Statistical Analysis Plan

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

Protocol Number: EDP 938-201

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CONFIDENTIAL

Statistical Analysis Plan Approval Form

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Reviewed/Approved by: [redacted]

LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
ANCOVA	analysis of covariance
BMI	body mass index
CaGI-S	Caregiver Global Impression of Severity
CaGI-C	Caregiver Global Impression of Change
CI	confidence intervals
DAIDS	Division of AIDS
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
LLN	lower limit of normal
LLOQ	lower limit of quantification
LOD	limit of detection
MAARI	Medically Attended Acute Respiratory Infection
MedDRA	Medical Dictionary for Regulatory Affairs
MMRM	Mixed-effect model for repeated measures
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic(s)
PKPD	Pharmacokinetic-Pharmacodynamic
PT	preferred term
QD	Once Daily
RESOLVE-P	Respiratory Observable Reported Outcome - Pediatric
RSV	respiratory syncytial virus
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	Safety (for the analysis population)

SAP	statistical analysis plan
SoA	Schedule of Assessments
SOC	system organ class
SSC	Study Steering Committee
TD	Target Detected
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TND	target not detected
ULN	upper limit of normal
WHO	World Health Organization

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1. INTRODUCTION

EDP-938 (also known as EPC-3938, EPS-3938, and EP-023938) is a novel, orally administered, non-fusion replication inhibitor of respiratory syncytial virus (RSV) that is being developed as a potential treatment for RSV infection. This Phase 2 study, EDP 938-201, is a randomized double-blind, placebo-controlled, 2-part study to evaluate the safety, tolerability, pharmacokinetics (PK), clinical outcome, and antiviral activity of orally administered EDP-938 regimens in hospitalized or non-hospitalized infants and children aged 28 days to 36 months infected with RSV.

The preparation of this Statistical Analysis Plan (SAP) is based on the International Conference on Harmonization (ICH) E9 guidelines [1] and study protocol Version 18.0 dated 09 July 2024. The SAP outlines the statistical analyses of the efficacy and safety data to support the clinical study report (CSR) and will be finalized prior to the database lock. Any changes to the SAP after finalization will be documented in the CSR. The table of contents and shells for the tables, figures, and listings (TFLs) will be produced in a separate document.

2. STUDY DESIGN

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

Each part of the study has 3 periods: Screening, Treatment, and Follow-up. For each subject, the duration of study will be approximately 29 days (Table 1). Study site visits and assessments are detailed in the Schedule of Assessments (SoA; Appendix 7.1).

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

Table 1

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

2.1 Dose and Treatment Schedule

Approximately 90 subjects are planned to be enrolled. Oral doses of EDP-938 or placebo will be administered once daily (QD). Initial doses are planned to be [redacted] in each age group:

Group 1 (Ages ≥6 to ≤36 months)

Group 2 (Ages ≥28 days to <6 months)

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

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

The study design is shown in *Figure 1*.

Part 1

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

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

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

Cohort 1 Age Group 2 will include subjects who are hospitalized at enrollment.

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

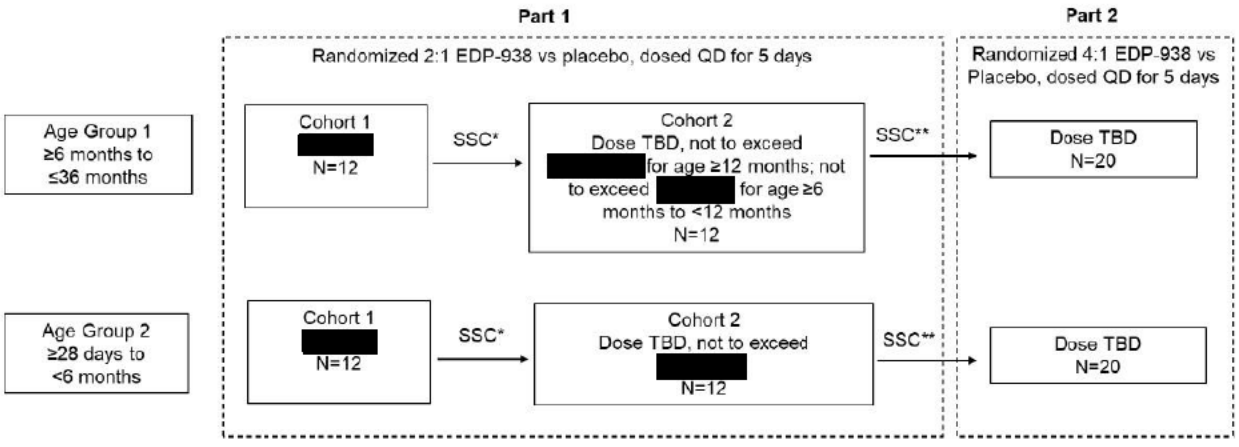
Additional Part 1 cohorts may be added, as deemed necessary by the SSC.

