Enanta Pharmaceuticals

EDP 938-104

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

6 June 2025

Statistical Analysis Plan

Version 1.0

Prepared by:

[redacted]

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List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CHF	Congestive Heart Failure
CI	Confidence Interval
CM	Concomitant Medication
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FSH	Follicle-Stimulating Hormone
GCV	Geometric Mean of Coefficient of Variation
HDPE	High-Density Polyethylene
HRQOL	Health-Related Quality of Life
ICE	Intercurrent Event
IA	Interim Analysis
ICF	Informed Consent Form
ICU	Intensive Care Unit
IRT	Interactive Response Technology
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
LOD	Limit of Detection
LRTI	Lower Respiratory Tract Infection
LRTD	Lower Respiratory Tract Disease
MAR	Missing at Random
MNAR	Missing Not at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intent-to-Treat

MMRM	Mixed Model Repeated Measures
N/A	Not applicable
NAAT	Nucleic Acid Amplification Test
NC	Not calculable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NP	Nasopharyngeal
PD	Protocol Deviation
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PKPD	Pharmacokinetic-Pharmacodynamic
PP	Per Protocol
PT	Preferred Term
QD	Quaque Die (Once Daily)
RiiQ	Respiratory Infection Intensity and Impact Questionnaire
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RT-qPCR	Quantitative Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SARS-CoV-2	Severe Acute Respiratory Syndrome-CoronaVirus-2
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SoA	Schedule of Assessments
SOC	System Organ Class
SpO2	Oxygen Saturation
TD	Target Detected
TEAE	Treatment-Emergent Adverse Event
TM	Trademark
TMF	Trial Master File
TND	Target not Detected
ULN	Upper Limit of Normal
URTD	Upper Respiratory Tract Disease
US	United States
WHO	World Health Organization

1. Introduction

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) and presents a significant health challenge in small children, elderly, and immunocompromised patients (Falsey A.R. et al., 2005; Hall et al., 2009; Shook and Lin, 2017). RSV is an important and often unrecognized cause of respiratory tract infection in adults, as well as an important cause of death in subjects older than 65 years and those with specific comorbidities such as chronic cardiopulmonary disease (Falsey A.R.et al., 2000). RSV is second only to influenza as a cause of medically significant respiratory tract illnesses in adults and is estimated to cause 177,000 hospitalizations and 14,000 annual deaths in US adults aged 65 years and older (NCIRD, 2020).

To address the unmet medical need for more effective antiviral therapies for RSV and based on the promising early nonclinical safety and pharmacological profile, Enanta Pharmaceuticals, Inc. is investigating EDP-938 in humans as a potential treatment for RSV infection (Ahmad A. et al., 2018). EDP 938-104 is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study designed to assess the efficacy and safety of EDP-938 compared with placebo in non-hospitalized adults with an acute RSV infection who are at high risk for disease progression and complications (i.e., age ≥65 years, congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD], or asthma).

This statistical analysis plan (SAP) outlines specifications of the statistical analyses of efficacy and safety data to support the clinical study report (CSR) for Study EDP 938-104. This SAP is based on protocol version 4.1 (dated 30 October 2023) and will be finalized prior to database lock. Any changes to the SAP after finalization will be documented in the CSR.

2. Objectives and Estimands

2.1 Primary Objective and Estimand

The primary objective is to evaluate the effect of EDP-938 compared with placebo on the progression of RSV infection by assessment of clinical symptoms.

The primary estimand is described in table 2-1.

Table 2-1: Summary of Estimand and Strategies for Managing Intercurrent Events for the Primary Endpoint

Objective	To demonstrate the superiority of EDP-938 to placebo on the progression of RSV infection in terms of time to resolution of RSV Lower Respiratory Tract Disease symptoms (LRTD) in subjects with acute RSV infection who are at high risk for complications.
Estimand Label	Estimand 1 (Primary efficacy)

Estimand Scientific Question of Interest	What is the hazard ratio of time to resolution of RSV LRTD symptoms with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation, and taking it censored at Day 33 if resolution is not achieved prior to study discontinuation, the use of prohibited medications or death.
Target Population	Non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma).
Endpoint	Time to resolution of RSV LRTD symptoms, defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by RiiQ™ score is zero or 1, through Day 33. Subjects are censored at Day 33 if resolution is not achieved.
Treatment Condition(s)	5-days treatment of EDP-938 800 mg vs placebo
Population-Level Summary	Hazard ratio of EDP-938 800 mg vs. placebo
ICE Strategy	
1. Treatment discontinuation	**Treatment policy strategy**: Use time to resolution regardless of treatment discontinuation status.
2. Study discontinuation	**Composite strategy:** Use time to resolution if resolution achieved prior to subject discontinuation; Subjects are censored at Day 33 if resolution is not achieved prior to discontinuation.
3. Use of prohibited medications (Protocol, Section 5.8)	**Composite strategy**: Use time to resolution if resolution achieved prior to the use of prohibited medications; Subjects are censored at Day 33 if resolution is not achieved prior to the use of prohibited medications.
4. Death	**Composite strategy**: Use time to resolution if resolution achieved prior to death; Subjects are censored at Day 33 if resolution is not achieved prior to death.
Rationale for Strategies	Treatment policy for treatment discontinuation as it is relevant to clinical practice. A composite variable strategy is taken to assume censor at Day 33 for study discontinuation, use of prohibited medications and death when no resolution achieved prior to the events. This is a conservative approach.

2.2 Secondary Objectives

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

2.2.1 Selected Secondary Efficacy Objectives, Estimand, and Endpoints

Estimands have been considered for some selected secondary objectives.

Estimand 2 - Secondary Efficacy Endpoint: To demonstrate the superiority of EDP-938 compared to placebo on the progression of RSV infection in terms of change from baseline in severity of RSV LRTD symptoms in subjects with acute RSV infection who are at high risk for complications.

Estimand Scientific Question of Interest: What is the mean difference in the change from baseline in severity of RSV LRTD symptoms at each key post-baseline visit (Days 3, 5, 9, 14 and 33) with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation and the worst result during the entire study is taken in the use of prohibited medications or death.

The estimand for the change from baseline for severity of RSV LRTD symptoms is defined as follows:

- **Target Population:** Non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)
- **Treatment Condition:** 5-days treatment of EDP-938 800 mg vs placebo
- **Endpoint:** Change from baseline in severity of RSV LRTD symptoms
- **Population-level summary:** Mean difference of EDP-938 800 mg vs. placebo in the change from baseline in severity of RSV LRTD symptoms at each key post-baseline visit
- **Intercurrent events and strategies** are described in Table 2-2:

Estimand 3 - Secondary Efficacy Endpoint: To demonstrate the superiority of EDP-938 compared to placebo on the progression of RSV infection in terms of change from baseline in RSV RNA viral load in subjects with acute RSV infection who are at high risk for complications.

Estimand Scientific Question of Interest: What is the mean difference in the change from baseline in RSV RNA viral load at each key post-baseline visit with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation and the worst result during the entire study is taken in the use of prohibited medications or death.

The estimand for the change from baseline of RSV viral load is defined as follows:

- **Target Population:** Non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)
- **Treatment Condition:** 5-days treatment of EDP-938 800 mg vs placebo
- **Endpoint:** Change from baseline in RSV RNA viral load
- **Population-level summary:** Mean difference of EDP-938 800 mg vs. placebo in the change from baseline in RSV RNA viral load at each post-baseline visit.
- **Intercurrent events and strategies** are described in Table 2-2:

Estimand 4 - Secondary Efficacy Endpoint: To demonstrate the superiority of EDP-938 to placebo on the progression of RSV infection in terms of the proportion of subjects with RSV RNA viral load target not detected (TND) in subjects with acute RSV infection who are at high risk for complications.

Estimand Scientific Question of Interest: What is the difference in proportion of subjects with RSV RNA viral load TND with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation and the worst result during the entire study is taken in the use of prohibited medications or death.

The estimand for the proportion of RSV viral load TND is defined as follows:

- **Target Population:** Non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)
- **Treatment Condition:** 5-days treatment of EDP-938 800 mg vs placebo
- **Endpoint:** Proportion of subjects with RSV RNA viral load TND
- **Population-level summary:** Difference in proportion of subjects treated with EDP-938 800 mg vs. placebo.
- **Intercurrent events and strategies** are described in Table 2-2:

Table 2-2: Summary of Estimands (2, 3, 4) and Strategies for Managing Intercurrent Events - Secondary Efficacy Endpoint

Intercurrent Event	**Strategy for Intercurrent Event**
Treatment Discontinuation	**Treatment policy strategy**: Estimate treatment effect using available data regardless of treatment discontinuation status.
Use of prohibited medications (Protocol, Section 5.8)	**Composite strategy:** After the use of prohibited medications, impute data using each subject's worst result during the entire study.

