturation
SSC	Study Steering Committee
SUSAR	suspected, unexpected, serious adverse reactions
TBD	to be determined
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T_{max}	time to reach C_{max}
ULN	upper limit of normal
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Name of Sponsor/Company: Enanta Pharmaceuticals, Inc.

Name of Investigational Product: EDP 938-201

Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 2-Part Study to Evaluate EDP-938 Regimens in Subjects Aged 28 Days to 36 Months Infected With Respiratory Syncytial Virus (RSV)

Protocol Number: EDP 938-201

Phase of Development: 2

Study Centers: This will be a multicenter global study and may include sites in North America, Europe, Asia-Pacific, Latin America, the Middle East, and Africa.

Number of Subjects Planned: Approximately 90 subjects are planned to be enrolled.

Planned Study Population: Hospitalized or non-hospitalized infants and children (aged 28 days to 36 months, inclusive), with RSV-associated respiratory tract infection and who test positive for RSV based on an approved diagnostic assay. Subjects will be enrolled simultaneously in two age groups: ≥6 months to ≤36 months (Age Group 1) and ≥28 days to <6 months (Age Group 2).

Investigational Product, Dosage, and Mode of Administration: EDP-938 will be supplied as [redacted] Oral doses of EDP-938 or placebo, [redacted] will be administered once daily (QD) for 5 days. The initial dose is planned to be [redacted] for both age groups.

Varying age-appropriate volumes of a fixed concentration ([redacted]) of EDP-938 or placebo will be administered to achieve the intended dose in each pediatric patient.

The study will be divided into 2 parts. A Study Steering Committee (SSC) will make recommendations to determine dose selection and cohort progression in Part 1 and Part 2.

Duration of Treatment: 5 days

Study Objectives

The primary efficacy objective is to evaluate the antiviral activity of EDP-938 in the pooled population (subjects from Part 1 and Part 2 together).

Part 1

Primary Objectives

- To evaluate the pharmacokinetics (PK) of EDP-938;
- To assess the safety and tolerability of EDP-938.

Secondary Objective

- To evaluate the antiviral activity of EDP-938.

Part 2 and Pooled Population

Primary Objective

- To evaluate the antiviral activity of EDP-938.

Secondary Objectives

- To assess the safety and tolerability of EDP-938;
- To evaluate the PK of EDP-938.
- To evaluate additional antiviral activity measures of EDP-938.
- To evaluate clinical outcomes of EDP-938.

Part 1, Part 2, and Pooled Population

[redacted]

Criteria for Evaluation

The primary efficacy endpoint is the daily change in RSV shedding in nasal swab samples determined using RT-qPCR from Baseline through the treatment phase in the pooled population (subjects from Part 1 and Part 2 together).

Part 1

Primary Endpoints

- PK parameters of EDP-938 including area under the curve (AUC) and predose concentrations;
- Safety and tolerability of EDP-938 compared to placebo as assessed by, but not limited to, adverse events (AEs), vital signs, and clinical laboratory results.

Secondary Endpoints

- AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR);
- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from Baseline through the treatment phase;
- Proportion of subjects with RSV RNA viral load below the limit of detection (LOD) in subjects receiving EDP-938 compared to placebo;
- Time to RSV RNA viral load being undetectable.

Part 2 and Pooled Population

Primary Endpoint

Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from Baseline through the treatment phase.

Secondary Endpoints

- Safety and tolerability of EDP-938 compared to placebo as assessed by, but not limited to, AEs, vital signs, and clinical laboratory results;
- AUC for RSV RNA viral load measured in nasal swab samples by RT-qPCR;
- Proportion of subjects with RSV RNA viral load below the LOD in subjects receiving EDP-938 compared to placebo;
- Time to RSV RNA viral load being undetectable;
- PK parameters of EDP-938 including AUC and predose concentrations;
- Time to discharge for hospitalized subjects;
- Time to use of oxygen for hospitalized subjects who are not receiving oxygen at the time they receive the first dose of study drug;
- Proportion of hospitalized subjects requiring oxygen supplementation or have an increased oxygen requirement;
- Time to mechanical ventilation for hospitalized subjects;

- Proportion of hospitalized subjects requiring mechanical ventilation;
- Deaths among hospitalized subjects;
- Time to hospitalization for initial outpatients who are subsequently hospitalized;
- Proportion of outpatients who are subsequently hospitalized or died;
- Time to resolution of symptoms for outpatients who are not hospitalized.

Part 1, Part 2, and Pooled Population

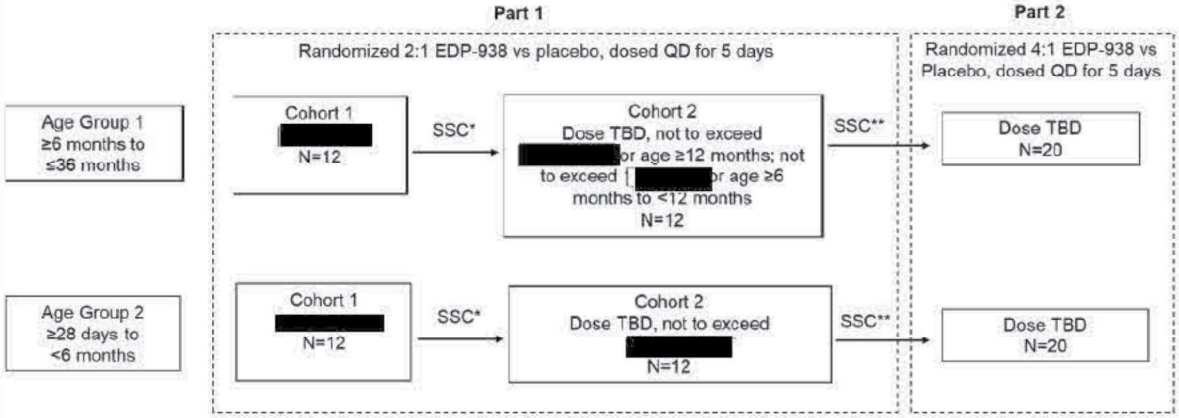
[redacted]

Overall Study Design:

This is a 2-part, randomized, double-blind, placebo-controlled, dose-ranging study. For each subject, the duration of study will be approximately 29 days. Each part of the study will consist of Screening, Treatment, and Follow-up periods.

Study Period	Duration
Screening (Day-1 to D1)	Up to 24 hours (note: assessments done as part of standard of care can be used as screening assessments if they are done within 72 hours)
Treatment (Day 1 to Day 5)	5 days
Follow-up (Day 6 to Day 28)	23 days
Approximate total duration of participation	29 days maximum

The overall study design is shown below. Approximately 90 subjects for both Part 1 and Part 2 are planned to be enrolled in 2 age groups.



QD = once daily; SSC = study steering committee; TBD = to be determined.

The SSC will review data from each cohort and will determine dose selection and cohort progression in Part 1 and Part 2.

**SSC will review available blinded data when at least 9 subjects have been randomized in Cohort 1 for each age group.*

*** SSC will review available blinded data when at least 6 subjects have been exposed to EDP-938 in Cohort 2 for each age group.*

The SSC will review data from each cohort and will determine dose selection and cohort progression in Part 1 and Part 2. The SSC will be blinded to treatment assignments. SSC members will include the Enanta Medical Monitor, an Enanta clinical pharmacology representative, a biostatistician, a pediatrician who is independent of the study conduct and who has expertise in respiratory infections, and the Contract Research Organization's Medical Monitor.

Additional subjects or cohort(s) may be enrolled based on emerging safety and PK data to potentially evaluate different doses, dosing regimens, or additional subjects at the same dose.

Part 1: Enrollment will begin simultaneously with Cohort 1 Age Group 1 and Cohort 1 Age Group 2. When at least 9 subjects have been randomized in Cohort 1, for each age group, the

SSC will review available blinded data, including at least safety and PK data, and will determine dosing for Part 1 Cohort 2 for each age group. The SSC will meet as required to review emerging safety and PK data to support dose decision and initiation of Cohort 2. Enrollment in Cohort 1 age groups will continue until 12 subjects have been enrolled.

Cohort 1 Age Group 1 will include subjects who may be hospitalized or non-hospitalized at enrollment. Cohort 1 Age Group 2 will include subjects who are hospitalized at enrollment.

Cohort 2 for both age groups will include subjects who may be hospitalized or non-hospitalized at enrollment.

Additional Part 1 cohorts may be added, as deemed necessary by the SSC.

Part 2: Both age groups will include subjects who may be hospitalized or non-hospitalized at enrollment. The start of dosing for each age group will be contingent upon at least 6 subjects in that age group being exposed to EDP-938 in Part 1 Cohort 2 and will be based on SSC recommendations. After completion of dosing in the Part 2 cohort, the SSC will review available blinded data, including at least safety and PK data, in that age group. Twenty subjects are planned for each age group, but additional subjects may be enrolled based on SSC recommendations to allow a sufficient number of subjects to determine doses for both age ranges.

Additional Part 2 cohorts may be added, as deemed necessary by the SSC.

In addition to the SSC responsible for dose escalation decisions based on blinded safety and PK data, to ensure that the safety of the subjects is thoroughly monitored, an Independent Data Monitoring Committee (IDMC) will review unblinded safety data. At a minimum, the IDMC will review data for each age group from Part 1 and subsequently from Part 2. Ad hoc meetings of the IDMC can be scheduled whenever deemed necessary. The IDMC will include 2 clinicians and a statistician who are independent of study conduct, Enanta, and the Contract Research Organization.

The study periods are summarized below. Study assessments are detailed in the Schedule of Assessments (SoA). For study assessments, a subject's hospitalization status (hospitalized or non-hospitalized) will be based on their status on the day of the visit.

Screening Period: At Screening, the subject's legal representative (henceforth referred to as "caregiver") must review and sign an informed consent form (ICF) before the subject undergoes any study-specific procedures.

After the ICF is signed, screening assessments will be done, including physical examination, ECG, vital sign and body measurements. Some procedures performed as part of standard of care (such as an RSV diagnostic test or safety laboratory tests) may be used to determine study eligibility if they are performed within 72 hours of when the ICF is signed, as specified in the SoA. Screening safety laboratory test samples will be sent to the local laboratory for expedited testing.

Subjects who have symptom onset, defined as the estimated onset of the first sign of respiratory infection, that does not exceed 7 days for Part 1 and 5 days for Part 2 before the signing of the ICF by their caregiver and whose swab sample tests positive for RSV will undergo further screening procedures to determine study eligibility. Screening should be completed as soon as

possible to ensure that subjects will be randomized and administered the first dose of study drug within 24 hours of signing the ICF.

Treatment Period (Days 1 to 5): Subjects who are eligible for the study will be randomized 2:1 (Part 1) or 4:1 (Part 2) to EDP-938:placebo. Subjects will be considered enrolled at the time of randomization.

Nasal swab samples will be collected throughout the treatment period for RSV viral load assessments. At each scheduled visit, the site Investigator or designee will complete the Professional ReSVinet clinical scoring system.

The subjects' caregiver will receive an eCOA [redacted] handheld device. This device will be used to complete the Parent/Guardian ReSVinet clinical scoring system beginning after randomization but before the first dose and subsequently QD at approximately the same time each day ± 2 hours. The palatability question should be completed postdose. The device should be brought to each site study visit.

The subjects' caregivers will receive instructions on the proper use and care of the eCOA device. If a caregiver is unable to use the eDiary, a paper diary may be used.

In a subset of subjects, the subjects' caregivers will also complete the [redacted] clinical scoring system on paper after randomization but before the first dose and subsequently twice daily, approximately every 12 hours.

Hospitalized Subjects

Subjects will receive EDP-938 or placebo QD orally for 5 days at approximately the same time every day (± 1 hour). Hospitalization duration will not be extended solely for study purposes. Hospitalized subjects who are discharged before Day 3 should return to the study site for Day 3 and Day 5 visits. Subjects who are discharged on or after Day 3 (but before Day 5), should return to the study site for the Day 5 visit.

Non-hospitalized Subjects

Subjects will receive the first dose of EDP-938 or placebo orally at the study site on Day 1 and will be monitored at the site for safety assessments over the first 3 hours postdose. Subjects' caregiver(s) will be instructed to administer EDP-938 or placebo QD at approximately the same time every day (± 1 hour) on Day 2 and Day 4. On Day 3 and Day 5 (End-of-Treatment visit; EOT), subjects should be dosed at the clinic. If a subject is unable to attend a study site visit, a home visit by study site personnel/home health staff may be arranged, if feasible.

Follow-up Period (Days 6 to 28): Follow-up visits will occur 4, 9, and 23 days after the last dose of study drug (study Days 9, 14, and 28) for all subjects including those who discontinue treatment early (before completing 5 days of dosing). The end-of-study visit (EOS, Day 28) is a follow-up visit for posttreatment safety assessments and may be conducted as a telephone call.

Early Termination

Subjects who discontinue treatment early (before completing 5 days of dosing) should return to the study site within 24 hours after the last dose of study drug for an EOT visit. Subjects should then return to the site 4 and 9 days after discontinuation of study drug for post-treatment follow-up Visits 1 and 2 (PT1, PT2). A follow-up visit for post-treatment safety assessments

also needs to be scheduled (23 days after study drug discontinuation) and may be conducted as a telephone call.

Subjects who discontinue the study early (before Day 28) should return to the study site within 24 hours if possible and no more than 48 hours later to complete the EOS procedures.

Addition or Replacement of Subjects

If the objectives of the study are not met (due to subject dropout, lack of sufficient data points, or other reason) or based on recommendation from the SSC, additional subjects may be enrolled. Subjects who withdraw from the study before receiving the first dose of study drug may be replaced. Subjects who withdraw from the study after receiving the first dose of study drug will not be replaced, except as recommended by the SSC.