Part 2

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

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

Figure 1: Study Design



QD = once daily; SSC = study steering committee; TBD = to be determined.
The SSC will review data from each cohort and will determine dose selection and cohort progression in Part 1 and Part 2.

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

** SSC will review available blinded data when at least 6 subjects have been randomized in Cohort 2 for each age group.

2.2 Treatment Assignment/Randomization and Blinding

The study will be double-blinded, meaning that the subjects and their caregivers, investigators, and site staff will be blinded to treatment assignment until the completion of the study.

Subjects will be randomized to a treatment group using an Interactive Web Response System.

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

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

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

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

Part 2, Age Group 1 and 2 (randomized 4:1)

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

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

3. OBJECTIVES AND ENDPOINTS

3.1 Objectives

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

3.1.1 Part 1: Primary and Secondary Objectives

Primary Objectives

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

Secondary Objective

- To evaluate the antiviral activity of EDP-938

3.1.2 Part 2 and Pooled Population: Primary and Secondary Objectives

Primary Objective

- To evaluate the antiviral activity of EDP-938

Secondary Objectives

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

[redacted]

[redacted]

3.2 Endpoints

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

3.2.1 Part 1: Primary and Secondary Endpoints

Primary Endpoints

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

Secondary Endpoints

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

3.2.2 Part 2 and Pooled Population: Primary and Secondary Endpoints

Primary Endpoint

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

Secondary Endpoints

- Safety and tolerability of EDP-938 compared to placebo as assessed by, but not limited to, AEs, vital signs, and clinical laboratory results;

- AUC for RSV RNA viral load measured in nasal swab samples by RT-qPCR;
- Proportion of subjects with RSV RNA viral load below the LOD in subjects receiving EDP-938 compared to placebo;
- Time to RSV RNA viral load being undetectable;
- PK parameters of EDP-938 including AUC and predose concentrations;
- Time to discharge for hospitalized subjects;
- Time to use of oxygen for hospitalized subjects who are not receiving oxygen at the time they receive the first dose of study drug;
- Proportion of hospitalized subjects requiring oxygen supplementation or have an increased oxygen requirement;
- Time to mechanical ventilation for hospitalized subjects;
- Proportion of hospitalized subjects requiring mechanical ventilation;
- Deaths among hospitalized subjects;
- Time to hospitalization for initial outpatients who are subsequently hospitalized;
- Proportion of outpatients who are subsequently hospitalized or died;
- Time to resolution of symptoms for outpatients who are not hospitalized.

[redacted]

[redacted]

4. STATISTICAL CONSIDERATIONS

4.1 General Considerations

All statistical procedures will be completed using SAS version 9.4 or higher.

Continuous variables will be summarized using descriptive statistics (i.e., n, mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum and maximum values). The mean, median and the percentiles will be rounded to one decimal place beyond the precision of the values being summarized; the SD will be rounded to 2 additional decimal places beyond this precision and the minimum and maximum values will be displayed in the same precision. If n=0, then display n and leave all other statistics blank. If n=1, display "N/A" for SD.

Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the number of subjects in the appropriate age group and treatment group within the analysis set of interest, unless otherwise specified. The denominator will be displayed when needed and the percentage will be rounded to one decimal place. If the frequency is 0, the percentage will not be displayed. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values where applicable.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings. All listings will be sorted by study part, treatment group, subject number, date/time and visit. The treatment group (randomized) as well as subject's sex, race, age and age group will be stated on each listing. Unless otherwise stated, data listings will be based on all subjects randomized.

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

Efficacy summary tables and figures will be presented by randomized treatment group and age group for Part 1 and Part 2 separately and will be labelled as follows. Additionally, efficacy summary tables and figures for efficacy endpoints for the pooled population will be summarized using pooled data (subjects from Parts 1 and 2) as appropriate. Other summaries including disposition, analysis populations, demographics, and baseline data will be displayed by treatment group, age group for Parts 1 and 2 separately. Parts 1 and 2 will also be pooled for these summaries.

Age Group:

- "≥6 to ≤36 months"
    - "≥6 to <12 months"
    - "≥12 to ≤36 months"
- "≥28 days to <6 months"
    - "≥28 days to <3 months"

- "≥3 to <6 months"

Treatment:

- "EDP-938"
- "Placebo"

Study Part:

- "Part 1"
- "Part 2"
- "Parts 1 and 2"

Safety summary tables and figures will be summarized separately for Part 1 and Part 2 as well as pooled Parts 1 and 2 data by the actual treatment group. In addition, pooled Parts 1 and 2 data will be summarized by age group.