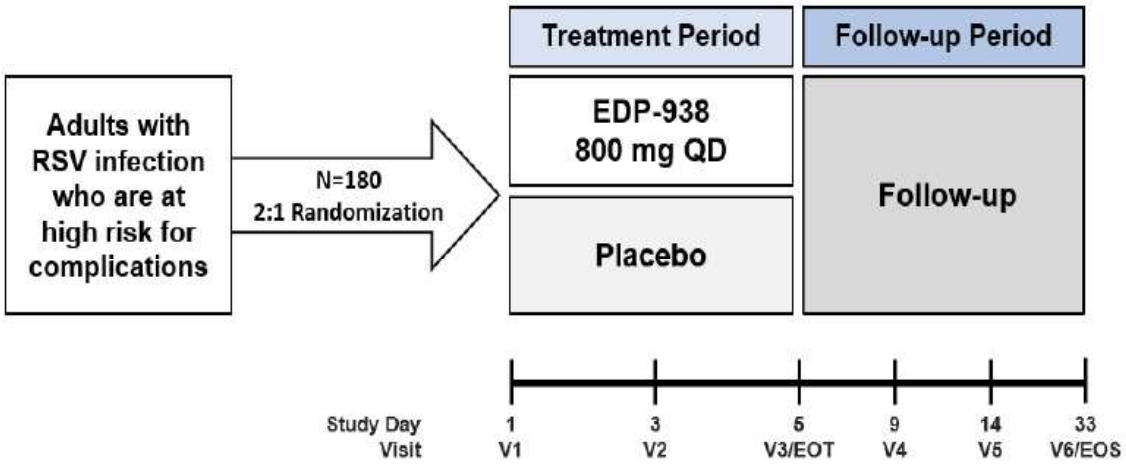
Death	**Composite strategy**: After death, impute data using the worst results from all subjects during the entire study.
Rationale for Strategies	Treatment policy for treatment discontinuation as it is relevant to clinical practice.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 2b, randomized, double-blind, placebo-controlled study of EDP-938 administered orally for the treatment of non-hospitalized adult subjects with confirmed RSV infection who are at high risk for disease progression and complications. Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized in a 2:1 ratio to receive 800 mg of EDP-938 or placebo QD for a total of 5 days and followed for an additional 28 days. Subject randomization will be stratified by the number of high-risk factors (i.e., ≤2 vs. >2) and the duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours). The total proportion of subjects either ≥65 to ≤74 years of age or patients with asthma combined will be capped at 20%. An overview of the study design is shown below in Figure 1. Study site visits and assessments are detailed in the Schedule of Assessments (SoA; Appendix 1).

Figure 1: Study Design



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

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

The study has 3 periods:

- Screening Period will occur on Visit 1 (Day 1) prior to randomization. During this period, subjects will review and sign an initial Rapid Viral Diagnostic Screening ICF. Subjects will undergo NAAT (nucleic acid amplification test) for RSV, SARS-CoV-2, and influenza. Subjects with positive results for RSV and negative for SARS-CoV-2 and influenza virus may proceed for further screening and will sign a Study ICF prior to performing any further study-specific assessments. After signing the Study ICF, subjects will undergo further screening procedures to determine study eligibility, including completing the RiiQ™ diary. Subjects meeting all study criteria and randomized into the study are considered enrolled.
- Treatment Period will be for 5 days, during which 3 study visits are scheduled as follows: Visit 1 (Day 1), Visit 2 (Day 3), and Visit 3/End-of-Treatment (EOT) visit on Day 5.
- Follow-up Period for follow-up assessments from Day 6 to Day 33 with visits on Visit 4 (Day 9), Visit 5 (Day 14) and will conclude at the Visit 6/End-of-Study (EOS) on Day 33 for post-treatment assessments.

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoints

Clinical efficacy:

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

- Percentage of subjects requiring invasive or noninvasive mechanical ventilation;
- Duration of invasive or noninvasive mechanical ventilation;
- Duration of treatment-emergent new use or increased use of medications to treat CHF;
- All-cause mortality.

Antiviral activity:

- RSV RNA viral load area under the curve (AUC) measured in nasopharyngeal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR) from Baseline at Days 3, 5, 9, and 14;
- Percentage of subjects with RSV RNA viral load Target Not Detected (TND) at any point during the study;
- Time to RSV RNA viral load TND;
- RSV RNA viral load change from Baseline at Days 3, 5, 9, and 14;
- Change in infectious RSV viral load over time by a quantitative cell-based infectivity assay.

Pharmacokinetics:

- Plasma concentrations of EDP-938 and its metabolites (EP-024766, EP-024636, EP-024594, and EP-024595).

Safety:

- Safety endpoints include, but are not limited to AEs (including SAEs, severe AEs, and AEs leading to discontinuation of the study drug), and clinically significant changes from baseline in vital sign measurements, pulse oximetry measurements, ECGs, and clinical laboratory test results (including chemistry and hematology).

3.3. Treatments

EDP-938 drug product tablets and the corresponding placebo tablets are supplied as 22 count (200 mg) tablets in white 60-cc high-density polyethylene (HDPE) bottles closed with a child-resistant polypropylene closure. Each HDPE bottle is induction sealed and contains a 1-g silica gel desiccant and a low moisture polyester coil. Subjects are instructed to take the investigational product (800 mg [4*200 mg] of EDP-938 or placebo) orally QD for 5 days.

4. General Statistical Considerations

All analyses will be conducted using SAS Version 9.4 or higher. Unless otherwise stated, a two-sided test will be used at a significance level (alpha) of 0.05 for all analyses. Two-sided 95% confidence intervals will be provided when appropriate. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999."

Continuous data will be described using descriptive statistics (i.e. n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum). For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation (SD)/ standard error (SE) will be displayed to two levels of precision greater than the data collected. If the precision of the values being summarized are too large (e.g. 3 or more decimal places), then limit the precision to two decimal places and follow the rules previously stated above. For derived data, the precision of values will be determined on a case-by-case basis. If n=0, then display n and leave all other statistics blank. If n=1, display "N/A" for SD and SE.

Categorical data will be described using the subject count and percentage in each category. When count data are presented, the percentage will be suppressed when the count is zero. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values where applicable. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places.

Summary Tables and Figures will be presented by treatment group. Tables and Figures values for treatment group will be labelled as follows: "EDP-938", "Placebo". Models will include stratification factors unless an insufficient amount of data exists where convergence or the analysis cannot be performed.

All subject data, including those derived, will be presented in individual subject data listings. Dates will be shown in subject Listings as they have been recorded. Unscheduled visit results will be included in date/time chronological order, within subject listings. All listings will be sorted by subject number, date/time and visit. The treatment group

(randomized) as well as subject's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all subjects randomized.

When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no records for this table/listing."). For analyses where convergence or the analysis cannot be performed, "NC" (not calculable) will be presented in summary tables.

Unless otherwise specified, baseline will be defined as the last non-missing measurement collected on or before the date/time (if applicable) of the first dose of study treatment. 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

For the reporting of this study CDISC SDTM Implementation Guide Version 3.3 and ADaM Implementation Guide Version 1.1 will be applied. A subject will be considered to have completed the study after his/her attendance at the last planned study visit (Day 33± 1 days), or the last unscheduled visit (if any occur), as applicable. For each subject his or her study completion status (Yes/No) is recorded on the End of Study CRF.

4.1 Sample Size

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

4.2 Randomization, Stratification, and Blinding

Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized on Day 1 in a 2:1 ratio to 800 mg of EDP-938 or placebo. Assignment to treatment groups will be determined by a computer-generated random sequence using an IRT. The IRT will be used to assign investigational product to each subject. To achieve between-group comparability, the randomization will be stratified by the number of high-risk factors (i.e., ≤2 vs. >2) and the duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours).

The study will be double-blinded, meaning subjects, investigators, site staff and the CRO/Sponsor study team will be blinded to treatment assignment until the completion of the study. During the study, investigators, site personnel, and blinded CRO/Sponsor study team 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.

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

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the [redacted] Medical Monitor should be notified within 24 hours of unblinding of the treatment and should inform the sponsor's Medical Monitor. Information relating to unblinding (e.g., the reason, date) should be clearly recorded in the subject's study file.

4.3 Analysis Populations

4.3.1 Safety Population

The safety (SAF) population will include all subjects who received at least one dose of study drug. All subjects will be analyzed in the treatment group that corresponds to the study drug received during the study.

4.3.2 Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population will include all randomized subjects positively diagnosed with RSV using the central RT-qPCR quantification who receive at least one dose of assigned study drug. The mITT population will be used for the efficacy analysis. Subjects will be analyzed as randomized.

4.3.3 Per Protocol (PP) Population

The per protocol (PP) population will include all subjects in the mITT population who completed 5-day Treatment Period and do not have major protocol deviations that may unduly influence RiiQ™ symptom scale scores. Subjects will be analyzed according to the treatment randomized.

4.3.4 Pharmacokinetic (PK) Population

The pharmacokinetic (PK) population will include all subjects receiving active study drug and having any measurable plasma concentration of study drug at any timepoint.

4.4 Data Handling Strategy

4.4.1 Study Days and Visit Windows

Study day is defined as the number of days from the date of first dose. Day 1 is the date of the first dose. For assessments or events that occur after the first dose date, study day is calculated as the date of interest minus first dose date plus 1 day. For assessments or events

that occur before the first dose date, study day is calculated as the date of interest minus the first dose date.

Analysis visits are based on study day as defined above and will be used for by-visit analyses or summaries unless otherwise specified in the respective analysis sections. Unscheduled visits and visits performed for early discontinuation will not be included in the by-visit summary or analyses. Laboratory results from unscheduled visits will be included in the shift tables and listings.

Subjects who prematurely discontinue study drug but remain in the study to complete the follow-up period are requested to complete the EOT visit, and this visit will be labeled as "Early Disc/EOT".

Subjects who withdraw from the study are requested to complete the EOS procedure and this visit will be labeled as "Early Disc/EOS".

Analysis visit windows are described in the tables below.