Eligibility Criteria
Inclusion Criteria

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

1. Male or female who is either ≥6 months to ≤36 months (for Age Group 1) or ≥28 days to <6 months (for Age Group 2), defined at the time of randomization. Subjects in Age Group 2 must have been born ≥29 weeks of gestation to be eligible. If a subject was born <29 weeks of gestation, the subject can only be enrolled in Age Group 1;
2. Subjects diagnosed with RSV infection using an approved diagnostic assay, without known and/or documented coinfection with SARS-CoV-2. If RSV infection is not confirmed, caregivers may be asked to sign a RSV Diagnostic Test ICF allowing a rapid antigen RSV test to be performed;
3. Subjects with signs of an acute respiratory illness (e.g., fever [or symptoms of fever], cough, nasal congestion, runny nose, rapid breathing, shortness of breath, or wheezing) with onset ≤7 days for Part 1 and ≤5 days for Part 2 before the time of signing the ICF; Note: Time of onset of signs is defined as the caregiver(s) estimated time of awareness of the first sign of respiratory infection or worsening from the subject's pre-existing respiratory signs.
4. Have a calculated creatinine clearance rate not below the lower limit of normal (LLN) for the subject's age as determined by the Schwartz equation (Schwartz & Work, 2009) at Screening;
5. In the Investigator's opinion, the subject's caregiver understands and is able to comply with protocol requirements, instructions, and protocol-stated restrictions, and the subject is likely to complete the study as planned.

Additional inclusion criterion for Part 1 Cohort 1, Age Group 2

6. Subject is currently or is planned to be hospitalized as a consequence of RSV infection and is not anticipated to be discharged in less than 24 hours after enrollment.

Exclusion Criteria

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

1. Use of, or anticipated need for, invasive mechanical ventilation, cardiopulmonary bypass, hemodialysis, or extracorporeal membrane oxygenation; or subjects who are not expected to survive the current illness;
2. Subjects who have a medical history or a concurrent illness that in the opinion of the Investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject, or that could prevent, limit, or confound the protocol-specified assessments. Examples include liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic conditions;
3. Subjects who are considered unable to take study drug orally. [redacted]
4. Subjects who have received blood products within 6 months of study drug administration;
5. Subjects with underlying immune deficiency (e.g., from confirmed human immunodeficiency virus infection or use of an immunosuppressive medication except immunoglobulin A deficiency);
6. Subjects who received (within 12 months before Screening) or who are currently on a waiting list for a bone marrow, stem cell, or solid organ transplant, or who received radiation or chemotherapy (within 12 months before screening);
7. Subjects who have had major surgery in the 6 weeks before randomization;
8. Subject receiving chronic oxygen therapy at home before admission;
9. Subjects who are being breastfed by a mother taking any of the excluded medications as noted in Section 5.9 (Prohibited Medications);
10. Subjects whose mother received an RSV vaccination while pregnant with the subject if they were born at term (>37 weeks of gestation) and are less than 12 months of age;
11. Receipt of systemic antiviral, antifungal, or antimycobacterial therapy within 7 days of Screening;
12. Subjects who received systemic medications other than corticosteroids (either chronically [more than 14 days] or within 21 days before randomization) that are known to modulate the host's immune response or increase viral shedding, such as immunomodulatory therapies.
13. In Part 2, subjects dosed with an investigational or approved medication that is intended to prevent or treat RSV infection within the following times before the first dose of study drug:
    - ribavirin: 35 days,
    - palivizumab: 100 days,
    - nirsevimab: 350 days,
    - other RSV-specific monoclonal antibody: 5 half-lives of the specific antibody,
    - RSV vaccines: 12 months.

14. [redacted]
15. Subjects who are enrolled in another investigational drug or vaccine study;
16. Known allergy/hypersensitivity or intolerance to EDP-938, placebo, or their excipients.

Statistical Methods

Detailed statistical analysis will be outlined in the statistical analysis plan, which will be developed and finalized before database lock. Parts 1 and 2 will be summarized separately unless stated otherwise.

Safety population: All subjects who receive any dose (including partial doses) of any study drug;

PK population: All subjects who receive one full dose of study drug and have blood samples with quantifiable plasma levels to allow estimation of PK parameters;

Efficacy population: All subjects who receive one full dose of study drug and have at least one evaluable measurement while on treatment.

[redacted]

Safety Analyses

Statistical methods for safety analyses will be descriptive statistics. Safety data, including AEs, vital sign measurements, concomitant medications, and laboratory values, will be summarized separately by treatment and age group. Parts 1 and 2 may be pooled for AEs and laboratory analyses where appropriate. Change from Baseline will be included in summary tables for vital sign measurements and laboratory parameters. Safety analyses will be summarized using the safety population.

Pharmacokinetic Analyses

Plasma concentration of EDP-938 will be used to estimate the PK parameters of EDP-938 using a population PK model, as allowed by the data. Plasma metabolites concentrations will be summarized. Subjects may be excluded from the PK analysis if their data do not allow for accurate assessment of the PK parameters.

At the end of the study (Parts 1 and 2), PK data obtained from all groups will be pooled for a population PK analysis, as allowed by the data. These results will be reported separately.

Efficacy Analyses

All efficacy analyses will be descriptive statistics. Efficacy analyses will be summarized using the efficacy population.

Antiviral activity will be assessed by RSV RNA viral load RT-qPCR and infectious viral culture performed on nasal swab samples obtained throughout the study. Daily change in RSV shedding in nasal swab samples from baseline through the treatment phase will be summarized. AUC for RSV RNA viral load will be summarized.

[redacted]

1. INTRODUCTION

1.1. Overview

EDP-938 (also known as [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 2 study, EDP 938-201, is a randomized double-blind, placebo-controlled, 2-part study to evaluate the safety, tolerability, pharmacokinetics (PK), clinical outcome, and antiviral activity of orally administered EDP-938 regimens in hospitalized or non-hospitalized infants and children aged 28 days to 36 months infected with RSV.

1.2. Background

Respiratory syncytial virus is the leading cause of lower respiratory tract infection and presents a significant health challenge in small children (Falsey, 2005; Hall et al., 2009; Shook & 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. 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. In 2015, overall RSV-ALRI mortality may have been 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). To address the unmet medical need for a safe and effective RSV therapy, and based on the promising early nonclinical data and favorable clinical data from an adult healthy subject RSV challenge study, this study is being conducted to investigate EDP-938 in infants and children (aged 28 days to 36 months) as a potential treatment for RSV infection.

1.3. Nonclinical Studies

1.3.1. Pharmacology

[redacted] It is highly specific for RSV with no cross-activity against other RNA or DNA viruses and no significant cytotoxicity. [redacted]

[redacted]

Details of all nonclinical studies can be found in the Investigator's Brochure.

1.3.2. Juvenile Toxicity Study

[redacted]

1.4. Clinical Studies

[redacted]

[redacted]

Study EDP 938-101 evaluated the antiviral activity, PK, and safety of EDP-938 in healthy adult subjects inoculated with RSV-A Memphis 37b. The primary objective of this two-part study was to evaluate the antiviral activity of EDP-938 compared with placebo in healthy adult subjects inoculated with RSV-A Memphis 37b.

In Part 1 of Study EDP 938-101, 115 subjects were randomized to 1 of 3 treatment groups for 5 days of oral suspension dosing as follows: EDP-938 (500 mg loading dose [LD] followed by 300 mg BID every 12 hours for a total of 10 doses, n = 38); EDP-938 (600 mg QD followed by a placebo dosed at 12 hour intervals, for a total of 10 doses, n = 39); placebo (n = 38) every 12 hours. In Part 2 of Study EDP 938-101, 63 subjects were randomized into 1 of 3 treatment groups for 5 days of EDP-938 oral suspension with doses being informed by Part 1 data and dosing as follows: EDP-938 (400 mg LD followed by 200 mg BID for a total of 10 doses (n = 21), EDP-938 600 mg LD followed by 300 mg once a day followed by a placebo dosed at 12 hours interval, for a total of 10 doses (n = 21), placebo every 12 hours (n = 21).

In both Parts 1 and 2, all EDP-938 regimens yielded highly significantly lower RSV viral load AUCs than their placebo group ($p<0.001$) and robustly lowered 10-point RSV total symptom score AUCs compared to placebo. Results for active treatment groups were similar, with no indication that one regimen was better than the other in either Part 1 or Part 2.

Following administration, EDP-938 was rapidly absorbed with systemic EDP-938 exposures that were generally comparable to those observed in the first-in-human study at similar doses, and a half-life that supports QD or BID dosing. Following multiple dose administration, the geometric mean C_{24} ranged from approximately 14.5- to 40-fold higher than the in vitro EC_{90} for RSV M37 (20 ng/mL). There was no correlation between efficacy endpoints (viral load AUC and total symptom score) and exposure to EDP-938 (AUC).

All dose regimens were well tolerated. AEs were infrequent, generally mild, and all resolved. There were no serious or severe AEs and no AEs that led to discontinuation of study drug. In Part 1, headache, dizziness, and diarrhea were more common in 1 or both EDP-938 arms than in the placebo arm. In Part 2, nausea, dizziness, and upper respiratory tract infection were more common in 1 of the EDP-938 arms than in the placebo arm. In Part 1, all AEs in EDP-938 recipients were mild except for a single event of dyspepsia that was considered moderate. In Part 2, all AEs in EDP-938 recipients were mild except for a single event of moderate vessel puncture site paraesthesia. Results for physical examinations, ECGs, spirometry, and laboratory tests, including liver function tests and cardiac enzymes, showed no pattern of changes, and any changes observed were generally discrete and were broadly comparable among EDP-938 and placebo treatment groups.

In this Phase 2a study of healthy adults inoculated with RSV, all 4 EDP-938 regimens were well tolerated and demonstrated robust reductions in both RSV RNA viral load levels and total symptom scores as compared to placebo, with favorable PK profiles and safety profiles that were comparable to placebo.

Study EDP 938-102 was a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study of EDP-938 administered orally for the treatment of acute upper respiratory tract infection due to RSV in ambulatory adult subjects.

Eighty-one subjects were randomized and received EDP-938 or matching placebo. In both treatment groups, 11 subjects had TEAEs. Most of the TEAEs were mild and not related to study drug. There were no deaths, other SAEs, or study discontinuations due to AEs. The safety profile was consistent with previous clinical studies in healthy subjects. EDP-938 exposures were consistent with those observed in subjects treated with EDP-938 in previous studies. The primary endpoint, total symptom score AUC from Day 1 through Day 14, was not met. The mean total symptom score AUC (days × score) was not statistically different between the 2 groups ($p=0.246$). Although the secondary antiviral endpoints were not met, a trend in favor of EDP-938 treatment group was observed with regard to the percentage of subjects achieving undetectable RSV RNA, with a statistically significant difference in favor of EDP-938 observed at the end of treatment at Day 5 ($p=0.033$).

1.5. Potential Risks and Benefits

EDP-938 is highly specific for RSV. [redacted] (see Section 1.3.2 for details about this study).

In clinical studies, EDP-938 has been safe and generally well tolerated, with AEs being infrequent, generally mild, and resolving in follow-up. [redacted]

The safety profile of EDP-938 continues to evolve through ongoing clinical studies and consequently not all risks associated with EDP-938 exposure are known. Based on data from the approximately [redacted] adults exposed to EDP-938 to date, no single safety event or pattern of events has been consistently identified to be associated with EDP-938 exposure and such reported AEs have been generally mild and occurring at a rate similar to placebo.

No serious adverse reactions are considered expected by the Sponsor for expedited reporting and identification of suspected unexpected serious adverse reactions in the Development Safety Update Report for EDP-938.

[redacted]

With regard to potential risks associated with trial participation, pediatric subjects enrolled to this study will undergo procedures including phlebotomy, ECG testing, and respiratory secretion sampling, (e.g., nasal swabs, that may cause discomfort to a child). Efforts have been made throughout the study to limit these procedures and, where possible, alternatives have been provided when such testing cannot readily be performed, such as heel sticks or finger sticks, and limited lead ECG testing. There is a requirement for repeated blood sampling throughout the study to monitor safety and PK. Efforts have been made to limit blood sample volumes as much as possible, e.g., screening may include assessment of recent laboratory tests, limiting blood draw frequencies and volumes and the provision of alternatives blood sampling methods as noted above.

[redacted]

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

- A Study Steering Committee (SSC) blinded to treatment assignment will ensure the continuing safety of subjects enrolled to the study through scheduled and as needed evaluations of data to inform dose selections and to review events that meet stopping rule criteria. See Section 4.2.1 for additional information about the SSC.
- An Independent Data Monitoring Committee (IDMC) unblinded to treatment assignment will ensure the safety of subjects enrolled to the study through reviews of safety data. See Section 4.2.2 for additional information about the IDMC.
- [redacted]

This is the first study that will evaluate the safety, PK, and efficacy of EDP-938 in pediatric patients with RSV, and consequently, the efficacy and safety of EDP-938 in pediatric patients are not known. Because EDP-938 has previously demonstrated clinical efficacy in the adult healthy volunteer RSV challenge study, pediatric subjects enrolled to this trial may also experience a rapid clearance of RSV infection and a reduction in the symptoms associated with RSV infection compared to those who do not receive EDP-938. However, it is possible that no such effect will be observed. Additionally, since this is a placebo-controlled trial, pediatric subjects enrolled to the placebo arm will not be expected to derive any such benefit. Consequently, subjects enrolled to the trial may experience no benefit with regard to impacting the rate of clearance of RSV or resolution of symptoms associated with RSV infection.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary efficacy objective is to evaluate the antiviral activity of EDP-938 in the pooled population (subjects from Part 1 and Part 2 together).