Table 4-1 Vital signs, oxygen saturation, ECG, safety laboratory tests, RSV RNA quantitation of viral load, EQ-5D-5L

Analysis Visit #	Analysis Visit Label	Target Day*	Derivation	Visit Window
1	Day 1	1	Based on date of assessment for V1, date of first dose of study drug	
3	Day 3	3	Based on date of assessment for V2	2 to 4**
5	Day 5	5	Based on date of assessment for V3 EOT	4 to 6**
9	Day 9	9	Based on date of assessment for V4	8 to 10
14	Day 14	14	Based on date of assessment for V5	13 to 15
33	Day 33	33	Based on date of assessment for V6 EOS	32 to 34

*When data are not collected on the target day, the data collected on the nearest date are used. For time to event analyses, the data collected on the actual day are used.
ECG is collected at Screening, V3 and V6. EQ-5D-5L is collected at each visit, excepting V2 (Day 3).

**The visit on Day 4 should be mapped to analysis Visit #3 unless there is an earlier analysis Visit #3.

Table 4-2 RiiQ™, PGI-C, PGI-S and Return to Usual Health/Activities questionnaires

Analysis Visit #	Analysis Visit Label	Target Day*	Derivation
1	Day 1	1	Study day =1
2	Day 2	2	Study day =2
3	Day 3	3	Study day =3
4	Day 4	4	Study day =4
5	Day 5	5	Study day =5
6	Day 6	6	Study day =6
7	Day 7	7	Study day =7
8	Day 8	8	Study day =8
9	Day 9	9	Study day =9
10	Day 10	10	Study day =10
11	Day 11	11	Study day =11
12	Day 12	12	Study day =12
13	Day 13	13	Study day =13
14	Day 14	14	Study day =14
15	Day 15	15	Study day =15
16	Day 16	16	Study day =16
17	Day 17	17	Study day =17
18	Day 18	18	Study day =18
19	Day 19	19	Study day =19
20	Day 20	20	Study day =20
21	Day 21	21	Study day =21
22	Day 22	22	Study day =22
23	Day 23	23	Study day =23

24	Day 24	24	Study day =24
25	Day 25	25	Study day =25
26	Day 26	26	Study day =26
27	Day 27	27	Study day =27
28	Day 28	28	Study day =28
29	Day 29	29	Study day =29
30	Day 30	30	Study day =30
31	Day 31	31	Study day =31
32	Day 32	32	Study day =32
33	Day 33	33	Study day =33

* RiiQ™ , PGI-C, PGI-S and Return to Usual Health/Activities questionnaires are completed once per day at approximately the same time of day (+/- 1 hour), pre-dose.

Table 4-3 Pharmacokinetics

Analysis Visit #	Analysis Visit Label	Target Day*	Derivation
1	Visit 1	1	Based on nominal visit of V1
3	Visit 2	3	Based on nominal visit of V2
5	Visit 3	5	Based on nominal visit of V3
97	Early Disc/EOT	NA	Based on nominal visit of EOT if subject discontinues treatment but remains in the study*
98	Early Disc/EOS	NA	Based on nominal visit of EOS if subject discontinues treatment and does not remain in the study*

*If a participant discontinues treatment prior to Visit 3 but remains in the study, a PK sample should be taken at the approximate time as the NP swab at the EOT Visit. The EOT visit should occur within 24 hours following the last dose of study drug. If the subject discontinues treatment prior to Visit 3 and does not remain in the study, a PK sample should be taken at the approximate time as the NP swab at the EOS visit. The EOS visit should occur within 24 to 48 hours after discontinuation.

4.4.2 Missing Date Imputation

Imputation rules for missing or partial AE start/end dates are defined as:

- Only Day of AE start date is missing:
  - If the AE start year and month are the same as that for the first dose date, then:
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date.
  - Otherwise, impute the AE start day as 1.
- If Day and Month of AE start date are missing:
  - If AE start year = first dose year, then:
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date.
  - Otherwise, impute the AE start MONTH as January and the DAY as 1.
- If Year of AE start date is missing:
  - If the year of AE start is missing or AE start date is completely missing, then query site and leave as missing.
- For missing and partial AE end dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.

Imputation rules for missing or partial medication/therapy start/stop dates are defined below:

- If only Day of CM start date is missing:
  - If the CM start year and month are the same as that for the first dose date, then:
    - If the full (or partial) CM end date is NOT before the first dose date or CM end date is missing, then impute the CM start day as the day of first dose date.
  - Otherwise, impute the CM start day as 1.
- If Day and Month of CM start date are missing:

  - If CM start year = first dose year, then:
    - If the full (or partial) CM end date is NOT before the first dose date or CM end date is missing, then impute the CM start Month and Day as the Month and Day of first dose date.
  - Otherwise, impute the CM start MONTH as January and the DAY as 1.
- If Year of CM start date is missing:
  - If the year of CM start is missing or CM start date is completely missing, then query site and leave as missing.
- For missing and partial CM end dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.

5 Subject Disposition

5.1 Disposition

All subjects who provided informed consent will be included in a summary of subject accountability. The number and percentage of randomized, treated, randomized and not treated, as well as the number and percentage of subjects in each analysis population (SAF, mITT, PP, PK) will be summarized by treatment group and overall. The number of subjects excluded from analysis sets and reasons for exclusion will also be summarized. The denominator for the calculation of percentages will be the number of subjects randomized.

The following categories will also be summarized for subject disposition:

- Completed study drug per the protocol;
- Discontinued study drug early and the reason for discontinuation;
- Completed the study;
- Withdrew from the study early and the reason for withdrawal.

Subjects will be considered as completing treatment unless dosing was permanently withdrawn prior to the end of treatment visit.

5.2 Protocol Deviations

All protocol deviations (PDs) will be entered and tracked in [redacted] Clinical Trial Management System (CTMS) by the study team throughout the conduct of the study in accordance with [redacted] Study Deviation Rules Document.

The PDs from the CTMS will be reviewed by the study team prior to unblinding and closure of the database, and a final list of significant protocol deviations, which may affect primary efficacy assessment and hence be excluded from the PP population (considered as major protocol deviations in the protocol), will be documented in the TMF prior to unblinding.

The sponsor will review data and determine if any additional criteria that are not listed in the CTMS may unduly influence the primary efficacy outcomes and therefore be excluded from the PP population prior to unblinding.

Significant protocol deviations will be summarized by treatment group using the mITT population. A listing will be also provided for significant protocol deviations.

6 Demographics and Baseline Characteristics

6.1 Demographics

A summary of demographics and baseline information will be presented descriptively by treatment group and for all subjects in the SAF and mITT populations. No statistical testing will be performed to compare between treatment groups on demographic and baseline characteristics.

Age (years), height (cm), weight (kg), BMI (kg/m^2), RSV viral load as measured by RT-qPCR (log10 copies/mL), RSV serology, total RiiQ^{TM} symptom score and scores from each symptom domain (LRTD, URTD, systemic symptoms), and scores from each impact domain (daily activities, emotion, social relationship) collected at baseline will be summarized using descriptive statistics.

The number and percentage of subjects with categorical baseline characteristics including age group (<65, ≥ 65 to ≤74, >74 years), sex (Male, Female), child-bearing potential (Yes, No) and postmenopausal status (Yes, No), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple [e.g, subjects with multiple races], Not Reported), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported), smoking history (Current, Previous, Never), RSV subgroup (RSV A, RSV B), stratification factors (number of high-risk factors [≤2, >2], duration of respiratory symptoms [≤48 hours, >48 hours to ≤72 hours]), CHF (Yes, No), COPD (Yes, No), asthma (Yes, No), past RSV vaccination (Yes, No) will also be reported. Percentages will be based on the total number of subjects in the SAF and mITT populations.

Subject demographic and baseline characteristics will also be presented in a listing.

6.2 Medical History

6.2.1 General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or higher. The number and percentage of subjects with CHF, COPD, asthma, and additional medical history will be summarized by treatment group and for each system organ class and preferred term. Percentages will be calculated based on number of subjects in the SAF population.

Subject medical history data including the diagnosis and status of CHF, COPD and asthma, and additional medical history will also be presented in a listing.

7 Treatments and Medications

7.1 Prior and Concomitant Medications

All medications taken within 1 month of signing informed consent and during the study throughout the end of the study will be collected on the CRF. All medications will be coded according to the World Health Organization (WHO) Drug Dictionary (WHO Drug Global SEP 2022 B3 or higher).

Prior medications are defined as those medications with a start date prior to the date of first dose of study drug. Concomitant medications are defined as any medications with a start date on or after the date of first dose of study drug or any medications with a start date prior to the date of first dose and a stop date after the date of first dose. Furthermore, a medication could be labeled as both a prior and concomitant medication if it was started prior to the first dose of study drug and continued after the first dose of study drug.

The number and percentages of subjects with at least one prior medication will be summarized by treatment group. The number and percentages of all prior medications will be summarized by treatment group and overall and listed by Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup) and preferred term. All summaries will be performed using the SAF population.

The number and percentages of subjects with at least one concomitant medication will be summarized by treatment group and overall. The number and percentages of all concomitant medications will be summarized by treatment group and listed by Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup) and preferred term. All summaries will be performed using the SAF population.

Prior and concomitant medications, including prohibited medication, will also be presented in a listing. Details for imputing missing or partial start and/or stop dates of medications are described in Section 4.4.2.

7.2 Prior and Concomitant Therapies

Prior and concomitant therapies include surgical interventions, procedures, or non-medication treatments (e.g. supplemental oxygen). All reported therapies will be coded using MedDRA Version 25.1 or higher and classified by system organ class (SOC) and preferred term (PT).

Prior therapies are defined as those therapies with a start date prior to the date of first dose of study drug. Concomitant therapies are defined as any therapies with a start date on or after the date of first dose of study drug or any therapies with a start date prior to the date of first dose and a stop date after the date of first dose.

Concomitant therapies will be summarized by treatment group based on the reported categories, as appliable, and SOC and PT. Both prior and concomitant therapies will be presented in a listing. Details for imputing missing or partial start and/or stop dates of therapies are described in Section 4.4.2.

7.3 Study Treatments

7.3.1 Extent of Exposure

Duration of study drug in days will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption (i.e. missed dose). Study drug exposure will be summarized by treatment group using the SAF and mITT populations.

A summary of each subject's exposure will also be presented in a listing.

7.3.2 Treatment Compliance

The study drug compliance rate will be calculated as: 100 * [total number of days dosed/ (total number of days planned per protocol)] except for subjects who discontinued treatment or study during the treatment period. The number of days dosed (for subjects who were lost to follow-up) or the number of days since first dose to the day of drug refusal (for subjects who refused to take study drug) is used as the denominator. Any dose taken will be counted as a day dosed (e.g., 1 tablet taken on Day 1 and 4 tablets taken on Days 2-5 would be counted as 5 days dosed).

Study drug compliance rate will be summarized for all subjects in the SAF and mITT populations with descriptive statistics by treatment group. Additionally, the number and percentages of subjects in each compliance rate category (<80% and ≥80%) will be also presented by treatment group.

A summary of each subject's compliance rate will also be presented in a listing.

8 Efficacy Analysis

All efficacy analysis will be based on mITT population unless otherwise specified. No adjustment will be made for multiplicity. Relevant subject data listings will be provided to support all efficacy analyses.

8.1 Overview of Statistical Methods and Sensitivity Analyses

Analysis methods and sensitivity analyses in estimation of the primary estimand and selected secondary estimands are summarized below.

8.1.1 Estimand 1 (Primary)

Estimand Description (Scientific Question of Interest): What is the hazard ratio of time to resolution of RSV LRTD symptoms with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ⩾65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation, and taking it censored at Day 33 if resolution is not achieved prior to study discontinuation, the use of prohibited medications or death.
Analysis Set: mITT
Imputation/Data/Censoring: Use time to resolution if resolution achieved prior to study discontinuation or the use of prohibited medications or death; Censoring at Day 33 if study discontinuation or death or prohibited medication use or no resolution at end of study.
Analysis Model/Method: A Cox Proportional Hazards model including treatment group, randomized stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)) and baseline RiiQ™ score. Stratified log-rank test will be used compare EDP-938 to placebo. The Efron method will be imposed on ties if the exact method does not converge. The estimated hazard ratio with associated 2-sided 95% CI and p-value comparing EDP-938 and placebo will be provided.
Sensitivity and Supplementary Analyses Sensitivity: (1) MI approach and pooling results using Rubin's method (Rubin D.B., 1987). (2) Reference-based multiple imputation and pooling results using Rubin's method. (3) repeated on PP population. Supplementary: (1) Kaplan-Meier method to derive the median event time with 95% CI for each treatment. (2) Alternative definition of resolution (complete resolution) – see Section 8.5.1.

8.1.2 Estimand 2 (Secondary)

Estimand Description (Scientific Question of Interest): What is mean difference in the change from baseline in severity of RSV LRTD symptoms at each key post-baseline visit with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ⩾65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation and the worst result during the entire study is taken in the use of prohibited medications or death.

Analysis Set: mITT
Imputation/Data/Censoring: In the case of use of prohibited medications or death, the worst result during the entire study is used as described in Section 2.2.1.
Analysis Model/Method: MMRM with unstructured covariance including terms for treatment group, Day and stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)) as fixed effects, and the associated baseline as a covariate, treatment group by Day interaction, stratification factor by Day interaction, associated baseline by Day interaction. If the unstructured covariance matrix fails to converge, then the following covariance structure will be assessed in this order: autoregressive, compound symmetry, Toeplitz. Least squares means and differences with 95% CIs and p-values will be presented. See Section 8.3.1 for further details.
Sensitivity and Supplementary Analyses Sensitivity: Sensitivity: (1) MI approach and pooling results using Rubin's method. (2) Reference-based multiple imputation and pooling results using Rubin's method.

8.1.3 Estimand 3 (Secondary)

Estimand Description (Scientific Question of Interest): What is mean difference in the change from baseline in RSV RNA viral load at each key post-baseline visit with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ⩾65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation and the worst result during the entire study is taken in the use of prohibited medications or death.
Analysis Set: mITT
Imputation/Data/Censoring: In the case of use of prohibited medications or death, the worst result during the entire study is used as described in Section 2.2.1.
Analysis Model/Method: MMRM with unstructured covariance including terms for treatment group, Day and stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)) as fixed effects, and the associated baseline as a covariate, treatment group by Day interaction, stratification factor by Day interaction, associated baseline by Day interaction. If the unstructured covariance matrix fails to converge, then the following covariance structure will be assessed in this order: autoregressive, compound symmetry, Toeplitz. Least squares means and differences with 95% CIs and p-values will be presented. See Section 8.3.1 for further details.
Sensitivity and Supplementary Analyses Sensitivity: Sensitivity: (1) MI approach and pooling results using Rubin's method. (2) Reference-based multiple imputation and pooling results using Rubin's method.

8.1.4 Estimand 4 (Secondary)

Estimand Description (Scientific Question of Interest): What is difference in proportion of subjects with RSV RNA viral load TND with 5-days treatment of EDP-938 800 mg vs placebo in non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ⩾65 years or high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)? Comparison is made irrespective of treatment discontinuation and the worst result during the entire study is taken in the use of prohibited medications or death.
Analysis Set: mITT
Imputation/Data/Censoring: In the case of use of prohibited medications or death, the worst result during the entire study is used as described in Section 14.2.1.
Analysis Model/Method: Cochran-Mantel Haenszel test controlling for the stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)). See Section 8.3.2 for details.
Sensitivity and Supplementary Analyses Sensitivity: Sensitivity: (1) MI approach and pooling results using Rubin's method. (2) Reference-based multiple imputation and pooling results using Rubin's method.

8.2 Primary Efficacy Endpoint

The primary efficacy endpoint is time to resolution of RSV LRTD symptoms (cough, short of breath, wheezing, coughing up phlegm / sputum) as assessed by the RiiQ™ symptom scale through Day 33.

The RiiQ™ records 13-item RSV symptom scores and 3 additional impact scales (Section 14.4.1). The 13-item diary uses a 4-point scale that consists of grading symptoms on the scale of 0 to 3, where Grade 0 is None, Grade 1 is Mild, Grade 2 is Moderate, and Grade 3 is Severe.

The 13 RSV symptoms assessed will comprise 3 domains:

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

8.2.1 Primary Analysis

The primary efficacy analysis will be based on mITT population and performed on time to resolution of RSV LRTD symptoms as assessed by RiiQ™ symptom scale through Day 33. A Cox Proportional Hazards model including treatment group, randomized stratification factor (duration of respiratory symptoms (≤48 hour vs. >48 hour to ≤72 hours), and baseline RiiQ™ score will be used to assess hazards ratio. Stratified log-rank test will be used compare EDP-938 to placebo. The Efron method will be imposed on ties

if the exact method does not converge. The estimated hazard ratio with associated 2-sided 95% CI and p-value comparing EDP-938 and placebo will be provided.

Time to resolution (in days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by RiiQ™ score is zero or 1. Consecutive timepoints is defined as two consecutive timepoints planned per protocol. The resolution of RSV LRTD symptoms is assessed by the RiiQ™ symptom scale through Day 33. Subjects without resolution prior to Day 33 will be censored at Day 33. Subjects who meet the resolution definition at baseline (score of 0 or 1 at Baseline and Day 2) will be excluded from the analysis.

The Kaplan-Meier method will be applied to time to resolution of RSV LRTD symptoms to derive the median event time and a CI for the median for each treatment arm. A Kaplan-Meier curve will display the probability estimates with resolution. Descriptive statistics on the graph will include the median and 95% CI at a minimum.

For subjects who withdraw or are withdrawn early from the study prior to achieving resolution, the reason for withdrawal will be considered. If a subject withdraws or is withdrawn due to a drug related AE regardless of resolution status, that subject will be censored at Day 33 in the analysis. Subjects who withdraw from the study due to other reasons and do not achieve resolution will be censored at Day 33. The follow-up time for these subjects will be censored on Day 33. Censoring also applies to subjects who complete study but do not have resolution.

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

8.3 Secondary Efficacy Endpoints

8.3.1 Clinical Efficacy

The following secondary endpoints will be compared between EDP-938 and placebo using the mITT set with the same method described in Section 8.2.1. The detail of the questionnaire of RiiQ™, PGI-S, PGI-C, EuroQol 5 Dimensions 5 Levels, Adult Return to Usual Health, and Adult Return to Usual Activities are described in Section 14.4.1 to Section 14.4.4.

- Time to resolution of each separate RSV LRTD symptom as assessed by RiiQ™ symptom scale score;
    - Time to resolution (days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) separately as assessed by RiiQ™ score is zero or 1.