2.1.1. Part 1: Primary and Secondary Objectives

Primary Objectives

- To evaluate the PK of EDP-938;
- To assess the safety and tolerability of EDP-938.

Secondary Objective

- To evaluate the antiviral activity of EDP-938.

2.1.2. Part 2 and Pooled Population: Primary and Secondary Objectives

Primary Objective

- To evaluate the antiviral activity of EDP-938.

Secondary Objectives

- To assess the safety and tolerability of EDP-938;
- To evaluate the PK of EDP-938.
- To evaluate additional antiviral activity measures of EDP-938.
- To evaluate clinical outcomes of EDP-938.

2.1.3. [redacted]

- [redacted]

2.2. Endpoints

The primary efficacy endpoint is the daily change in RSV shedding in nasal swab samples determined using RT-qPCR from Baseline through the treatment phase in the pooled population (subjects from Part 1 and Part 2 together).

2.2.1. Part 1: Primary and Secondary Endpoints

Primary Endpoints

- PK parameters of EDP-938 including AUC and predose concentrations;
- Safety and tolerability of EDP-938 compared to placebo as assessed by, but not limited to, AEs, vital signs, and clinical laboratory results.

Secondary Endpoints

- AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR);
- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from Baseline through the treatment phase;
- Proportion of subjects with RSV RNA viral load below the limit of detection (LOD) in subjects receiving EDP-938 compared to placebo;
- Time to RSV RNA viral load being undetectable.

2.2.2. Part 2 and Pooled Population: Primary and Secondary Endpoints

Primary Endpoint

Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from baseline through the treatment phase.

Secondary Endpoints

- Safety and tolerability of EDP-938 compared to placebo as assessed by, but not limited to, AEs, vital signs, and clinical laboratory results;
- AUC for RSV RNA viral load measured in nasal swab samples by RT-qPCR;
- Proportion of subjects with RSV RNA viral load below the LOD in subjects receiving EDP-938 compared to placebo;
- Time to RSV RNA viral load being undetectable;
- PK parameters of EDP-938 including AUC and predose concentrations;
- Time to discharge for hospitalized subjects;
- Time to use of oxygen for hospitalized subjects who are not receiving oxygen at the time they receive the first dose of study drug;

- Proportion of hospitalized subjects requiring oxygen supplementation or have an increased oxygen requirement;
- Time to mechanical ventilation for hospitalized subjects;
- Proportion of hospitalized subjects requiring mechanical ventilation;
- Deaths among hospitalized subjects;
- Time to hospitalization for initial outpatients who are subsequently hospitalized;
- Proportion of outpatients who are subsequently hospitalized or died;
- Time to resolution of symptoms for outpatients who are not hospitalized.

2.2.3. [redacted]

3. SELECTION OF SUBJECTS

3.1. Subject Inclusion Criteria

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

1. Male or female who is either ≥6 months to ≤36 months (for Age Group 1) or ≥28 days to <6 months (for Age Group 2), defined at the time of randomization. Subjects in Age Group 2 must have been born ≥29 weeks of gestation to be eligible. If a subject was born <29 weeks of gestation, the subject can only be enrolled in Age Group 1;
2. Subjects diagnosed with RSV infection using an approved diagnostic assay, without known and/or documented coinfection with SARS-CoV-2. If RSV infection is not confirmed, caregivers may be asked to sign a RSV Diagnostic Test ICF allowing a rapid antigen RSV test to be performed;
3. Subjects with signs of an acute respiratory illness (e.g., fever [or symptoms of fever], cough, nasal congestion, runny nose, rapid breathing, shortness of breath, or wheezing) with onset ≤7 days for Part 1 and ≤5 days for Part 2 before the time of signing the informed consent form (ICF);

   Note: Time of onset of signs is defined as the caregiver(s) estimated time of awareness of the first sign of respiratory infection or worsening from the subject's pre-existing respiratory signs.
4. Have a calculated creatinine clearance rate not below the lower limit of normal (LLN) for the subject's age as determined by the Schwartz equation (Schwartz & Work, 2009) at Screening;
5. In the Investigator's opinion, the subject's caregiver understands and is able to comply with protocol requirements, instructions, and protocol-stated restrictions, and the subject is likely to complete the study as planned.

Additional inclusion criterion for Part 1 Cohort 1, Age Group 2

6. Subject is currently or is planned to be hospitalized as a consequence of RSV infection and is not anticipated to be discharged in less than 24 hours after enrollment.

3.2. Subject Exclusion Criteria

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

1. Use of, or anticipated need for, invasive mechanical ventilation, cardiopulmonary bypass, hemodialysis, or extracorporeal membrane oxygenation; or subjects who are not expected to survive the current illness;
2. Subjects who have a medical history or a concurrent illness that in the opinion of the Investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject, or that could prevent, limit, or confound the protocol-specified assessments. Examples include liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic conditions;

3. Subjects who are considered unable to take study drug orally, [redacted]
4. Subjects who have received blood products within 6 months of study drug administration;
5. Subjects with underlying immune deficiency (e.g., from confirmed human immunodeficiency virus infection or use of an immunosuppressive medication except immunoglobulin A deficiency);
6. Subjects who received (within 12 months before Screening) or who are currently on a waiting list for a bone marrow, stem cell, or solid organ transplant, or who received radiation or chemotherapy (within 12 months before screening);
7. Subjects who have had major surgery in the 6 weeks before randomization;
8. Subject receiving chronic oxygen therapy at home before admission;
9. Subjects who are being breastfed by a mother taking any of the excluded medications as noted in Section 5.9 (Prohibited Medication);
10. Subjects whose mother received an RSV vaccination while pregnant with the subject if they were born at term (≥37 weeks of gestation) and are less than 12 months of age;
11. Receipt of systemic antiviral, antifungal, or antimycobacterial therapy within 7 days of Screening;
12. Subjects who received systemic medications other than corticosteroids (either chronically [more than 14 days] or within 21 days before randomization) that are known to modulate the host's immune response or increase viral shedding, such as immunomodulatory therapies;
13. In Part 2, subjects dosed with an investigational or approved medication that is intended to prevent or treat RSV infection within the following times before the first dose of study drug:
    - ribavirin: 35 days,
    - palivizumab: 100 days,
    - nirsevimab: 350 days,
    - other RSV-specific monoclonal antibody: 5 half-lives of the specific antibody,
    - RSV vaccines: 12 months.
14. [redacted]
15. Subjects who are enrolled in another investigational drug or vaccine study;
16. Known allergy/hypersensitivity or intolerance to EDP-938, placebo, or their excipients.

4. STUDY DESIGN

This is a Phase 2, dose-ranging, randomized, double-blind, placebo-controlled, 2-part study to evaluate the safety, tolerability, PK, clinical outcome, and antiviral activity of orally administered EDP-938 regimens in infants and children aged 28 days to 36 months with RSV--associated respiratory tract infection, who are hospitalized or non-hospitalized.

Each part of the study has 3 periods: Screening, Treatment, and Follow-up. For each subject, the duration of study will be approximately 29 days (Table 1). Study site visits and assessments are detailed in the Schedule of Assessments (SoA; Appendix 1).

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

Table 1: Durations of Study Periods

Study Period	Duration
Screening (Day-1 to D1)	Up to 24 hours (note: some assessments done as part of standard of care can be used as screening assessments if they are done within 72 hours)
Treatment (Day 1 to Day 5)	5 days
Follow-up (Day 6 to Day 28)	23 days
Approximate total duration of participation	29 days maximum

4.1. Dose and Treatment Schedule

Approximately 90 subjects are planned to be enrolled. Oral doses of EDP-938 or placebo, [redacted] will be administered QD. Initial doses are planned to be 5 mg/kg in each age group:

- Group 1 (Ages ≥6 to ≤36 months);
- Group 2 (Ages ≥28 days to <6 months);

Varying age-appropriate volumes of a fixed concentration ([redacted]) of EDP-938 or placebo will be administered to achieve the intended dose in each pediatric patient.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized 2:1 (Part 1) or 4:1 (Part 2) to EDP-938:placebo.

The study design is shown in Figure 1.

Part 1

Enrollment will begin simultaneously with Cohort 1 Age Group 1 and Cohort 1 Age Group 2. When at least 9 subjects have been randomized in Cohort 1, for each age group, the SSC will review available blinded data, including at least safety and PK data, and will determine dosing for Part 1 Cohort 2 for each age group. The SSC will meet as required to review emerging safety and PK data to support dose decision and initiation of Cohort 2. Enrollment in Cohort 1 age groups will continue until 12 subjects have been enrolled.

Cohort 1 Age Group 1 will include subjects who may be hospitalized or non-hospitalized at enrollment. Cohort 1 Age Group 2 will include subjects who are hospitalized at enrollment.

Cohort 2 for both age groups will include subjects who may be hospitalized or non-hospitalized at enrollment.

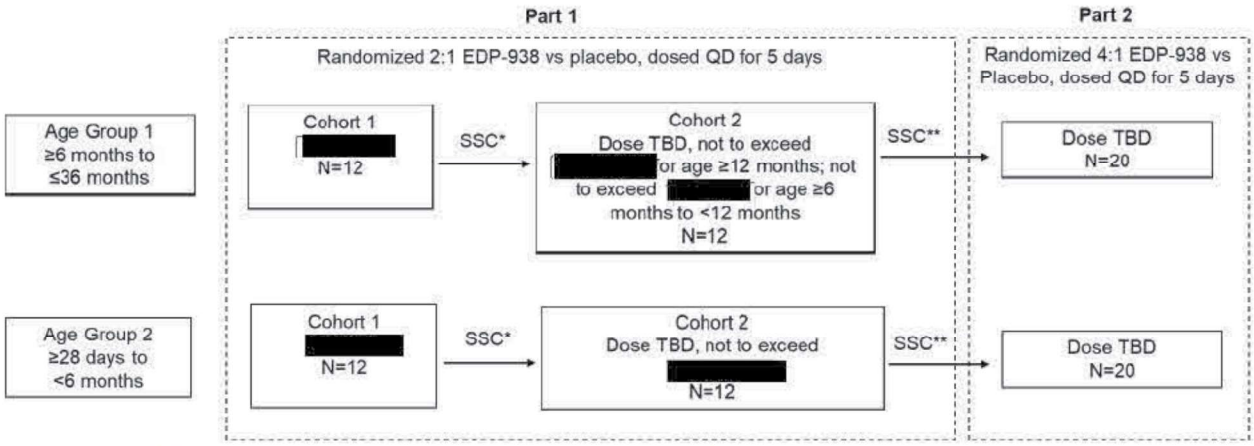
Additional Part 1 cohorts may be added, as deemed necessary by the SSC.

Part 2

Both age groups will include subjects who may be hospitalized or non-hospitalized at enrollment. The start of dosing for each age group will be contingent upon at least 6 subjects in that age group being exposed to EDP-938 in Part 1 Cohort 2 and will be based on SSC recommendations. After completion of dosing in the Part 2 cohort, the SSC will review available blinded data, including at least safety and PK data, in that age group. Twenty subjects are planned for each age group, but additional subjects may be enrolled based on SSC recommendations to allow a sufficient number of subjects to determine doses for both age ranges.

Additional Part 2 cohorts may be added, as deemed necessary by the SSC.

Figure 1: Study Design



QD = once daily; SSC = study steering committee; TBD = to be determined.

The SSC will review data from each cohort and will determine dose selection and cohort progression in Part 1 and Part 2.

**SSC will review available blinded data when at least 9 subjects have been randomized in Cohort 1 for each age group.*

*** SSC will review available blinded data when at least 6 subjects have been exposed to EDP-938 in Cohort 2 for each age group.*

4.2. Study Monitoring Committees

4.2.1. Study Steering Committee

An SSC blinded to treatment assignment will ensure the continuing safety of subjects enrolled to the study through scheduled and as needed evaluations of data to inform dose selections and to review events that meet stopping rule criteria. The SSC will have access to available blinded data, including at least safety and PK data. As described in Section 4.1, the SSC will review data from each cohort and will determine dose selection and cohort progression in Part 1 and Part 2. The SSC will include the Enanta Medical Monitor, an Enanta clinical pharmacology

representative, a biostatistician, a pediatrician with expertise in respiratory infections and who is independent of the study conduct, and the Contract Research Organization's Medical Monitor.

The SSC will not allow progression to the next cohort/part if there are two or more of the same study drug-related Grade 3 adverse events, one or more study drug-related Grade 4 adverse events, or one or more study drug-related serious adverse events. In order to proceed to the next cohort under these circumstances, the IDMC would be required to review the relevant data and agree with proceeding.

4.2.2. Independent Data Monitoring Committee

In addition to the SSC responsible for dose escalation decisions based on blinded safety and PK data, to ensure that the safety of the subjects is thoroughly monitored, an IDMC will review unblinded safety data. At a minimum, the IDMC will review data for each age group from Part 1 and subsequently from Part 2. Ad hoc meetings of the IDMC can be scheduled whenever deemed necessary. The IDMC will include 2 clinicians and a statistician who are independent of study conduct, Enanta, and the Contract Research Organization. Further information about the IDMC will be provided in the IDMC Charter.

4.3. Alterations to Planned Doses and Cohort Progression Guidelines

The SSC may recommend modifications, such as if:

- More subjects should be evaluated in any cohort to more fully characterize the safety and PK profile of EDP-938;
- For each age group, enrollment into the Part 1 Cohort 2 can proceed at the proposed dose;
- For each age group, enrollment into the Part 2 Cohort can proceed at the proposed dose.