- Time to resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ symptom scale score;
    - Time to resolution (days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) and each of the 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ score is zero or 1.
- Time to resolution of all RSV symptoms as assessed by RiiQ™ symptom scale score;
    - Time to resolution (days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the 13 RSV symptoms as assessed by RiiQ™ score is zero or 1.
- Time to resolution of Upper Respiratory Tract Disease (URTD) (sore throat and nasal congestion), LRTD, and 2 systemic symptoms through Day 33 as assessed by RiiQ™ symptom scale score;
    - Time to resolution (days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the 2 URTD symptoms (nasal congestion and sore throat) and each of the 4 LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) and each of the 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ score is zero or 1.
- Time to no or mild impact of RSV disease on daily activities, emotions, and social relationships as assessed by RiiQ™ impact scale score;
    - Time to no or mild impact (days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the 3 impact scores (daily activities, emotions, and social relationships) of RSV disease as assessed by RiiQ™ score is zero or 1.
- Time to resolution of RSV infection symptoms as assessed by Patient Global Impression of Severity (PGI-S) scale score;
    - Time to resolution (days) is defined as the time from first dose to first of 2 consecutive timepoints where the response assessed by PGI-S is “None”.
- Time to improvement in RSV disease as assessed by Patient Global Impression of Change (PGI-C) scale score;
    - Time to improvement (days) is defined as the time from first dose to first timepoint where the response assessed by PGI-C is “Much better”.
- Time to return to usual health as assessed by ‘Adult Return to Usual Health’ question;

  - Time to return to usual health (days) is defined as the time from first dose to first timepoint where the response as assessed by Adult Return to Usual Health is "Yes" (1).

- Time to return to usual activities as assessed by the 'Adult Return to Usual Activities' question;
  - Time to return to usual activities (days) is defined as the time from first dose to first timepoint where the response as assessed by Adult Return to Usual Activities is "Yes" (1).

The following continuous endpoints will be compared between EDP-938 and placebo using a mixed-effect model for repeated measures (MMRM), using sample SAS code described in Section 14.5.1. The model includes treatment group, Day (2, 3, 5, 7, 9, 14, and 33 for RiiQ related endpoints and 5, 9, 14, 33 for EQ-5D-5L) as class variable, and stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)) as fixed effects, and the associated baseline as a covariate, treatment group by Day interaction, stratification factor by Day interaction, associated baseline by Day interaction, as factors. Treatment groups will be compared at scheduled post-baseline timepoints (Days 2, 3, 5, 7, 9, 14, and 33 for RiiQ related endpoints and 5, 9, 14, 33 for EQ-5D-5L). An unstructured variance-covariance matrix will be imposed. If the unstructured covariance matrix fails to converge, then the following covariance structure will be assessed in this order: autoregressive, compound symmetry, Toeplitz. The Satterthwaite approximation will be used to estimate the denominator degrees of freedom. The least-squares means and two-sided 95% CIs will be presented for individual groups and the difference between groups. The p-value will be presented for the difference between treatment groups at each post-baseline timepoint. This analysis will be performed using SAS Proc Mixed.

Descriptive statistics will also be generated for the actual values, change from baseline and percent change from baseline for each endpoint below.

- Change from Baseline in severity of RSV LRTD symptoms through Day 33 as assessed by RiiQ™ symptom scale score;
- Change from Baseline for RiiQ™ impact scale score through Day 33;
- Change from Baseline for Health-Related Quality of Life (HRQOL) through Day 33 as assessed by EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire;

The following secondary endpoints will be summarized descriptively.

- Duration of treatment-emergent use of antibiotics;
- Duration of treatment-emergent new use or increased dose of bronchodilators or systemic or inhaled corticosteroids;
- Duration of new or increased oxygen supplementation;
- Duration of hospitalization for RSV infection or other causes;
- Duration of ICU stay for RSV infection or other causes;

- Duration of invasive or noninvasive mechanical ventilation;
- Duration of treatment-emergent new use or increased use of medications to treat CHF;

The following secondary endpoints of the percentage, or the proportion of subjects at Day 33 will be summarized for each treatment group and will be analyzed using a Cochran-Mantel-Haenszel test controlling for the stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)). Additionally, the number and proportion of subjects with each endpoint will be summarized for each treatment group, and their respective 95% CIs will be reported based on the normal approximation. The adjusted difference in proportions between 2 treatment groups will be computed as a weighted average of the treatment differences across strata using the Mantel-Haenszel weights, and the associated 95% CI will be provided using Sato variance estimator (Sato, 1989).

- Percentage of participants with post-baseline RSV-related complications;
    - RSV-related complications include RSV pneumonia, bacterial lung infections, bacteremia, acute respiratory failure, sepsis, or septic shock.
- Percentage of subjects with new antibiotic use, or new or increased use of bronchodilators, systemic or inhaled corticosteroids, or oxygen supplementation;
- Percentage of subjects with unscheduled medically attended visits (i.e., outpatient clinic, urgent care center, or emergency room visits) for RSV infection or other causes;
- Percentage of subjects requiring hospitalization for RSV infection or other causes;
- Percentage of subjects requiring admission to intensive care unit (ICU) for RSV infection or other causes;
- Percentage of subjects requiring invasive or noninvasive mechanical ventilation;
- All-cause mortality.

8.3.2 Antiviral activity

For antiviral activity analysis, the RSV RNA viral load will be measured in nasopharyngeal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR) on Days 1, 3, 5, 9 and 14. Viral load values reported as TD (Target Detected, but below LLOQ) will be set to an average of LOD (limit of detection) and LLOQ (lower limit of quantification). Viral load values reported as TND (Target Not Detected) will be set to zero. Viral load data will be transformed using a log10 scale before analyses. In case of zero value, the log transformed value will be also set as zero. For the RT-qPCR assay used for detection and quantification of RSV A and RSV B, the LLOQ is

1000 copies/mL for RSV A and 250 copies/mL for RSV B and the LOD is 620 copies/mL for RSV A and 80 copies/mL for RSV B.

The RSV type of each subject will be decided based on the RSV-A RT-qPCR test result and the RSV-B RT qPCR as follows: after the imputation of TD and TND, the RSV RT-qPCR Log10 Copies/mL results from all nasopharyngeal swab specimen collection time points will be summed for the RSV-A RT-qPCR test result and separately summed for the RSV-B RT-qPCR test result. The RSV subtype (A or B) classification of the subject's infection will be assigned to the RSV subtype corresponding to the RSV RT-qPCR assay which generates the greatest sum, as long as this resulting RSV subtype data is consistent with biologic plausibility. After RSV subtype classification, only the viral load data from that corresponding RSV RT-qPCR assay will be used for further analysis.

- RSV RNA viral load AUC measured in nasopharyngeal swab samples by RT-qPCR from Baseline at Days 3, 5, 9, and 14

  The RSV RNA viral load AUC will be calculated using the trapezoid rule (Matthews et al., 1990). The AUC will require at least 2 non-missing data points. Subjects with missing or undetectable RSV RNA viral load at baseline will be excluded from the analysis. It will be based on all available assessments collected on Days 1/baseline, 3, 5, 9, 14 and the actual date/time of each assessment will be used for the calculation. For the baseline viral load (Day 1), time is set as 0. For each assessment post first dose, the actual time in days is computed as difference between the date/time of the assessment and the date/time of the first dose. The AUC is also standardized to 14 days by multiplying $14/t_{last}$ where t_{last} is the actual time in days of the last available assessment. Additionally, the AUC from Day 1 through Day 3, the AUC from Day 1 through Day 5, and the AUC from Day 1 through Day 9 will be also derived and standardized similarly as for AUC from Day 1 through Day 14. Additional assessments may be added to the existing windows depending on data availability.

  An ANCOVA model with treatment group and stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)) as factors, and the baseline RSV RNA viral load as a covariate will be performed for the RSV RNA viral load AUC from Day 1 through Day 3, from Day 1 through Day 5, and from Day 1 through Day 9, and from Day 1 through Day 14, respectively. Treatment groups will be compared using a type III sum-of-squares. The least-squares means, SEs and two-sided 95% confidence intervals (CI) will be presented for individual groups and the difference between groups.

- Percentage of subjects with RSV RNA viral load TND at any point during the study

The proportion of subjects with RSV RNA viral load TND will be analyzed on Days 1, 3, 5, 9, and 14, respectively. Treatment groups will be compared at each visit day using a Cochran-Mantel Haenszel test controlling for the stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)). Additionally, the number and proportion of subjects with RSV RNA viral load TND will be summarized for each treatment group, and their respective 95% CIs will be reported based on the normal approximation. The adjusted difference in proportions between the 2 treatment groups will be computed as a weighted average of the treatment differences across strata using the Mantel-Haenszel weights, and the associated 95% CI will be provided using the Sato variance estimator (Sato, 1989).

- Time to RSV RNA viral load TND

  Time to RSV RNA viral load TND will be analyzed using a Cox Proportional Hazards model. Stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)), baseline RSV RNA viral load will be included. Time to RSV viral load TND will be defined as the time between the date of first dose to the first date of achieving viral load TND. Subjects who discontinue early without achieving viral load TND will be censored on Day 14 assessment date. A Kaplan-Meier curve will display the probability estimates of achieving RSV RNA viral load TND. Descriptive statistics on the graph will include the median and 95% confidence interval at a minimum.

- RSV RNA viral load change from Baseline at Days 3, 5, 9, and 14

  An MMRM approach as described in Section 14.5.1 will be used to the RSV RNA viral load change from baseline at Days 3, 5, 9, and 14. Descriptive statistics will also be displayed for RSV RNA viral load and change from baseline by visit (Days 1, 3, 5, 9 and 14) and will include at a minimum the number of non-missing measurements, mean, standard deviation, median, minimum, 25th percentile, 75th percentile, maximum, and 95% CI for the mean.

The following line graph of RSV RNA viral load will be produced:

Observed mean viral load ± 95% confidence interval by Days (1, 3, 5, 9 and 14) for each treatment group.

- RSV Serology

  Samples for RSV serology assessment using the RSV neutralization antibody assay are collected at Visit 1 (baseline) and at Visit 6 (EOS). Change from baseline in RSV antibody levels will be analyzed. RSV serology results will be reported in a listing. For subgroup analysis purpose, RSV neutralization titer will be categorized as follows:

  - High: >=median of serology value
  - Low: <median of serology value.