Additional cohort(s) may be enrolled based on recommendations from the SSC review of available blinded data to potentially evaluate different doses, dosing regimens, or additional subjects at the same dose.

Once the SSC has reviewed the PK and safety data of the highest dose within each age group that will be used in Part 1, it may recommend that the protocol eligibility in Part 2 be expanded to include subjects with concurrent illness.

A PK analysis will be conducted to support the dose for the next dose cohort in that same age group and dose selection will be guided by the totality of the safety, tolerability, and PK data. The SSC will make recommendations to determine which cohorts to initiate and which dose levels to administer.

4.4. Rationale for Study Design

This is the first study investigating the use of EDP-938 in pediatric patients. Based on current RSV guidance documents, the pathophysiology of RSV disease is believed to be different between adults and pediatric patients. Therefore, methods of efficacy extrapolation from adults to pediatric patients may not be appropriate. Thus, the goal of this first EDP-938 pediatric clinical trial is to evaluate the safety, tolerability, PK, clinical outcomes, and antiviral activity of

EDP-938 in pediatric patients ≥28 days to ≤36 months of age who are infected with RSV and who may be hospitalized or non-hospitalized. This study is designed to support dose selection within each age group/cohort and to provide data to support dose selection for future pediatric clinical trials.

4.4.1. 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 in children or adults. Currently, only 2 drugs are approved for treatment or prevention of RSV lower respiratory tract infection in pediatric patients: aerosolized ribavirin (a nucleoside analog) for treatment and palivizumab (a monoclonal antibody that targets the RSV fusion protein) for the prevention of serious lower respiratory tract disease caused by RSV in high risk children. However, analyses performed subsequent to the approval of aerosolized ribavirin suggest that it failed to impart any clinically significant benefits (Randolph & Wang, 1996), and currently it is not recommended for routine treatment of RSV (Piedimonte & Perez, 2014). There are also concerns about the toxicity, teratogenicity, and high cost of inhaled ribavirin (Chemaly, Aitken, Wolfe, Jain, & Boeckh, 2016). Current management of RSV bronchiolitis remains mostly supportive care such as oxygen for hypoxemia and intravenous fluids for dehydration. Consequently, clinicians have no safe and highly effective treatment for RSV infection, which is an issue of significant concern for those providing medical care for pediatric patients at risk of severe RSV disease.

This Phase 2 study aims to evaluate the safety, tolerability, PK, and antiviral activity of EDP-938 administered orally in pediatric patients ≥28 days to ≤36 months of age who are infected with RSV. The design of the study (randomized, double-blind, placebo-controlled, dose-ranging) is consistent with recent RSV guidance from regulatory agencies (EMA; FDA).

While this initial Phase 2 trial should identify the optimal dose and treatment duration of EDP-938 with regard to PK, safety, and antiviral activity in children aged 28 days to 36 months, we will also be exploring the use of instruments for RSV signs and symptoms that may be relevant to a later stage of EDP-938 development in the pediatric population.

The study will be conducted in 2 parts. In Part 1, the primary endpoints will be safety, tolerability, and PK. In Part 2, the primary endpoint will be antiviral activity. In Part 1, subjects will be randomized 2:1 to EDP-938:placebo. The SSC will make recommendations to determine dose selection and cohort progression in Part 1 and Part 2.

Safety data on EDP-938 available to date supports the enrollment of both age groups, 6 months to 36 months and 28 days to less than 6 months. At least 2 dosing cohorts will be evaluated in Part 1. Part 1 Cohort 1 of both age groups will evaluate an initially selected dose of [redacted], which is anticipated to yield exposures that are safe and efficacious. As these exposures are predicted based on modeling and simulation using adult data (Section 4.4.2 for dose rationale), dose adjustments based on pediatric data may be needed. Therefore, a higher or lower dose will be explored in Cohort 2. If adequate exposures are achieved in Cohort 1 with no safety concerns, a higher dose that is not expected to exceed safe exposures in nonclinical studies and clinical studies may still be explored in Cohort 2 to evaluate the safety and PK of EDP-938 across a dose range. Additional cohorts in Part 1 may be added, as needed. Following completion of Part 1 for a specific age group and based on SSC review, enrollment in Part 2 for that same age group may begin.

In Part 2, subjects will be randomized 4:1 to EDP-938:placebo. Part 2 doses will be selected based on review of Part 1 data and will enable better characterization of the clinical efficacy of EDP-938. The key antiviral activity assessment will be the daily change in RSV shedding in nasal swab samples determined using RT-qPCR from Baseline through the treatment phase. The AUC for RSV RNA viral load quantitation by nasal swab while on treatment and during the follow-up visits (up to Day 14) will be assessed in this study. The use of RSV RNA viral load AUC as the assessment of antiviral activity has been previously employed in this setting, including the EDP 938-101 adult human challenge study (Section 1.4).

The eligible population comprises hospitalized or non-hospitalized individuals, who have an RSV infection. The requirement for hospitalization of subjects in Part 1 Cohort 1 Age Group 2 allows for dosing of EDP-938 to occur in a monitored and supervised environment for regular PK, clinical, and laboratory safety assessments.

At this stage of development, pediatric subjects with significant comorbidities are excluded. Similarly, the study also excludes those who are not considered to be medically stable or requiring urgent or emergency medical care. Also excluded are those with known liver, kidney, heart and/or neurologic disease.

Because the window for optimal intervention for RSV infection may be relatively short, the symptom window and screening process are optimized to allow for rapid identification of children with RSV and who are otherwise appropriate for the study, so that EDP-938 or placebo can be initiated at the earliest possible timepoint. In a published Phase 1b study, treatment with a RSV fusion inhibitor was able to demonstrate an antiviral effect trend on pediatric patients infected with RSV with a median symptom duration of approximately 5 to 7 days prior to administration of the first dose of treatment (Martinón-Torres et al., 2020). In addition, studies have shown that RSV viral replication in infants can persist above a detection threshold for more than 30 days from the onset of symptoms (Brint et al., 2017) and symptoms, such as cough, can persist for more than 14 days from the initial onset (Toback et al., 2015). Although RSV infections may persist for several weeks, the symptom window will need to balance the need for early therapeutic intervention for optimal efficacy and also take into consideration changes to the clinical management of children with RSV due to the COVID-19 pandemic. Children with RSV infections are cared for a longer time period at home and the disease severity threshold for hospitalization has increased in order to mitigate the risk of contracting or spreading COVID-19 (Ujiie, Tsuzuki, Nakamoto, & Iwamoto, 2021). Thus, the study design requires that subjects be enrolled within 7 days (Part 1) or 5 days (Part 2) of the onset of symptoms, and Screening should be completed as soon as possible to ensure that subjects will be randomized and administered the first dose of study drug within 24 hours of signing the ICF. This design is considered appropriate to support optimal efficacy assessments.

A dosing duration of 5 days was selected because EDP-938 was demonstrated to be generally safe and efficacious in Study EDP 938-101, in which healthy adult subjects, inoculated with RSV, received EDP-938 either QD or BID for up to 5 days. [redacted]

The double-blind design using a matched placebo for EDP-938 allows for the most unbiased assessment of the clinical safety and antiviral activity of, and clinical outcome to EDP-938.

Subject safety is also assured through regularly scheduled assessments of AEs and safety laboratory tests.

4.4.2. Justification of EDP-938 Dose

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

[redacted]

As summarized in Section 1.4, Study EDP 938-101 was a Phase 2a study that aimed to evaluate the safety, PK, and antiviral activity of multiple doses of orally administered EDP-938 against RSV infection in the healthy subject virus challenge model. The study had 2 parts. Part 1 tested doses of 600 mg QD and an LD of 500 mg followed by 300 mg BID, and Part 2 tested doses of 400 mg LD followed by 200 mg BID, and 600 mg LD followed by 300 mg QD. The treatment duration was 5 days. All 4 treatment arms were superior to placebo with regard to reductions in viral load (by RNA quantitation [primary endpoint]) and total symptoms scores (total symptom score [secondary endpoint]).

In Study EDP 938-101, EDP-938 was rapidly absorbed, and had a half-life that supports QD or BID dosing. Based on predose concentrations, steady state appeared to be reached after approximately 2 doses of EDP-938. Following 5 days of dosing, the geometric mean plasma C_{24} was approximately 14.5- and 25-fold higher than the in vitro EC_{90} of RSV M37 for the 300 mg QD group and the 600 mg QD group, respectively. Similarly, the geometric mean plasma C_{12} was approximately 25- and 40-fold higher than the in vitro EC_{90} of RSV M37 for the 400 mg LD/200 mg BID group and the 500 mg LD/300 mg BID group, respectively. There was no correlation between efficacy endpoints (viral load AUC and total symptom score) and exposure to EDP-938 (AUC).

All 4 dose regimens of EDP-938 were well tolerated. There were no SAEs or severe TEAEs and no TEAEs lead to withdrawal from the study or to discontinuation of study drug. TEAEs were also generally mild, with events of moderate intensity being very infrequent among EDP-938 recipients. There were no clinically significant laboratory abnormalities or ECG findings.

Data from [redacted] and EDP 938-101 (Part 1) were used to develop an integrated model that characterizes the population PK of EDP-938, and the effect of treatment on RSV viral kinetics, and clinical symptom scores. [redacted]

[redacted]

As mentioned above, in adults (Study EDP 938-101), doses of 600 mg QD, LD of 500 mg followed by 300 mg BID, 400 mg LD followed by 200 mg BID, and 600 mg LD followed by 300 mg QD, all administered for 5 days, were generally well-tolerated with safety profiles that were similar to placebo, and achieved comparable efficacy in terms of reductions in RSV viral load and symptom scores and were all superior compared to placebo.

Therefore, to aid in pediatric dose selection, projected pediatric exposures were compared to those of adult subjects receiving EDP-938 for 5 days at doses of [redacted] QD (to establish a minimally effective dose) and [redacted] QD (to establish a safety threshold). The 5th percentile of the minimum concentration at trough (C_{24}) on Day 1 in adults at [redacted] QD ([redacted]) was defined as the exposure threshold for efficacy; the corresponding 95th percentile of the $AUC_{0\text{-}tau}$ on Day 5 at [redacted] QD ([redacted]) was used as the exposure threshold for safety. The C_{24} threshold ([redacted]) is at least twice the in vitro EC_{90} against RSV-infected human cells and thus achieving this value on Day 1 is expected to be efficacious. The Day 5 $AUC_{0\text{-}tau}$ threshold was used for safety as it represents steady state exposures. The Day 5 peak concentration (C_{max}) was evaluated in a similar manner to $AUC_{0\text{-}tau}$ and did not alter the dose selection below.

The simulations indicate that QD dosing for 5 days at an initial dose of [redacted] across all age groups is expected to provide exposures above the exposure threshold for efficacy ([redacted]), based on the C_{24} on Day 1 following a [redacted] QD dose in adults. For each age group, a maximum dose was also chosen to allow for a dose-ranging study design, provided that the projected Day 5 $AUC_{0\text{-}tau}$ does not exceed [redacted] (based on [redacted] QD dose in adults).

[redacted]

[redacted]

In summary, [redacted] is the initial starting dose across all age groups. In Age Group 1 (≥6 months to ≤36 months), doses will not exceed [redacted] for subjects <12 months, and [redacted] for subjects ≥12 months. In Age Group 2 (≥28 days to <6 months), doses will not exceed [redacted]

The predicted median (5th to 95th percentile) dose-equivalent exposures for C_{24} (Day 1) and AUC_{0-24} (Day 5) for each pediatric age group and for adults are presented in Table 2.

Table 2: [redacted]

5. STUDY DRUG AND TREATMENT OF SUBJECTS

5.1. Description of Study Drug

EDP-938 and placebo will be provided as [redacted] Additional information is provided in the Pharmacy Manual.

The excipients used in the EDP-938 pediatric [redacted] as well as the EDP-938 placebo [redacted] are [redacted]. In addition to the previously mentioned excipients, [redacted] are added to the EDP-938 placebo [redacted].

5.2. Packaging and Labeling

EDP-938 drug product and placebo will be supplied as a pediatric [redacted] in [redacted] EDP-938 or placebo. [redacted]

All 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.

Additional information will be provided in the Pharmacy Manual.

5.3. Storage

EDP-938 and placebo drug product will be stored and shipped in accordance with the EDP 938-201 Pharmacy Manual. Shipments will use an insulated shipper and contain a temperature-monitoring device. Documentation will be maintained at the clinical study site as outlined in the Pharmacy Manual.

[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. Subject's weight should also be recorded in the pharmacy records.

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

5.5. Handling and Disposal

All study drug bottles at the site [redacted] returned by subjects' caregivers as well as those that have not been used 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.

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. Subjects will be randomized to the initial EDP-938 or placebo treatment group as shown below:

Part 1, Cohort 1, Age Group 1 and 2 (randomized 2:1)

- [redacted] of EDP-938 orally QD for 5 days (8 subjects);
- [redacted] placebo orally QD for 5 days (4 subjects).

The dose for Part 1 Cohort 2 for each age group will be determined based on review of Part 1 Cohort 1 data.

Part 2 (randomized 4:1)

EDP-938 orally QD for 5 days: dose to be determined

- Oral EDP-938 QD for 5 days: dose to be determined (16 subjects);
- Oral placebo QD for 5 days: dose to be determined (4 subjects).

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. Subjects who have completed screening assessments and are eligible for participation in the study will be randomized before the first dose of study drug (Day 1).

5.7. Study Drug Dose and Administration

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

Hospitalized Subjects

Following randomization, subjects will be administered EDP-938 or placebo QD orally [redacted] for 5 days at approximately the same time every day (±1 hour) on each of the 4 subsequent days.

If subjects are discharged before Day 5, the subject's caregiver will be instructed to administer EDP-938/placebo to the subjects QD at approximately the same time every day (±1 hour) on each of the remaining dosing days. On Day 3 and Day 5, as applicable, [redacted] tudy visits should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site when possible.

Non-hospitalized Subjects

Following randomization, subjects will be administered the first dose of EDP-938 or placebo orally [redacted] while at the study site on Day 1. After the first dose, the subject's caregivers will be instructed on the administration and the timing of administration (administer EDP-938 or placebo to the subjects QD at approximately the same time [± 1 hour] on Day 2 and Day 4). Study visits should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site when possible. [redacted] f a subject is unable to attend a study site visit, a home visit by study site personnel/home health staff may be arranged, if feasible.

The time and date that each dose was administered on-site should be documented in source documents. For non-hospitalized subjects, the time and date will be documented in source documents based on the caregiver's recall.

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

- No more than 1 dose should be taken on any calendar day; and
- There must be at least 20 hours between doses.

In case of vomiting or regurgitation, the subject should not be redosed. If the subject vomits, regurgitates, or does not completely swallow the study drug, it should be recorded in source documents.

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

5.7.1. Dispensing of Study Drug

Study drug must be prepared and dispensed by a qualified pharmacist or other authorized site staff with appropriate training.

[redacted]

Dispensed study drug will be provided to subjects' caregivers. Subjects' caregivers will receive instructions on study drug storage (see Section 5.3) and dosing (see Section 5.7). [redacted]

5.7.2. Treatment Compliance

For non-hospitalized subjects, the subject's caregiver will be instructed to bring all study drug [redacted] to the site on Day 3, Day 5, or the End-of-Treatment (EOT) visit (for subjects who discontinue study drug). Both accountability and study drug compliance (via syringe counts) will be reviewed at each study site visit as indicated in the SoA (Appendix 1). [redacted] the site staff will ask the subject's caregiver why any doses were missed, including administration of partial doses, if applicable. Repeated noncompliance of study drug dosing for any subject, despite continued educational efforts, should be discussed by the Investigator with [redacted] or the Sponsor's Medical Monitor to consider possible discontinuation of the subject from the study.

5.8. Prior and Concomitant Medication

The subject's caregiver will be instructed on the use of concomitant medications during the study. All subjects enrolled in the study must not be administered prohibited concomitant medications and therapies through the end-of-study. 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).

Prior medications administered to the subjects up to 1 month before the first dose of study drug must be recorded at Screening. Only relevant medications and therapies should be recorded if they were discontinued more than 1 month before signing the ICF. All subjects will receive supportive care according to local institution standards and applicable guidelines.

Concomitant medications and therapies are permitted as indicated for the management of study subjects with the exception of the medications and therapies noted in Section 5.9.

5.9. Prohibited Medications and Therapies

Systemic antiviral, antifungal, and antimycobacterial therapies are prohibited within 7 days of Screening and for the duration of the study.

The following are also prohibited:

- Systemic medications other than corticosteroids (either chronically [more than 14 days] or within 21 days before randomization and for the duration of the study) that are known to modulate the host's immune response or increase viral shedding, such as immunomodulatory therapies. In Part 2 only: Investigational or approved medication that is intended to prevent or treat RSV infection is prohibited within the following times before the first dose of study drug and for the duration of the study:
  - ribavirin: 35 days,
  - palivizumab: 100 days,
  - nirsevimab: 350 days,
  - other RSV specific monoclonal antibody: 5 half-lives of the specific antibody,
  - RSV vaccines: 12 months.

Note: If after enrollment the initiation of ribavirin is considered medically appropriate, please contact the Medical Monitor.

- [redacted]
- Blood products within 6 months of study drug administration and for the duration of the study.

Breastfeeding mothers should also comply with the prohibited medication and therapies list.

6. BLINDING AND UNBLINDING

6.1. Blinding

The study will be double-blinded, meaning that the subjects and their caregivers, 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] for purpose of generating and monitoring the randomization list;
- Unblinded Enanta representatives not associated with the day-to-day conduct of the study;
- 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.

6.2. Unblinding

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

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

For unblinding, if the local [redacted] cannot be reached, sites at all locations should call the following 24/7 global medical coverage hotline: [redacted]. The [redacted] medical email address is [redacted].

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

The [redacted] 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.

6.3. Access to Results for Individual Subjects

During the conduct of the study, Investigators, site personnel, and blinded Contract Research Organization/Sponsor staff will not have access to results for individual subjects that could impact clinician assessments, including results for RSV viral load, confirmatory respiratory pathogen panel testing, biomarkers, and PK.

7. STUDY CONDUCT AND VISIT SCHEDULE

7.1. Study Site Visits

Key aspects of each part of the study (Screening, Treatment Period [Days 1 through 5]), and Follow-up) are summarized below. Assessments are presented in the SoA (Appendix 1).

For study assessments, a subject's hospitalization status (hospitalized or non-hospitalized) will be based on their status on the day of the visit.

Study sites will be responsible for following up with subjects for any missed study site visits. Communication (such as telephone calls, emails, or other electronic communication methods) with parent(s)/subject's caregiver(s) to facilitate compliance with study procedures between outpatient study visits are encouraged. If a subject is unable to attend a study site visit, a home visit by study site personnel/home health staff may be arranged, if feasible.

7.1.1. Screening Period

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

The subject's legal representative (henceforth referred to as "caregiver") must review and sign an institutional review board (IRB) or ethics committee (EC)-approved ICF and provide authorization to use protected health information (see Section 12.1.3) before the subject undergoes any study-specific procedures. By signing the ICF, the caregiver will indicate that he or she understands the purpose of, and procedures required for, the study and is willing for the subject to participate in the study.

Some procedures performed as part of standard of care before Screening may be used in determining study eligibility, such as RSV diagnostic test or safety laboratory tests (as specified in the SoA) if they are performed within 72 hours before the ICF is signed. If any assessment is

anticipated to fall outside of that window, the Investigator should consult with the [redacted] to determine if the subject can proceed. Screening safety laboratory test samples will be sent to the local laboratory for expedited testing.

RSV diagnosis at Screening will be performed using an approved diagnostic assay locally. A nasal swab will be collected.

Subjects who have symptom onset, defined as the estimated onset of the first sign of respiratory infection and which does not exceed 7 days for Part 1 and 5 days for Part 2, before the signing of the ICF by their caregiver and whose swab sample tests positive for RSV will undergo further screening procedures to determine study eligibility.

Subjects will be randomized after all screening activities that allow assessment of inclusion/exclusion criteria have been completed to the satisfaction of the Investigator. Subjects will be randomized 2:1 (Part 1) or 4:1 (Part 2) to EDP-938:placebo.

7.1.2. Treatment Period (Day 1)

All study assessments on Day 1 are detailed in the SoA (Appendix 1).

All subjects (hospitalized and non-hospitalized) should undergo screening assessments, determined whether eligible, and be randomized and dosed within 24 hours of signing consent. If a subject needs to return the next day from Screening to complete Day 1 assessments, vital sign assessments should be repeated predose.

The following assessments must be done between randomization and dosing:

- Parent/Guardian ReSVinet clinical scoring system;
- Parent/Guardian [redacted] clinical scoring system, in a subset of subjects;
- Clinical evaluation (Section 8.9);
- Vital signs.

Subjects will be administered a dose of EDP-938/placebo on-site. Subjects will be monitored at the site for safety assessments over the first 3 hours postdose. Hospitalized subjects will have ongoing monitoring as a component of standard of care. The subjects' caregivers will also receive instruction on the appropriate storage and transport of study drug (see Section 5.3).

On Day 1, one nasal swab sample will be collected.

The subjects' caregiver will receive an electronic data capture handheld device [redacted] to use for the duration of the study. This device will be used to complete the Parent/Guardian ReSVinet clinical scoring system (QD at approximately the same time each day ±2 hours) beginning after randomization, prior to dose. The palatability question should be completed postdose. The subject's caregiver will receive instructions on the proper use and care of the eCOA device, and the device should be brought to each study visit. If a caregiver is unable to use the eDiary, a paper diary may be used.

In a subset of subjects, the subject's caregiver will also complete the [redacted] clinical scoring system on paper after randomization but before the first dose and subsequently twice daily, approximately every 12 hours.

7.1.3. Treatment Period Days 2 to 5

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

Hospitalized Subjects

Subjects will receive EDP-938 or placebo QD at approximately the same time every day (±1 hour) on each of the 4 subsequent days after dosing on Day 1. Hospitalization duration will not be extended solely for study purposes. At discharge, the subject's caregiver will be instructed to administer EDP-938 or placebo QD at approximately the same time every day (±1 hour) on each of the remaining dosing days. After discharge, subsequent assessments will follow the schedule for non-hospitalized subjects.

Hospitalized subjects who are discharged before Day 3 should return to the study site for Day 3 and Day 5 visits. Subjects who are discharged on or after Day 3 (but before Day 5), should return to the study site for the Day 5 visit.

Non-hospitalized Subjects

Subjects' caregiver(s) will be instructed to administer EDP-938 or placebo to subjects QD at approximately the same time every day (±1 hour) on Day 2 and Day 4. On Day 3 and Day 5 (EOT), subjects should be dosed at the clinic. It is recommended that the study visits on Day 3 and Day 5 be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site, when possible. If a subject is unable to attend a study site visit, a home visit by study site personnel may be arranged, if feasible.

7.1.4. Follow-up Period (Days 6 to 28)

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

Follow-up visits will occur 4, 9, and 23 days (study Days 9, 14, and 28 [end-of-study; EOS]) after the last dose of study drug for all subjects including those who discontinue treatment early (before completing 5 days of dosing). The eCOA eDiary device should be returned to the site on or before Day 14 (or post-treatment visit 2 [PT2]).

The Day 28 (EOS Visit) is a follow-up visit for post-treatment safety assessments and may be conducted as a telephone call.

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. Addition or Replacement of Subjects

If the objectives of the study are not met (due to subject dropout, lack of sufficient data points, or other reason) or based on recommendation from the SSC, additional subjects may be enrolled. Subjects who withdraw from the study before receiving the first dose of study drug may be replaced. Subjects who withdraw from the study after receiving the first dose of study drug will not be replaced, except as recommended by the SSC.

7.3. Subject Withdrawal/Early Termination

Subjects may be withdrawn at any time at the request of their caregiver(s) or at the discretion of the Investigator or Enanta Pharmaceuticals, Inc. for safety, behavioral, or administrative reasons. However, the Investigator should consult with the [redacted] where possible before prematurely removing a subject. For any subject who is withdrawn by their caregiver, the Investigator should inquire about the reason for withdrawal, request that the subject's caregiver returns all unused investigational product(s), request that the subject returns for the EOT, PT1, and PT2 visits (≤24 hours after last dose, 4, and 9 days after last dose) (if applicable) and the EOS Visit, and follow-up with the subject's caregiver regarding any unresolved AEs. If a subject's caregiver 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.

7.3.1. Withdrawal Criteria

Subjects may be discontinued from the study at any time if the subject's caregiver, 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);
- Study terminated by the Sponsor;
- Other.

7.3.2. Procedures for Early Discontinuation of Treatment or Early Discontinuation of Study

Subjects who discontinue treatment early (before completing 5 days of dosing) should return to the study site within 24 hours after the last dose of study drug for an EOT visit. Subjects should then return to the site 4 and 9 days (PT1 and PT2 visits) after discontinuation of study drug for post-treatment follow-up visits. A follow-up visit for post-treatment safety assessments also needs to be scheduled (23 days after study drug discontinuation) and may be conducted as a telephone call.

Subjects who discontinue the study early (before Day 28) should return to the study site within 24 hours if possible and no more than 48 hours later to complete the EOS procedures and return eCOA handheld device 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's caregiver who does not return to the site for the EOT or EOS Visit at least 3 times using the caregiver preferred method of communication,

followed by a letter requiring delivery notification if the 3 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 11.2.

7.3.3. 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). If multiple assessments are scheduled for the same timepoint, it is recommended that noninvasive procedures being done before more invasive procedures, eg, first complete [redacted] and ReSVinet Scoring System (parent/guardian on ReSVinet eCoA and clinician scoring could be concurrent), then ECG, then vital signs/SpO_2, then nasal swab, and finally blood draw.

8.2. Demographics and Medical History

Demographics and baseline characteristics including age (months and days), gestational age (in weeks), gender or sex, race, ethnicity, and medical history will be obtained from each subject and entered in source documents and either interactive response technology (IRT) or eCRFs as reported during Screening. Significant medical history including surgeries will be obtained by consulting with the subject's caregiver. As a rule, all medical events occurring within the last 6 months should be recorded. For events that occurred more than 6 months before Screening (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.

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.

8.3. Prior and Concomitant Treatment

Medications taken within 1 month of signing the ICF, blood products administered within 6 months of study drug administration, and medications taken during the study will be recorded with indication, dosage, route of administration, and start and stop dates of administration. Only relevant medications and therapies should be recorded if they were discontinued more than 1 month before signing the ICF (see Section 5.8). Subjects' caregivers will be questioned about concomitant medication at each study site visit. Concomitant therapies will be collected from the time of consent. This will include requirement for hydration and feeding by intravenous (IV) catheter/nasogastric tube and requirement for and duration of oxygen supplementation/noninvasive mechanical ventilation support.

8.4. Vital Sign Measurements

Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, body temperature, and pulse oximetry (to measure peripheral capillary oxygen saturation [SpO_2]).