- Change in infectious RSV viral load over time by a quantitative cell-based infectivity assay

  An MMRM approach described in Section 14.5.1 will be used for change from baseline in infectious RSV viral load at Days 3, 5, 9, and 14. Descriptive statistics will also be displayed for change in infectious RSV viral load over time by a quantitative cell-based infectivity assay.

8.4 Sensitivity Analysis

8.4.1 Primary Endpoint

Sensitivity analysis will be conducted on the missing data for the primary endpoint (Estimand 1) for the resolution of RSV LRTD symptoms. Multiple imputation techniques will be applied to the primary analysis model (Section 14.2) and performed sensitivity analysis using Robin's rules via SAS PROC MIANALYZE.

Sensitivity analysis will also be performed using reference-based multiple imputation (Section 13.3).

The primary efficacy analysis will be repeated on the PP population.

8.4.2 Selected Secondary Endpoints

Sensitivity analysis will be performed for the secondary endpoints below (Estimand 2, 3, and 4) using multiple imputation and reference-based multiple imputation as in section 13.2 and section 13.3.

- Change from baseline in severity of RSV LRTD symptoms through Day 33 as assessed by RiiQ^{TM} symptom scale score;
- RSV RNA viral load change from baseline at Days 3, 5, 9, and 14;
- Percentage of subjects with RSV RNA viral load Target Not Detected (TND) at any point during the study.

8.5 Additional Analysis

8.5.1 Primary Endpoint

Additional analyses for the primary endpoint (Estimand 1) will be conducted as described in Section 8.2.1 using the mITT population with the following definition.

- Time to complete resolution (in days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough,

short of breath, wheezing, coughing up phlegm [sputum]) as assessed by RiiQ™ score is zero. The last timepoint where the score is 0 is considered 'complete'.

8.5.2 Selected Secondary Endpoint

Additional analyses for the following secondary endpoints will be conducted as described in Section 8.2.1 using the mITT population with the following definition.

- Time to complete resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ symptom scale score;
    - Time to complete resolution (days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the four LRTD symptoms (i.e., cough, short of breath, wheezing, coughing up phlegm [sputum]) and each of the 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ score is zero. The last timepoint where the score of 0 is considered 'complete'.
- Time to complete resolution of all RSV symptoms as assessed by RiiQ™ symptom scale score;
    - Time to complete resolution (days) is defined as the time from first dose to first of 2 consecutive timepoints where each of the 13 RSV symptoms as assessed by RiiQ™ score is zero. The last timepoint where the score of 0 is considered 'complete'.

8.6 Subgroup Analysis

Subgroup analyses will be performed on the primary (Estimand 1) and selected secondary efficacy endpoints (Estimand 2, 3, and 4). The following baseline variables may be considered, if there are enough subjects in the subgroups to support the planned analyses:

- Sex (female vs male);
- Region (US vs ex-US);
- Race (White vs Others)
- RSV neutralization titer (High vs Low);
- Duration of respiratory symptoms (≤48 hours vs >48 hours to ≤72 hours);
- RSV subset (RSV-A vs RSV-B).
- Presence of individual risk factors: to be confirmed once enrollment is close to be completed.
    - Age (<65 years of age vs >=65 to ≤74 years of age vs >74 years of age);
    - CHF (Yes vs No);
    - COPD (Yes vs No);

- Asthma (Yes vs No).

8.6.1 Primary Endpoint

The analysis for the primary endpoint will be similar to the analysis described in Section 8.2.1 with subgroup and subgroup-by-treatment interaction included in the model.

8.6.2 Selected Secondary Endpoints

The selected secondary efficacy endpoints are as follows:

- RSV RNA viral load change from Baseline at Days 3, 5, 9, and 14;
- Percentage of subjects with RSV RNA viral load TND at any point during the study;
- Change from Baseline in severity of RSV LRTD symptoms through Day 33 as assessed by RiiQ^{TM} symptom scale score.

The MMRM described in Section 8.3.1 will be used with subgroup and subgroup-by-treatment-by-Day interaction included in the model instead of treatment group-by-Day interaction.

8.7 Additional Subgroup Analysis

The following subgroup analyses will be performed on the primary (estimand 1) and the secondary endpoints for the complete resolution of RSV symptoms as described in Section 8.5 with subgroup and subgroup-by-treatment interaction included in the model, if allowed by the data.

- Duration of respiratory symptoms (≤48 hours vs >48 hours to ≤72 hours);
- CHF (Yes vs No);
- COPD (Yes vs No);

The following endpoints will be analyzed for the higher risk sub-populations, defined below

- Primary endpoint (estimand 1);
- Time to resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ symptom scale score;
- Time to resolution of all RSV symptoms as assessed by RiiQ™ symptom scale score;
- Time to complete resolution of RSV Lower Respiratory Tract Disease (LRTD) symptoms (cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) symptom scale through Day 33;

- Time to complete resolution of LRTD symptoms and 2 systemic symptoms (feeling feverish and fatigue [tiredness]) as assessed by RiiQ™ symptom scale score;
- Time to complete resolution of all RSV symptoms as assessed by RiiQ™ symptom scale score.

Higher risk sub-populations:

- All subjects in the mITT population excluding those who are <65 years of age with asthma as the only condition that predisposes to complications after RSV infection;
- All subjects in the mITT population excluding those who are ≥65 to ≤74 years of age with no other condition that predisposes to complications after RSV infection;
- All subjects in the mITT population excluding (1) those who are <65 years of age with asthma as the only condition that predisposes to complications after RSV infection and (2) those who are ≥65 to ≤74 years of age with no other condition that predisposes to complications after RSV infection.

9 Safety Analysis

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

9.1 Adverse Events

Adverse events will be coded using MedDRA Version 25.1 or higher and summarized by system organ class (SOC) and preferred term (PT) and treatment group. All subjects in the SAF Population will be included in the summaries. AEs will be classified as pre-treatment AEs and treatment emergent adverse events (TEAEs) and are defined as follows:

- Pre-treatment AE: A pre-treatment event is any event that meets the criteria for an AE/SAE and occurs after the subject signs the Rapid Viral Diagnostic Screening ICF but before receiving the first administration of study drug.

- TEAE: A TEAE is defined as an AE occurring or worsening on or after the first dose of study drug.
- Treatment-Related AEs: AE will be defined as related if causality is related or possibly related. AEs where the causality is missing will be assumed to be related in table summaries but will be presented as missing in the listings.
- Grade AEs: Grade AEs (serious and non-serious) in accordance with the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) Version 5 as follows: Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), Life-threatening (Grade 4), Death (Grade 5). AEs with missing severity will be assumed to be severe in tables summaries but will be presented as missing in the listings.

Where a subject has the same adverse event, based on preferred terminology, reported multiple times, the subject will only be counted once at the preferred terminology level in adverse event frequency tables. Where a subject has multiple adverse events within the same system organ class, the subject will only be counted once at the system organ class level in adverse event frequency tables. When reporting adverse events by severity, in addition to providing a summary table based on the event selection criteria detailed above, summary table will also be provided based on the most severe event - independent of relationship to study treatment.

Summaries of AEs will include the following:

- Overall summary of TEAEs including the number of TEAEs and the number and percentage of subjects with any of the following: TEAEs, study drug related TEAEs, maximum severity TEAE according to NCI-CTCAE scale, TEAEs by severity, TEAEs leading to study drug discontinuation, TEAEs leading to death, serious TEAEs, and study drug related serious TEAEs.
- TEAEs By SOC and PT
- Study Drug-Related TEAEs – by SOC and PT
- TEAEs of Grade 3 or Higher – by SOC and PT
- TEAEs by Maximum Grade – by SOC and PT
- TEAEs leading to study drug discontinuation – by SOC and PT
- AEs leading to death – by SOC and PT
- Serious TEAEs – by SOC and PT
- Study Drug-Related Serious TEAEs – by SOC and PT

9.2 Clinical Laboratory Evaluation

Laboratory assessments (including chemistry and hematology) will be reported as mean change from Baseline across scheduled visits, and as the incidence rate of shift change from Baseline. Laboratory results will be graded using NCI-CTCAE version 5. Shift from Baseline tables will be generated for each treatment group.

Change from baseline will also be displayed as treatment-emergent abnormal, high, or low results. The following details the summary types, where LLN = lower limit of normal and ULN = upper limit of normal.

- For categorical variables: Treatment-emergent abnormal is defined as a change from normal at Baseline to abnormal at any post-Baseline visit.
- For continuous variables:
    - Treatment-emergent high is defined as a change from a result less than or equal to the high limit at Baseline to a value greater than the high limit at any time post-Baseline;
    - Results will be reported according to any value greater than the high limit, any value greater than 2× ULN and 3× ULN;
    - Treatment-emergent low is defined as a change from a result greater than or equal to the low limit at Baseline to a value less than the low limit at any time post-Baseline;
    - Results will be reported to any value less than the lower limit, any value less than 2× LLN and 3× LLN (i.e., ½ LLN and 1/3 LLN).

When there are multiple values within a visit for a particular laboratory variable, the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). Results will be reported in shift tables according to laboratory directions.

9.3 Vital Sign Measurements

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

9.4 Physical Examination

Physical examination data will be provided in data listings.

9.5 Electrocardiogram

ECG data will be provided in data listings.

9.6 Pulse Oximetry

Pulse oximetry measurements will be summarized descriptively for change from Baseline and percent of subjects with pulse oximetry ≤93% by visit and treatment group. Pulse oximetry data for subjects will also be presented in a listing.