8.5. Electrocardiograms

ECGs will be performed locally. A standard bedside 12-lead ECG machine that calculates heart rate and measures PR, QRS, QT, RR, and QT interval corrected for heart rate according to Fridericia (QTcF) intervals is strongly preferred but in cases where a 12-lead ECG is not possible or feasible, a 6-lead ECG may be used.

During the collection of ECGs, subjects should be calm, resting quietly, or sleeping if possible. If blood sampling and a nasal swab are scheduled for the same timepoint as ECG recording, those assessments should be done after the ECG.

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

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

All subjects with new abnormal cardiac laboratory values or abnormal ECG results after receiving study drug should have echocardiograms. For echocardiogram results, only clinically significant abnormalities should be recorded as AEs.

8.6. 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 as AEs.

8.7. Body Weight and Length, and Head Circumference

Body weight and length should be obtained with the subject unclothed, in a diaper only, or in light clothes and no shoes, as per standard of care. Body length and head circumference will be documented at Screening only.

8.8. 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 with the caregiver including well-being of the subject, if there were any medical problems recently or if any new medicines were taken since the last visit/assessment. Signs and symptoms that are part of the natural progression of RSV infection do not need to be captured as AEs.

It is the Investigator's responsibility to ensure all necessary information is documented in the subject source notes and eCRF.

8.9. Clinical Evaluation

Clinical evaluation will include but not be limited to the following evaluations of the clinical course of RSV infection:

- Vital signs (respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, SpO_2, and body temperature);

- Level of care (e.g., ICU, translational care unit, ward floor, home);
- Duration of hospitalization if hospitalized;
- Incidence of MAARI including hospitalizations, outpatient clinic visits, emergency department visits, and telephone visits due to acute respiratory infection;
- Requirement for and duration of oxygen supplementation/noninvasive mechanical ventilation support (e.g., nasal cannula, face mask, continuous positive airway pressure) and/or invasive mechanical ventilation support (e.g., endotracheal-mechanical ventilation or mechanical ventilation via tracheostomy);
- Requirement for hydration and feeding by IV catheter/nasogastric tube.

On Day 1, these assessments must be done predose.

8.10. Clinical Scoring Systems

8.10.1. Professional ReSVinet Clinical Scoring System

The site Investigator or designee will perform ongoing clinical assessment scoring of the progression of RSV infection using the Professional ReSVinet clinical scoring system at scheduled time points through Day 14. Whenever possible, the same assessor should complete the scoring. A copy of the scoring system is provided in Appendix 2.

8.10.2. Parent/Guardian ReSVinet Clinical Scoring System and Palatability Question

During the study, subjects' parent(s)/guardian(s) will assess the severity of RSV-related signs and symptoms and complete the required response in the Parent/Guardian ReSVinet clinical scoring system using a handheld eCOA eDiary. They will also assess the palatability of study drug. A copy of the scoring system and the palatability question is provided in Appendix 3.

The eCOA eDiary will be provided to the parent(s)/guardian(s) on Day 1, and the Investigator/study site personnel will instruct the parent(s)/caregiver(s) on the completion of the eCOA eDiary. The eCOA eDiary should be returned to the study site at the Day 14 visit (or PT2).

On Day 1, the ReSVinet Scoring System assessment should be completed before administration of the first dose of study drug. Subsequently the eCOA eDiary should be completed predose QD each day through Day 14 and at approximately the same time each day ±2 hours. The palatability question should be completed as soon as possible after each dose of study drug is administered.

The eCOA eDiary will automatically record the date and time of the eCOA assessments. Entries should be recorded by the caregiver at approximately the same time each day. Whenever possible, the same parent/caregiver should complete the eCOA eDiary and should be the primary caregiver of the child who has sufficient opportunity to notice or observe the signs and symptoms being evaluated in the eCOA eDiary. Study site personnel will review the completion of the parent/caregiver eCOA on a regular basis to ensure that the eCOA eDiary is completed correctly and on schedule to avoid missing or incorrect data. If a caregiver is unable to use the eDiary, a paper diary may be used.

8.10.3. [redacted]

[redacted]

8.11. Laboratory and Diagnostic Procedures

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

The maximum blood volume collected at a single collection is approximately [redacted] and the maximum total blood volume collected in study for each subject is approximately [redacted]. Maximum blood draw volumes will be adjusted to be within accepted minimal risk guidelines as per local standard of care.

Procedures performed as part of standard of care up to 72 hours before informed consent may be used in determining study eligibility and to determine baseline values.

For subjects who have screening and randomization separated by more than 24 hours, blood sampling for clinical laboratory tests should be done predose on Day 1 for baseline values. This blood sampling does not need to be done for subjects who have randomization within 24 hours after screening because the screening clinical laboratory test results will be used as the baseline values.

All unblinded laboratory values will be reviewed by the Investigator, documented, and the results will be maintained in the source documents. All out-of-range laboratory findings require an interpretation as to whether 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).

Blood and urine samples for clinical laboratory assessments will be collected according to the SoA (Appendix 1) and all clinical laboratory assessments will be performed at the local site laboratory. Clinical laboratory tests include biochemistry, hematology, and cardiac biomarkers. Cardiac biomarkers will be tested as maximum blood draw volumes allow according to local guidelines. All subjects with new abnormal cardiac laboratory values after receiving study drug

should have echocardiograms. Urinalysis will only be conducted in subjects who are either toilet trained and able to provide a specimen or are already catheterized or fitted with a urine collection bag.

The subject's estimated creatinine clearance will be calculated using the subject's serum creatinine (Cr_{serum}) value, height, and the appropriate equation (Schwartz & Work, 2009):

$$\text{Glomerular filtration rate (mL/min per 1.73 m}^2\text{)} = 0.413 * \text{height}/Cr_{serum}$$

A Laboratory Manual will be provided to the site detailing sample collection, and the kit contents, supply reordering process, sample handling, storage and shipping for samples processed at the central laboratory.

Age-appropriate routine standard of care measures to reduce stress and pain, which may be associated with protocol-required procedures (e.g., venipuncture), are encouraged.

Table 3: Clinical and Respiratory Syncytial Virus Laboratory Evaluations

Chemistry panel Alanine aminotransferase Albumin, serum Alkaline phosphatase, serum Amylase [a] Aspartate aminotransferase Bilirubin, total and direct [a] Blood urea nitrogen Creatinine, serum Electrolyte panel (sodium, potassium, chloride, bicarbonate) Glucose, serum	**Hematology panel** Hemoglobin Hematocrit Differential white blood cell count. Percentage and absolute (basophils, eosinophils, lymphocytes, monocytes, neutrophils) Platelets Red blood cell count White blood cell count [redacted]
URINALYSIS [b] 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)	**RSV-SPECIFIC TESTS (from nasal swab samples) [d]** • RSV diagnostic test using an approved assay (on-site) • Confirmatory respiratory pathogen testing, including RSV, by an RT-PCR-based assay (central/reference laboratory) • RSV viral load quantification (RT-qPCR) (reference laboratory) • RSV sequence evaluation (reference laboratory, archived)

Abbreviations: [redacted] RSV = respiratory syncytial virus; RT-PCR = reverse transcription polymerase chain reaction; RT-qPCR = reverse transcriptase-quantitative polymerase chain reaction

[a] Amylase and direct bilirubin are not required for screening but should be collected at subsequent draws.
[b] Urinalysis only for subjects who are either toilet trained and able to provide a specimen, or are already catheterized or fitted with a urine collection bag.
[redacted]
[d] Residual swab sample fluids will be stored and may be used for biomarker research, if warranted.

8.12. Virology Assessments

Virology assessments and tests (see Table 3) will be performed using nasal swab samples collected at timepoints indicated in the SoA (Appendix 1) and as further described in the Laboratory Manual, including swab collection, sampling, and handling procedures.

Appropriate nasal swabs to assess RSV viral load (RT-qPCR and quantitative viral culture) and viral sequence should be taken by an appropriately trained study team member. At each visit, a single swab will be collected. Samples should be taken at approximately the same time each day before study drug administration. Nasal swabs should be frozen as soon as possible after being collected. The actual times of sample collection must be recorded in the source.

At Screening, RSV diagnosis will be based on an approved diagnostic assay performed locally. Other virology assessments will be sent to the central/reference laboratory.

8.12.1. Respiratory Syncytial Virus Rapid Diagnostic Test

After the subject's caregiver reviews and signs the ICF, subjects will undergo a screen for RSV using an approved diagnostic assay performed locally. If an RSV diagnostic test is performed as part of standard of care before screening, that test result may be used in determining study eligibility if the test was performed within 72 hours before the ICF is signed.

Subjects who have symptom onset, defined as the estimated onset of the first sign of respiratory infection or worsening of pre-existing respiratory signs and which does not exceed 7 days for Part 1 or 5 days for Part 2 before the signing of the consent by their caregiver and whose swab sample tests positive for RSV at Screening (or previously, see following text) will undergo further screening procedures to determine study eligibility. Results will be recorded in the source documents.

8.12.2. Confirmatory Respiratory Pathogen Testing

Following randomization on Day 1, a nasal swab sample collected before taking the first dose of EDP-938 or placebo will be tested for other respiratory pathogens. This testing will be performed to identify other co-pathogens that may include adenovirus, coronaviruses including SARS-CoV-2, human metapneumovirus, human rhinovirus/enterovirus, influenza, parainfluenza virus, *Chlamydophila pneumoniae*, and/or *Mycoplasma pneumoniae*, which may impact the course of a subject's illness.

8.12.3. Respiratory Syncytial Virus Viral Load Quantification

The RSV viral load will be measured in nasal swabs by infectious virus quantitative culture and RT-qPCR assay.

8.12.4. Respiratory Syncytial Virus Subgroup/Genotype Determination

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

8.12.5. Viral Resistance

Nasal swab sample(s) may be analyzed for monitoring potential viral resistance. Resistance monitoring, if performed, will be conducted by population and/or deep sequencing of the RSV genes to assess the emergence of resistance-associated variants. Phenotypic analysis may also be performed to determine the susceptibility of the resistance variants to EDP-938.

8.13. Pharmacokinetic Samples

Subjects will have blood (plasma) samples collected at the following time points for PK analysis:

Hospitalized Subjects

- Visit 1: 3 hours postdose;
- Visit 2: predose;
- Visit 5: predose.

Non-hospitalized Subjects

- Visit 1: 3 hours postdose;
- Visit 3: predose;
- Visit 5: predose.

The predose samples should be collected at approximately the same time as the nasal swab sample(s). For the postdose sample collected on Day 1, a window of ±30 minutes for the sampling time is acceptable. 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 before 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.

The method of sampling for PK blood draws is at the discretion of the Investigator. Samples taken via peripherally inserted central catheter line, indwelling catheter access, individual peripheral phlebotomies, or an IV line (or comparable means of access) are preferred, however, in instances where samples are unable to be obtained from a second line, alternative methods (capillary blood sampling via heel sticks or finger sticks) are allowed.

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

EDP-938 and its metabolites [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.

Pharmacokinetic samples may be stored and used for future metabolite and/or further evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical study report.

8.14. Exploratory Biomarker Sample Collection

Residual nasal swab and PK sample volume will be stored and may be used for biomarker research, if warranted. This exploratory testing may include measures of host proteins and viral markers other than those previously described in the protocol. These samples will not be used for human genomic testing. The samples will be stored for up to 1 year after the finalization of the clinical study report.

Refer to the Laboratory Manual for further details for sample collection, processing, and storage.

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. AEs also may be detected when they are volunteered by the subject during or between study site visits or through physical examination, laboratory test, or other assessments.

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

9.1.3. Serious Adverse Events

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

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

  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an 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)

AEs will be evaluated and documented using the grading scales contained in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

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 (i.e., screen failures), AEs will only be recorded in the source documents. For subjects enrolled into the study (i.e., randomized), all AEs will be recorded in the subject's AE eCRF and the SAE Form (if applicable). The site should record all AEs regardless of the intensity, seriousness, or relationship to study drug.

AEs (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 (e.g., flu syndrome) rather than as individual signs or symptoms. If no specific diagnosis or syndrome is identified, AEs should be reported as separate and individual events.

An AE includes the following:

- Progression or exacerbation of the subject's underlying disease. Clinical sequelae that result from disease progression, such as pleural effusion or small bowel obstruction, are reportable as AEs;
- Pre-existing event that increases in frequency or intensity;
- Condition detected or diagnosed during the study period, even though it may have been present, in retrospect, before the first dose of study drug;
- Laboratory abnormalities outside of normal limits with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the Investigator, including those requiring therapeutic intervention;
- 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 (e.g., surgery, endoscopy, tooth extraction, etc); however, the condition (the "triggering event") that leads to the procedure may be an AE;
- Pre-existing conditions present or detected before the first dose of study drug that do not worsen.

9.2.2. Assigning Attribution of Adverse Events

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

- **Related:** There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug has 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 4.

Table 4: 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 5. One outcome must be entered into the appropriate field on the AE and (if appropriate) SAE Form for each event as discussed in the corresponding instructions.

Table 5: Classification and Definition of Adverse Event Outcomes

Classification	Definition
Recovered/Resolved	Resolution of an adverse event with no residual signs or symptoms.
Recovered/Resolved with Sequelae	Resolution of an adverse event with residual signs or symptom.
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 AE.
Unknown	Outcome of an adverse event is not known (e.g., 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] via email at [redacted]

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

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

Enanta Pharmaceuticals, Inc. or its designees, as study Sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSAR) involving the study drug to all regulatory authorities, and participating investigators, in accordance with US Food and Drug Administration (FDA), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements, as applicable.

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 5), the subject dies, the event stabilizes and is not expected to further resolve with the maximum time limit for stabilization defined as 30 days after the occurrence of the event, or when alternative therapy is instituted, whichever occurs first. If alternative therapy is instituted, it should be documented. Enanta Pharmaceuticals, Inc. may request that the Investigator perform or arrange for supplemental measurements or evaluations to further clarify the nature of the event.

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.

10. SUBJECT SAFETY MANAGEMENT/STUDY STOPPING RULES

10.1. Study Stopping Rules

If any of the following 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 SSC.

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

10.2. Individual Subject Discontinuation Criteria

If one (or more) of the following changes occur, the subject should discontinue study drug and should be followed until resolution (return to baseline) or stabilization of change (to be agreed upon with the Sponsor). The Sponsor should be informed even if the change occurs outside of the treatment period (but before the end of the study).

- A TEAE which is considered clinically significant (e.g., meeting Grades 3 [severe] or 4 [potentially life-threatening] criteria) and is attributed to study drug and/or which is thought to preclude further safe administration of study drug;
- An AE/SAE, drug reaction, or complication, whether related or not to study drug, which precludes continuation of treatment with study drug;
- The Principal Investigator's opinion that it is not in the subject's best interest to continue study participation.

10.3. Cohort Discontinuation Criteria

Further enrollment within a cohort or enrollment to subsequent cohorts will be discontinued once it has been established that safety risk(s) such as the following occur:

- If any unacceptable toxicity (as determined by the Sponsor Medical Monitor) occurs;
- If the SSC considers an event or multiple events to represent an unacceptable risk to the health and well-being of subjects at that or higher dose levels.

10.4. Site or Study Discontinuation

10.4.1. 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.

10.4.2. 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.

10.4.3. 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. Sample Size Considerations

[redacted]

11.2. 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. Statistical methods are primarily descriptive in nature and will be used to guide decisions as to the clinical relevance of findings. No formal statistical analysis is planned. Parts 1 and 2 will be summarized separately unless stated otherwise.

Unless otherwise specified, baseline will be defined as the last non-missing measurement before the first dose of study drug. For analyses of nasal swab data and analyses of RSV-related signs and symptoms, if assessments before the first dose of study drug are not available, a post-treatment assessment collected no more than 60 minutes after the first dose of study drug will be used as the baseline value. 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 before unblinding.

The presence of a coinfection will be taken into consideration when analyzing the results of the study.

11.3. Analysis Populations

- Safety population: All subjects who receive any dose (including partial doses) of any study drug;
- PK population: All subjects who receive one full dose of study drug and have blood samples with quantifiable plasma levels to allow estimation of PK parameters;
- Efficacy population: All subjects who receive one full dose of study drug;
- Modified Intention to Treat 3 (mITT-3) population: All subjects who receive one full dose of study drug and have onset of the first sign of respiratory infection within 3 days before randomization.
- Modified Intention to Treat 5 (mITT-5) population: All subjects who receive one full dose of study drug and have onset of the first sign of respiratory infection within 5 days before randomization.

11.4. Subject Disposition and Demographic Data

The number of subjects screened, randomized, and in the safety, PK, clinical, and antiviral activity 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 safety population. Appropriate baseline characteristics will be included in addition to demographic characteristics. No statistical testing will be performed.

11.5. Safety Analyses

Statistical methods for the safety analyses will be primarily descriptive in nature. The safety population will be used for the respective analyses. Parts 1 and 2 may be pooled for AEs and laboratory analyses where appropriate.

11.5.1. 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.

11.5.2. Study Drug Exposure

Drug exposure will be summarized.

11.5.3. Adverse Events

AEs will be summarized by the Medical Dictionary for Regulatory Activities system organ class and preferred term by treatment group. All subjects in the safety population will be included in the summaries. Treatment-emergent AEs are defined as reported AEs that first occurred or worsened during the post-Baseline phase compared to Baseline (Day 1, Predose). 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.

11.5.4. 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.

11.5.5. 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. Oxygen saturation (SpO_2) measurements will be summarized by visit and treatment.

11.5.6. Electrocardiograms

Screening and subsequent ECG data will be provided in data listings.

11.5.7. Concomitant Medications and Therapies

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 safety population will be summarized by treatment group.

11.5.8. Physical Examinations

Physical examination data will be provided in data listings.

11.6. Pharmacokinetic Analyses

Plasma concentration of EDP-938 will be used to estimate the PK parameters of EDP-938 using a population PK model, as allowed by the data. Plasma metabolites concentrations will be summarized. Subjects may be excluded from the PK analysis if their data do not allow for accurate assessment of the PK parameters.

[redacted]

11.7. Efficacy Analyses

All efficacy analyses will be descriptive statistics. Antiviral activity, clinical outcome, and other efficacy data will be summarized separately by treatment and age group. Efficacy analyses will be summarized using the efficacy population.

11.7.1. Antiviral Activity Analyses

Antiviral activity will be assessed by RSV RNA viral load RT-qPCR and infectious virus culture performed on nasal swab samples obtained throughout the study. Data will be summarized by age group and treatment group as well as overall. Daily change in RSV shedding in nasal swab samples from baseline through the treatment phase will be summarized. AUC for RSV RNA viral load will be summarized.

11.8. [redacted]

[redacted]

11.8.2. [redacted]

[redacted]

[redacted]

11.9. Interim Analyses

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

12. STUDY ADMINISTRATION

12.1. Ethical Considerations

12.1.1. Ethical Conduct of the Study

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

12.1.2. Ethical Review

It is the Investigator's responsibility to ensure that this protocol is reviewed and approved by an appropriate IRB/EC that conforms to the regulations set forth in FDA 21 Code of Federal Regulations 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's caregiver, and all advertisements that may be used for study-specific recruitment to the IRB/EC for review and approval before commencing study-specific assessments. A copy of the ICF approved by the IRB/EC must be forwarded to Enanta Pharmaceuticals, Inc. for regulatory purposes.

Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/EC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects.

12.1.3. Written Informed Consent

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

The subject's caregiver must provide a signed and dated ICF before enrollment into this study. If RSV infection is not confirmed, caregivers may be asked to sign a RSV Diagnostic Test ICF allowing a rapid antigen RSV test to be performed. 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's caregiver before Screening that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Enanta Pharmaceuticals, Inc. and its 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's caregiver authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject's caregiver. If a subject's caregiver withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject's caregiver and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

12.1.4. Investigator Compliance

No modifications to the protocol should be made without the approval of both the Investigator and Enanta Pharmaceuticals, Inc.

If it is necessary to amend the protocol during the study, 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.

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

12.2. Data Collection

Initial subject screening data such as informed consent, age, inclusion/exclusion criteria met/not met, RSV symptoms, and limited demographics, will be collected in the IRT system. Data from screen failures will be collected in IRT only.

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.

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 at least 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. 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. Demographic data collected in eCRF are listed in Section 8.2. As indicated in the ICF, subject's caregiver will give permission for representatives of the Sponsor, regulatory authorities, and the IRB/EC to inspect their medical records to verify the information collected. They 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 caregiver'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.

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14. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Period	**Screening[1,2]**	**Treatment**					**Follow-Up**			**For non-hospitalized subjects, V2 and V4 assessments will be done at home. (X) is for V2 and V4 assessments for hospitalized subjects.**
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**PT1**	**PT2**	**PT3[3]**	
Day	**Day-1 to Day 1**	**1**	**2**	**3 (±1)[4]**	**4**	**5 (±1) EOT[5]**	**9 (±1)**	**14 (±2)**	**28 (±4) EOS[5]**	**Notes[6]; Protocol Section**
Screening/Administrative										
Study site visit	X	X		X		X	X	X	X	
RSV diagnostic test and informed consent form	X									If RSV infection has not been confirmed using an approved diagnostic assay, caregivers may be asked to sign a RSV Diagnostic Test ICF to allow a rapid antigen RSV test to be performed.
Informed consent form	X									Section 12.1.3
Demographics	X									Section 8.2
Medical history	X									Section 8.2
Inclusion/Exclusion	X									Section 3
Body weight	X					X				Section 8.7
Body length/head circumference	X									Section 8.7
Study Drug Administration Subjects will be randomized and administered the first dose of study drug within 24 hours of signing the ICF.										
Randomization		X								Subjects will be randomized 2:1 in Part 1 and 4:1 in Part 2 to EDP 938:placebo. Parent/Guardian ReSVinet clinical scoring system Day 1 assessment, clinical evaluation, and vital signs must be done between randomization and dosing. Section 5.6
Dispense/ Administer study drug		X	X	X	X	X				Study drug should be administered QD from D1 through D5 at approximately the same time (±1 hr) every day. Section 5.7
Study drug accountability		X		X		X*				[redacted] on D3 and D5 for non-hospitalized patients. If V5 is conducted before D5 due to the visit window, caregivers should be contacted as soon as possible after D5 dosing to collect the date and time of dosing. Section 5.4
Clinical Efficacy Evaluations										
Professional ReSVinet clinical scoring system		X		X		X	X	X		The visit assessment will be completed by the Site Investigator (or designee). The ReSVinet D1 assessment must be predose. Section 8.10.1

Study Period	**Screening[1,2]**	**Treatment**					**Follow-Up**			**For non-hospitalized subjects, V2 and V4 assessments will be done at home. (X) is for V2 and V4 assessments for hospitalized subjects.**
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**PT1**	**PT2**	**PT3[3]**	
Day	**Day-1 to Day 1**	**1**	**2**	**3 (±1)[4]**	**4**	**5 (±1) EOT[5]**	**9 (±1)**	**14 (±2)**	**28 (±4) EOS[5]**	**Notes[6]; Protocol Section**
Parent/Guardian ReSVinet clinical scoring system and palatability question		Once daily from predose on D1 through D14								Caregiver(s) should complete the Parent/Guardian ReSVinet clinical scoring system using the eCOA handheld eDiary for both hospitalized and non-hospitalized subjects. The ReSVinet D1 assessment must be predose, and subsequent assessments should be completed predose at the same time **daily** (±2 hr) **for 14 days.** The palatability assessment should be completed after each dose of study drug is administered. If a caregiver is unable to use the eDiary, a paper diary may be used. Section 8.10.2
Parent/Guardian [redacted] clinical scoring system)		Twice daily on D1 through D14								Caregiver(s) should complete the Parent/Guardian [redacted] clinical scoring system on paper for both hospitalized and non-hospitalized subjects. The D1 assessment must be completed predose, and subsequent assessments should be completed twice daily, approximately every 12 hours, for 14 days. If D1 assessment is completed in the afternoon, only one assessment is expected for that day. [redacted] will be completed in a subset of subjects. Section 8.10.3
Clinical Safety Evaluations										
Vital sign measurements (including SpO_2)	X	X		X		X	X	X		If Screening and V1 occur on the same calendar day, vital signs measurements do not need to be repeated and the Screening measurements will be used as baseline values. If Screening and V1 occur on different calendar days, V1 measurements should be taken pre-dose as baseline values. Starting on D1, vital signs should be performed QD on marked study site visit days. Section 8.4
Physical examination	X			X		X	X	X		Full PE at Screening. Subsequent PEs done at discretion of Investigator will be targeted to new signs and symptoms, including specific assessments of changes from previous status. Section 8.6
ECG	X					X				12-lead ECG strongly preferred but where not possible, 6-lead ECG may be performed. If blood sampling and/or a nasal swab are scheduled for the same timepoint as ECG recording, those assessments should be done after the ECG. Section 8.5
Procedures										Residual samples from blood and/or nasal swab volume may be used for exploratory biomarker analyses. Section 8.14
Nasal swab		X		X		X	X	X		Swab samples should be taken at approx. same time before study drug administration. One swab will be collected at each visit. Section 8.12

Study Period	Screening[1,2]	Treatment					Follow-Up			For non-hospitalized subjects, V2 and V4 assessments will be done at home. (X) is for V2 and V4 assessments for hospitalized subjects.
Visit	Screening	V1	V2	V3	V4	V5	PT1	PT2	PT3[3]	
Day	Day-1 to Day 1	1	2	3 (±1)[4]	4	5 (±1) EOT[5]	9 (±1)	14 (±2)	28 (±4) EOS[5]	Notes[6]; Protocol Section
Blood sampling for clinical laboratory tests	X	X*		X		X				Clinical laboratory tests include biochemistry, hematology, and cardiac biomarkers. All clinical laboratory tests that will be evaluated in the study are specified in Table 3. Evaluations will be conducted by local laboratories. *For subjects who have screening and randomization separated by more than 24 hours, blood sampling for clinical laboratory tests should be done predose on Day 1 for baseline values. This blood sampling does not need to be done for subjects who have randomization within 24 hours after screening because the screening clinical laboratory test results will be used as the baseline values. Section 8.11
Urinalysis	X					X				Urine will be collected only from subjects who are either toilet trained and able to provide a specimen or are already catheterized or fitted with a urine collection bag, Section 8.11
Blood sampling for PK		X	(X)	X		X				**Hospitalized subjects** • Visit 1: 3 hours postdose • Visit 2: predose • Visit 5: predose **Non-hospitalized subjects** • Visit 1: 3 hours postdose • Visit 3: predose • Visit 5: predose All subjects: Predose samples should be collected at approximately the same time as the nasal swab sample(s). For the postdose collection on Day 1, a window of ±30 minutes for the sampling time is acceptable. The time and date of PK sample collection will be recorded in source and eCRF. Section 8.13