10 Pharmacokinetics

Blood (plasma) samples for PK analysis will be collected on Visit 1 (postdose; at least 1 hour after dosing or right before the subject leaves the site, whichever is later), Visit 2 and Visit 3 (predose, at the same approximate time as that of the nasopharyngeal swab collection).

At the EOS Visit, a PK sample is only required for subjects who discontinue the study before the last dose of study drug is taken. The PK sample should be collected at the same approximate time as that of the nasopharyngeal swab collection. At the EOT Visit, if a subject discontinues treatment before Visit 3 but remains in the study, a PK sample should be taken at the approximate time as the NP swab at the EOT visit.

Actual date and time of PK sample collection will be recorded in the eCRF. In addition, the date and time of last dose taken prior to the PK sample collection will be recorded by the site in the eCRF.

Summary of plasma concentration data will be descriptive in nature. Available plasma concentration-time data in the PK Population will be summarized by treatment group.

10.1 Concentration-Time Data

For subjects in the PK population, the concentration data for EDP-938 and each metabolite will be summarized by visit, and nominal time. For predose samples, nominal time will be set to 0. For postdose samples, nominal time will be assigned based on the closest postdose integer hour. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. If more than 50% of subjects have concentration values below BLQ, descriptive statistics will not be presented except for maximum and BLQ will be displayed for mean and minimum. Descriptive statistics (number of subjects, arithmetic mean, standard deviation (SD), % coefficient of variation (%CV), median, minimum, maximum, geometric mean, and %CV of the geometric mean (%GCV) will be displayed.

Mean (+/- SD) EDP-938 plasma PK concentrations will be plotted over time. Listing for the PK sampling time and concentrations of EDP-938 and each metabolite will be provided.

11 Interim Analysis and DSMB

An interim analysis (IA) may be performed when at least 50% of the subjects complete the study. The IA will be conducted by a small team of people who are not directly involved in daily study conduct. The following endpoints will be summarized in the same manner as described in the earlier sections.

- Time to resolution of RSV Lower Respiratory Tract Disease (LRTD) symptoms
- Time to resolution of each separate RSV LRTD symptom
- Time to resolution of LRTD symptoms and 2 systemic symptoms
- Time to resolution of all RSV symptoms
- Percentage of participants with post-baseline RSV-related complications
- Time to RSV RNA viral load TND
- RSV RNA viral load change from Baseline at Days 3, 5, 9, and 14
- Percentage of subjects with RSV RNA viral load Target Not Detected (TND) at any point during the study
- Change from Baseline in severity of RSV LRTD symptoms through Day 33 as assessed by RiiQ^{TM} symptom scale score
- Safety: AE

An independent Data Safety Monitoring Board (DSMB) will be responsible for reviewing the safety data on an ongoing basis for the duration of the study. The objectives, role, and responsibilities of the DSMB, as well as the data cut off dates and the DSMB meeting schedule are documented in the DSMB Charter.

The DSMB Charter also describes the format and frequency of the DSMB meetings. The first data review meeting to review safety will be conducted when 25% of the subjects have completed the study. Subsequent meeting will be conducted when 50% of the subjects complete the study. The final meeting will be conducted after all subjects have completed the study. The DSMB will assess safety data. The DSMB can also convene unscheduled meetings when necessary.

DSMB safety reports will be generated using statistical methods described in Section 9.

12 Changes in the Planned Analysis

This SAP includes the following changes in the analysis planned in the protocol:

- Region, Race and Seropositivity are not in the list of subgroups in the Protocol, but subgroup analysis for these factors is considered relevant for the interpretation of the results.
- Statistical analysis of RSV serology was not described in the protocol, but as samples are collected with the aim of analyzing RSV serology, details for their statistical evaluation have been added in this SAP.
- Details about the estimands framework, intercurrent events and estimand-related sensitivity analyses for the primary endpoint and three secondary endpoints have been added according to FDA request.
    - Time to resolution of RSV Lower Respiratory Tract Disease (LRTD) symptoms (cough, short of breath, wheezing, coughing up phlegm [sputum]) as assessed by the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) symptom scale through Day 33.
    - Change from baseline in severity of RSV LRTD symptoms through Day 33 as assessed by RiiQ^{TM} symptom scale score.
    - RSV RNA viral load change from baseline at Days 3, 5, 9, and 14.
    - Percentage of subjects with RSV RNA viral load Target Not Detected (TND) at any point during the study.
    - Target population has been defined as “Non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years **or** high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)”, while in the protocol it was defined as “Non-hospitalized adult subjects with acute RSV infection who are at high risk for complications (age ≥65 years **and** high-risk cardiovascular or pulmonary conditions such as CHF, COPD, or asthma)”. Protocol definition would have led to the exclusion of subjects younger than 65 years old.
    - Multiple imputation techniques will be used in the estimand related analyses for sensitivity analysis when any missing data is present, contrary

to what stated in the protocol that multiple imputation techniques would not be used if the amount of missing data is not significant (i.e., less than 5% in any given treatment group).

- Subgroup analysis for RSV vaccination in the past was added according to FDA request.
- Resistance to EDP-938 in RSV obtained from nasopharyngeal swab samples will not be included in this analysis or in the Clinical Study Report as it will be analyzed separately and reported in a separate report.
- Analyses of time to resolution for the primary and selected secondary endpoints using the score of 0 were added to Section 8.5.
- The stratification factor: the number of high-risk factors (i.e., ≤2 vs. >2) has been removed from all statistical models as there is an imbalance between ≤2 and >2 found from blinded data review.
- The subgroup: RSV vaccine received in the past (Yes vs No) was removed from Section 8.6 (Subgroup Analysis) as there were not enough subjects who received RSV vaccine in the past.
- Analyses for higher risk sub-populations were added to Section 8.7.

[redacted]

13 References

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14 Appendices

14.1 Appendix 1: Schedule of Assessments

Period	**Screening**	**Treatment**					**Follow-up**				
Day	**1**	**1**	**2**	**3(±1d)[a]**	**4**	**5(±1d)[a]**	**6-8**	**9 (±1d)**	**10-13**	**14 (±1d)**	**33 (±1d)**
Visit	**Screening**	**V1 Randomization**		**V2**		**V3 EOT**		**V4**		**V5**	**V6 EOS**
Study site visit[b]	X	X		X		X		X		X	X
ICF for Rapid Viral Diagnostic Screening	X										
NP/nasal swab for rapid Viral Diagnostic Screening	X										
ICF for Study participation	X										
Inclusion/Exclusion criteria	X	X									
Demographics	X										
Medical, smoking and disease history[c]	X										
Prior therapies	X										
Concomitant therapies[d]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs and SpO_2	X[e]	X[e]		X		X		X		X	X
12-Lead ECG (resting)	X					X					X
Physical examination[f]	X										
Weight, height[g], and BMI	X			X		X		X		X	X
FSH (if needed)		X									
Randomization		X									
Study drug dosing[h]		X	X	X	X	X					
Study drug accountability		X		X[i]		X[i]					X
Clinical laboratory tests[j]		X		X		X		X		X	X
Pregnancy test[k]	X	X									X

Period	**Screening**	**Treatment**					**Follow-up**				
Day	**1**	**1**	**2**	**3(±1d)[a]**	**4**	**5(±1d)[a]**	**6-8**	**9 (±1d)**	**10-13**	**14 (±1d)**	**33 (±1d)**
Visit	**Screening**	**V1 Randomization**		**V2**		**V3 EOT**		**V4**		**V5**	**V6 EOS**
PK sample collection[l,m]		X		X		X					X[m]
NP swab sample[n]		X[d]		X		X[o]		X		X	X[o]
RSV serology sample		X									X
[redacted]											
Electronic device dispensation/return		X									X
RiiQ™ [q]	X[e]	X[e]	X	X	X	X	X	X	X	X	X
PGI-C[q]		X	X	X	X	X	X	X	X	X	X
PGI-S[q]		X	X	X	X	X	X	X	X	X	X
EQ-5D-5L		X				X		X		X	X
Return to Usual Health/ Activities questions[q]		X	X	X	X	X	X	X	X	X	X
Assess ICU admissions, hospitalization, and medically attended visits	X	X	X	X	X	X	X	X	X	X	X

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

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

14.2 Appendix 2: Multiple Imputation Models

Missing (or excluded) data will be imputed using multiple imputation (MI) methodology.

The multiple imputation approach will be tested on blinded data and thus should be confirmed, and any changes documented before database lock in the blinded review. Any post-unblinding modifications to the multiple imputation model or approaches to address missing data due to unexpected data issues after unblinding treatment will be described in the Clinical Study Report.

14.2.1 Data Pre-processing

The mITT will be used for this analysis. In the case of use of prohibited medications or death, the worst result in the study will be used to impute the missing data first.

For Estimand 1 and 2, the eCRF data will be transposed to give a single record per subject per analysis set with variables at each scheduled timepoint from Day 1 to Day 33 for each relevant component score as tabulated below:

Table 13-1 Terms in MI Models

Procedure/measure	Day 1	Day 2	Day 3	Day 4	…	Day 33
RiiQ™ score	x	2.0	x	1.0	…	2.0

For Estimand 3 and 4, the eCRF data will be transposed to give a single record per subject per analysis set with variables at each scheduled timepoint of Day 1, Day 3, Day 5, Day 9, and Day 14.

14.2.2 Imputation Model for Estimand 1 and 2

For mITT analysis set, multiple imputation model under the missing at random (MAR) assumption will be performed for each randomized group. The MI model will be fitted using SAS® PROC MI with the Fully Conditional Specification (FCS) logistic regression which will impute all missing values in one step to impute 100 multiply imputed data sets. The model will include treatment group, stratification factor (duration of respiratory symptoms) and time point (Day 1, 2, 3, 5, 7, 9, 14, 33). The seed number will be set to 857214.