Study Period	Screening[1,2]	Treatment					Follow-Up			For non-hospitalized subjects, V2 and V4 assessments will be done at home. (X) is for V2 and V4 assessments for hospitalized subjects.
Visit	Screening	V1	V2	V3	V4	V5	PT1	PT2	PT3[3]	
Day	Day-1 to Day 1	1	2	3 (±1)[4]	4	5 (±1) EOT[5]	9 (±1)	14 (±2)	28 (±4) EOS[5]	Notes[6]; Protocol Section
Ongoing Subject Review										
Concomitant treatment	X	X	(X)	X	(X)	X	X	X	X	Section 8.3
Healthcare resource utilization		X	(X)	X	(X)	X	X	X	X	Evaluate level of care (e.g., ICU, translational care unit, ward floor, home), duration of hospitalization if hospitalized, incidence of MAARI, requirement for and duration of oxygen supplementation/noninvasive mechanical ventilation support and/or invasive mechanical ventilation support and requirement for hydration and feeding by IV catheter/nasogastric tube. Section 8.9
Adverse events	X	X	(X)	X	(X)	X	X	X	X	If V5 is conducted before D5 due to the visit window, caregivers should be contacted as soon as possible after D5 dosing to assess AEs, concomitant treatments, and healthcare utilization. Section 8.8

Abbreviations: approx. = approximately, D = day; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; eCRF = electronic case report form; EOS = end-of-study; MAARI = medically attended acute respiratory infection; EOT = End-of-Treatment; ICF = informed consent form; ICU = intensive care unit; PE = physical examination; PK = pharmacokinetics; PT = post-treatment visit; QD = once daily; RSV = respiratory syncytial virus; SpO_2 = peripheral capillary oxygen saturation; V = visit

[1] Procedures performed as part of standard of care within 72 hours before the informed consent is signed may be used in determining study eligibility and/or as baseline values.
[2] Screening should be completed as soon as possible to ensure that subjects will be randomized and administered the first dose of study drug within 24 hours of signing the ICF.
[3] PT3 assessment may be conducted as a telephone call.
[4] If Visit 3 occurs on Day 4 due to the visit window, Visit 5 should occur on Day 5 or Day 6.
[5] Subjects who discontinue treatment early (before completing 5 days of dosing) should return to the study site within 24 hours following the last dose of study drug for an EOT visit. Follow-up visits will be scheduled 4 days (PT1, Day 9), 9 days (PT2, Day 14), and 23 days (PT3), Day 28 [EOS]) after the last dose of study drug was administered. Assessments should be performed as indicated, respectively for the Day 9 (PT1), Day 14 (PT2), and Day 28 (EOS/PT3) visit. Subjects who discontinue the study early (before Day 28) should return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.
[6] If multiple assessments are scheduled for the same timepoint, it is recommended that noninvasive procedures being done before more invasive procedures, e.g., first complete questionnaires (parent/guardian and clinician questionnaires could be concurrent), then ECG, then vital signs/SpO_2, then nasal swab and finally blood draw.

APPENDIX 2. PROFESSIONAL RESVINET CLINICAL SCORING SYSTEM

To be completed by site Investigator or designee

Assessment Period	Item	0 points	1 point	2 points	3 points
Over the last 24 hours	**1 Feeding intolerance**	**None**	**Mild** Decreased appetite and/or had isolated vomiting with coughing.	**Partial** Frequently vomits with coughing, rejected feeds but able to tolerate fluids sufficiently to ensure hydration.	**Total** Intolerance or absolute rejection of feeds, unable to maintain adequate hydration orally. Required nasogastric and/or intravenous fluids
Over the last 24 hours	**2 Medical intervention**	**None**	**Basic** Nasal secretion aspiration performed, trial of nebulized bronchodilators, antipyretics.	**Intermediate** Oxygen therapy required. Supplementary testing needed (eg, chest X-rays, blood gases). Ongoing nebulized bronchodilators.	**High** Required respiratory support with positive pressure (either non-invasive in continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or high-flow O_2; or invasive through endotracheal tube).
As examined	**3 Respiratory difficulty**	**None**	**Mild** Not feeling as usual but does not look severely ill. Respiratory wheezing audible only with stethoscope, good air entry. If modified Wood Downes, Wang score, or any other respiratory distress score is applied, it indicates mild severity.	**Moderate** Makes some extra-respiratory effort (intercostal and/or tracheosternal retraction). Expiratory wheezing is audible even without stethoscope, and air entry may be decreased in localized areas with stethoscope. If modified Wood Downes, Wang score, or any other respiratory distress score is applied, it indicates moderate severity.	**Severe** Respiratory effort is obvious. Inspiratory and expiratory wheezing and/or clearly decreased air entry with stethoscope. If modified Wood Downes, Wang score, or any other respiratory distress score is applied, it indicates high severity.

To be completed by site Investigator or designee

Assessment Period	Item	0 points	1 point	2 points	3 points
Over the last 24 hours	**4 Respiratory frequency**	**Normal** <2 m: 40-50 bpm 2-6 m: 35-45 bpm 6-12 m: 30-40 bpm 12-24 m: 25-35 bpm 24-36 m: 20-30 bpm	**Mild or occasional tachypnea** Episodes of tachypnea are present but well tolerated, limited in time, and self-resolving or responding to aspiration of secretions or nebulization.	**Prolonged or recurrent tachypnea** Tachypnea persisted or recurred despite aspiration of secretions and/or nebulization with bronchodilators.	**Severe alteration** Severe and sustained tachypnea. Breathing that is very superficial and rapid. Normal/low rate breath with obvious increased respiratory effort and/or mental status changes. Rates of severe tachypnea: <2 m: >70 bpm 2-6 m: >60 bpm 6-12 m: >55 bpm 12-24 m: >50 bpm 24-36 m: >40 bpm
Over the last 24 hours	**5 Apnea**	**No**			**Yes** At least one episode of medically documented apnea or one which is strongly suggested by history.
As examined	**6 General Condition**	**Normal**	**Mild** Not feeling as usual, child was mildly uncomfortable but does not appear to be severely ill. Parents are not alarmed. Could wait in the waiting room or even stay at home.	**Moderate** Patient looks ill and required medical examination and eventually further complementary exams and/ or therapy. Parents are concerned. Cannot wait in the waiting room.	**Severe** Agitated, apathetic, lethargic. Severity is self-evident. Parents are very concerned. Immediate medical evaluation and/or intervention were required.
Over the last 24 hours	**7 Fever**	**No**	**Yes, Mild** fever, central temp <38.5°C	**Yes, Moderate** fever, central temp >38.5°C	

Source of information other than assessment period: Table 1 in Justicia-Grande et al, PLOS One, 2016 (doi:10.1371/journal.pone.0157665.t001)
Abbreviations: m = months

APPENDIX 3. PARENT/GUARDIAN RESVINET CLINICAL SCORING SYSTEM AND PALATABILITY QUESTION

To be completed by parent/caregiver

Assessment Period	Item	0 points	1 point	2 points	3 points
Over the last 24 hours	**1 Feeding intolerance**	**None**	**Mild** Decreased appetite (the child ate less than usual) and/or had isolated vomiting with coughing.	**Partial** Frequently vomits with coughing, but the child does not vomit with every feed. Feeding exhausts the child.	**Total** The child is unable to feed him/herself. The use of a nasogastric tube or parenteral nutrition was required.
Over the last 24 hours	**2 Medical intervention**	**None**	**Basic** The child's respiratory secretions needed to be removed, he or she was examined by a doctor or received occasional nebulized medication. Medication to treat fever was given.	**Intermediate** The child required oxygen therapy, underwent a chest X-ray, or a blood sample was taken. Treatment with nebulized medication was given regularly.	**High** The child required respiratory support with a machine. Respiratory support was given through a special mask applied to the nose or mouth or resting on the child's face, or through an endotracheal tube.
When the diary was completed	**3 Respiratory difficulty**	**None**	**Mild** The child was not breathing normally, but he/she does not seem to have any difficulty when breathing in.	**Moderate** The child finds breathing is an effort. Respiratory noises can be heard just by pressing your ear close to his or her chest (without a stethoscope)	**Severe** Respiratory effort is obvious. The child makes significant movements of his/her chest, the chest even collapses with every movement, and muscles of neck and belly were used. A lot of respiratory noise is heard without pressing the ear close to the child's chest.

To be completed by parent/caregiver

Assessment Period	Item	0 points	1 point	2 points	3 points
Over the last 24 hours	**4 Respiratory frequency**	**Normal**	**Mild or occasional tachypnea** The child was breathing more rapidly but it was well tolerated, or the breathing became normal after removing secretions from the child's airways or administering nebulized medication.	**Prolonged or recurrent tachypnea** The child was breathing more rapidly and persistently, even after receiving nebulized medication or removing secretions from the child's airway.	**Severe alteration** The child breathed quickly and superficially, or really deeply. The child was agitated or drowsy. The child was severely short of breath.
Over the last 24 hours	**5 Apnea**	**No**			**Yes** The child stopped breathing. It may have been necessary to stimulate him/her to start normal breathing.
When the diary was completed	**6 General Condition**	**Normal**	**Mild** The child is not feeling as usual, but there does not seem to be anything to worry about.	**Moderate** Child looked ill, and medical examination was required, but it did not feel like a life-threatening situation.	**Severe** Child was agitated, apathetic, and/or lethargic. He/she required urgent medical attention. There was no need to be a doctor to see that the condition of the child is worrying.
Over the last 24 hours	**7 Fever**	**No**	**Yes, Mild** Rectal or tympanic temperature <38.5°C, or axillar temperature <38°C	**Yes, Moderate** Rectal or tympanic temperature >38.5°C, or axillar temperature >38°C	

Source of information other than assessment period: Table 2 in Justicia-Grande et al, PLOS One, 2016 (doi:10.1371/journal.pone.0157665.t001)
m = months

Palatability Question

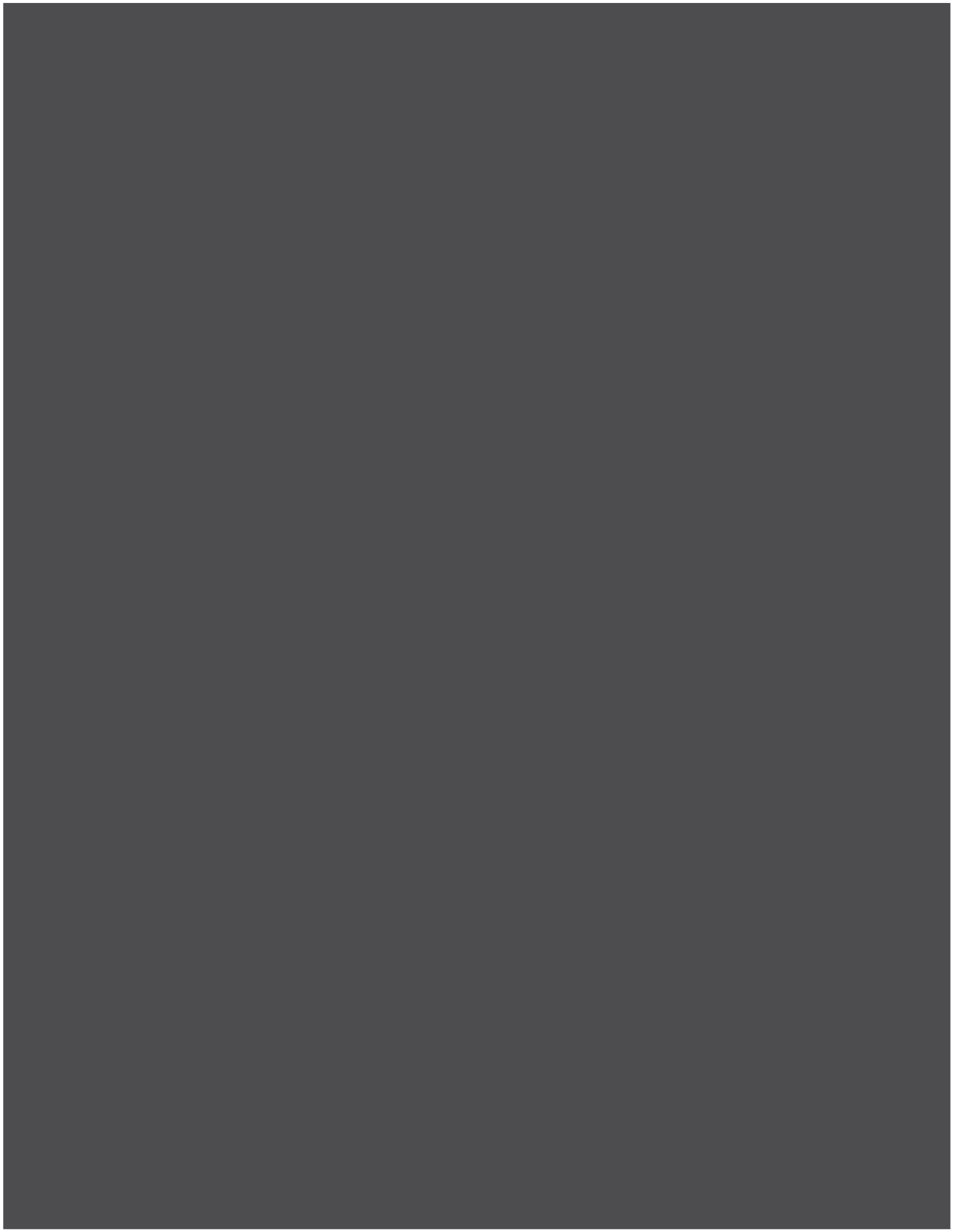
Did the child take the medicine? (yes/no)

Select all that apply:

- ☐ Successfully swallowed the medicine without vomiting within 2 minutes of swallowing;
- ☐ Took the study medication easily;

- The facial expression suggested that he/she did not like the taste;
- Cried after tasting it;
- Would not open mouth or turned head away to avoid it;
- Spit out or coughed it out;
- Gagged or vomited (within 2 minutes of swallowing medicine).

[redacted]



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