14.2.3 Imputation Model for Estimand 3 and 4

This imputation will be based on log10 scale RSA RNA viral load data.

Step 1:

For mITT analysis set, partial imputation assuming MAR will be carried out to impute intermittent (non-monotone) missing data based on a multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method.

The imputation models will include treatment group, stratification factor (duration of respiratory symptoms) and time point (Day 1, 3, 5, 9, 14).

The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior with seed 857214. Note that only quantitative variables can be included in this step using MCMC and classification variables need to be included using indicator variables (though classification variables can be included in Step 2). In the case of non-convergence or non-estimability issues, a ridge prior and a single model per analysis set will be considered with treatment indicator variables added as explanatory variables to the model (rather than imputation being by treatment).

Step 2:

In the case of the mITT analysis sets, a MAR approach will be taken to the 2nd imputation step using the 100 multiply imputed datasets created for each analysis set as output in Imputation Step 1 as the input to Multiple Imputation MAR Step 2.

The remaining monotone missing data will be imputed using sequential regression multiple imputation, where a separate regression model is estimated for imputation of each variable (i.e., measurement at each time point). Each regression model will include treatment group, stratification factor (duration of respiratory symptoms (i.e., ≤48 hours vs. >48 hours to ≤72 hours)) and as per Step 1 and chronological in terms of each timepoint from Day 1, 3, 5, 9, 14 to Day 33. The random seed number for the sequential regression multiple imputation using MAR will be 293654.

The minimum values for imputed variables will be set to 0 to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. All results will be rounded to 2 decimal places.

14.2.4 Post-processing

For Estimand 1, time to resolution of RSV LRTD symptoms will be calculated with Cox proportional model for each of the 100 imputations.
For Estimand 2 and 3, LS means and differences for corresponding endpoints will be calculated with MMRM for each of the 100 imputations.
For Estimand 4, the imputed value that equal to 0 after rounding will be TND for the next analysis. The differences in proportion of subjects with RSV RNA viral load TND will be calculated with CMH test for each of the 100 imputations.

5. Pooling of Results: results will be combined using the SAS PROC MIANALYZE. The corresponding confidence intervals and p-values will be produced from the pooling of the results.

14.3 Appendix 3: Reference-Based Multiple Imputation Analysis for Sensitivity Analysis

This approach is used for the sensitivity analysis and is included following an FDA recommendation dated June 06, 2024 to assess the robustness of results. The MI model will be tested prior to breaking the blind. For Estimand 1 and 2, the multiple imputation will be done by each of the RSV LRTD symptoms as ordinal variable using a FCS logistic regression method (cumulative logit model). For Estimand 3 and 4, the multiple imputation will be done for RSV RNA viral load only using a regression method.

1. Pre-Processing:
The mITT will be used for this analysis. In the case of use of prohibited medications or death, the worst result in the study will be used to impute the missing data first. The data will be transposed to give a single record per subject per analysis set with variables at each scheduled timepoints.

2. For Estimand 1 and 2: A Reference-based MI approach under MNAR assumption with seed 293658 will then be applied to generate 100 multiply imputed datasets. The MI model will be fitted using SAS® PROC MI with the Fully Conditional Specification (FCS) logistic regression with a MNAR statement which will impute all missing values in one step. The model will include stratification factor (duration of respiratory symptoms) and time point (Day 1, 2, 3, 5, 7, 9, 14, and Day 33).

3. For Estimand 3 and 4:

This imputation will be based on log10 scale RSA RNA viral load data.

(a) MI Step 1 (MCMC): In the case of no intermittent missing data, this step will be skipped and Step 2 will instead generate the 100 multiply imputed datasets directly. Multiple imputation models under the missing at random (MAR) assumption will be performed to impute intermittent missing separately for each randomized group based on a multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method.The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. The seed number will be set to 857218. The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior with 100 imputations. Note that only quantitative variables can be included in this step using MCMC and classification variables need to be included using

indicator variables. The imputation models will include stratification factor (duration of respiratory symptoms) and time point (Day 1, 3, 5, 9. 14).
(b) MI Step 2 (MNAR): A Reference-based MI approach under MNAR assumption with seed 293658 will then be applied to generate a single imputation for each of the 100 multiply imputed datasets under MI Step 1. The remaining, monotone missing data for all patients will be imputed using sequential regression MI model estimated based on data from the placebo group only. The minimum values for imputed variables will be set to 0 to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. All results will be rounded to 2 decimal places. The imputation models will include stratification factor (duration of respiratory symptoms) and time point (Day 1, 3, 5, 9. 14).

4. Post-Processing:
For Estimand 1, time to resolution of RSV LRTD symptoms will be calculated with Cox proportional model for each of the 100 imputations.
For Estimand 2 and 3, LS means and differences for corresponding endpoints will be calculated with MMRM for each of the 100 imputations.
For Estimand 4, the imputed value that equal to 0 after rounding will be TND for the next analysis. The differences in proportion of subjects with RSV RNA viral load TND will be calculated with CMH test for each of the 100 imputations.

5. Pooling of Results: results will be combined using the SAS PROC MIANALYZE. The corresponding confidence intervals and p-values will be produced from the pooling of the results.

14.4 Appendix 4: Questionnaire Scoring

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

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

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

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

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

RiiQ™	Items on RiiQ™
LRTD Symptoms	Question 1: Cough
	Question 2: Wheezing
	Question 3: Shortness of breath
	Question 4: Coughing up phlegm/sputum
URTD Symptoms	Question 5: Nasal congestion
	Question 6: Sore throat
Systemic Symptoms	Question 7: Headache
	Question 8: Feeling feverish
	Question 9: Neck pain
	Question 10: Body aches and pain
	Question 11: Fatigue/tiredness
	Question 12: Interrupted sleep
	Question 13: Loss of appetite
Daily Activities	Question 14: Get out of bed
	Question 15: Prepare meals/get your own food
	Question 16: Perform usual activities
	Question 17: Leave the home
	Question 18: Concentrate on tasks
	Question 19: Take care of yourself
	Question 20: Go out of the room you are in
Emotions	Question 21: Irritable
	Question 22: Helpless
	Question 23: Worried
	Question 24: Frustrated
Social Relationships	Question 25: People worrying about you
	Question 26: Being a burden
	Question 27: People being annoyed with you
	Question 28: Needing to depend on people
	Question 29: People having to do extra things for you
RiiQ™ Total Score	Average of RiiQ™ scale Scores

RiiQ™ scale scores are obtained by taking the average of the responses on the corresponding non-missing items for each scale. If there are <=50% missing responses for items within a scale, the missing value score(s) will be replaced with the mean score of the remaining item scores. Otherwise, the scale score will be set to missing if there are >50% missing data. Higher scores indicate worse symptoms. Thus, a negative change from baseline for a score indicates improvement.

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

Subjects will assess the severity of RSV infection symptoms at their worst day by question: “In the past 24 hours, what was the severity of your overall RSV-related symptoms at their worst?” using PGI-S scale: 0 = None, 1 = Mild, 2 = Moderate or 3 = Severe.

Also, subjects will assess perceptions of improvement or deterioration in the severity of RSV symptoms by question: “In the past 24 hours, what best describes the overall change in your RSV-related symptoms?” compared to the subject started to take the study drug before using the PGI-C scale: 2 = Much better, 1 = A little better, 0 = No change or -1 = A little worse and -2 = Much worse.

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

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life. The EQ-5D-5L consists of a descriptive system and a visual analogue scale. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The visual analogue scale records the subject’s self-rated health on a vertical scale (0 to 100).

The EQ-5D-5L will be converted into a single index value. The summary index can be derived from the EQ-5D-5L descriptive system and using the standard value sets. Documents containing information on the crosswalk project, tables for values for all 3125 health states and the EQ-5D-5L Index Value Calculator can be downloaded from the EuroQol website. The EQ-5D-5L index score is on a scale from 0 (worst imaginable health state) to 1 (best imaginable health state).

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

The subjects will assess return to usual health and activities with 2 (Yes = 1/No = 0) questions below:

- Have you returned to your usual health today?
- Have you returned to your usual activities today?

14.5 Appendix 5: Statistical Methods -Sample SAS Codes

14.5.1 Example SAS code for analysis using MMRM

```
PROC MIXED DATA=ADTSS;
 CLASS USUBJID HIGHRISK DURRESP TRT01P DAY;
 MODEL CHGTSS= TRT01P DAY HIGHRISK DURRESP TSSBASE
TRT01P*DAY HIGHRISK*DAY DURRESP*DAY TSSBASE*DAY/DDFM=
Satterthwaite;
 REPEATED DAY/ SUBJECT=USUBJID TYPE=UN;
 LSMEANS DAY*TRT01P/ DIFF CL ALPHA=0.05;
RUN;
```

If the unstructured covariance matrix (TYPE=UN) fails to converge, then the following covariance structure will be assessed in this order: autoregressive, compound symmetry, Toeplitz.

14.5.2 Example SAS code for analyses using ANCOVA

```
PROC MIXED DATA=ADRSV;
 CLASS HIGHRISK DURRESP TRT01P;
 MODEL AUCRSV= RSVBASE HIGHRISK DURRESP TRT01P;
 LSMEANS TRT01P/DIFF CL;
RUN;
```

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Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	06 June 2025 | 16:23
Certified Delivered	Security Checked	06 June 2025 | 16:25
Signing Complete	Security Checked	06 June 2025 | 16:34
Completed	Security Checked	06 June 2025 | 16:34

Payment Events	Status	Timestamps

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