For the reporting of this study both CDISC SDTM (SDTM Implementation Guide version 3.3 or later) and ADaM (ADaM Implementation Guide version 1.1 or later) standards will be applied. A subject will be considered to have completed the study after his/her attendance at the last planned study visit (Day 28 ± 4 day), 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.

4.2 Sample Size Considerations

No formal hypothesis testing is planned for Parts 1 or 2 of this study. Therefore, no formal sample size justification is provided. Approximately 90 subjects will participate in this study: 12 subjects are planned in each cohort of the age groups in Part 1 (24 subjects in each age group). In Part 2, 20 subjects are planned in each of the age groups. Additional subjects may be added based on SSC recommendations.

4.3 Handling of Dropouts or Missing Data

In general, missing data will not be imputed and all summary statistics will be reported based upon observed data. In particular, incomplete dates for adverse events and concomitant medication use (*Section 4.3.1*) are presented. For any other data which has partial dates, which are required for use in time related calculations, these dates will be completed using a suitably conservative approach. Dates will be shown in subject listings as they have been recorded.

4.3.1 Missing Dates

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.
        - If the full (or partial) AE end date is before the first dose date, then impute the AE start Month and Day as the Month and Day of AE end date after imputation.
    - If AE start date > first dose year, impute the AE start MONTH as January and the DAY as 1.
    - If AE start year < first dose year, then:
        - If the full (or partial) AE end date is NOT before the 31st of December of AE start year, or AE end date is missing, then impute the AE start MONTH as December and the DAY as 31.
        - Otherwise, if the full (or partial) AE end date is before the 31st of December and AE start year, then impute the AE start Month and Day as the Month and Day of AE end date after imputation.
- 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 adverse event 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.

<u>Imputation rules for missing or partial medication start/stop dates are defined below:</u>

- 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.
  - If the full (or partial) CM end date is before the first dose date, then impute the CM start Month and Day as the Month and Day of CM end date after imputation.
- If CM start date > first dose year, impute the CM start MONTH as January and the DAY as 1.
- If CM start year < first dose year, then:
  - If the full (or partial) CM end date is NOT before the 31st of December of CM start year, or CM end date is missing, then impute the CM start MONTH as December and the DAY as 31.
  - Otherwise, if the full (or partial) CM end date is before the 31st of December and CM start year, then impute the CM start Month and Day as the Month and Day of CM end date after imputation.

- 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.

4.4 Analysis Populations

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

4.4.1 Full or Partial Dose

A full or partial dose is determined by clinical pharmacology and medical teams. If all treated subjects receive at least one full dose of study drug, then the Efficacy Population and the Safety Population will be the same.

A full dose of study drug is defined as a dose taken on a given day as confirmed by Dose Admin Form with the following criteria from the palatability questionnaire:

- *A "Yes" answer to "Successfully swallowed the medicine without vomiting within 2 minutes of swallowing"*

AND

- *Absence of a "Yes" answer to "Spit out or coughed it out"*

AND

- *Absence of a "Yes" answer to Gagged or vomited (within 2 minutes of swallowing medicine)*

A partial dose of study drug is defined as a dose taken on a given day with the following criteria from the palatability questionnaire:

- *A "No" answer to "Successfully swallowed the medicine without vomiting within 2 minutes of swallowing"*

OR

- *A "Yes" answer to "Spit it out or coughed it out"*

OR

- *A "Yes" answer to "Gagged or vomited (within 2 minutes of swallowing medicine"*

4.5 Analysis Visit Windows

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

Analysis visit windows are described in the tables below.

For vital signs, safety laboratory tests, Professional ReSVinet, and RSV RNA quantitation of viral load:

Analysis Visit #	Analysis Visit Label	Target Day	Derivation	Visit Window
1	Day 1	1	Based on nominal visit	
3	Day 3	3	Based on date of assessment	2 to 4*

5	Day 5	5	Based on date of assessment	4 to 6*
9	Day 9	9	Based on date of assessment	8 to 11
14	Day 14	14	Based on date of assessment	12 to 16

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

For eCOA eDiary (Parent/Guardian ReSVinet, Palatability Questionnaire), RESOLVE-P:

Analysis Visit #	Analysis Visit Label	Target Day	Timepoint* Assessment	Derivation
1	Day 1	1	AM	Study day =1
1	Day 1	1	PM	Study day =1
2	Day 2	2	AM	Study day =2
2	Day 2	2	PM	Study day =2
3	Day 3	3	AM	Study day =3
3	Day 3	3	PM	Study day =3
4	Day 4	4	AM	Study day =4
4	Day 4	4	PM	Study day =4
5	Day 5	5	AM	Study day =5
5	Day 5	5	PM	Study day =5
6	Day 6	6	AM	Study day =6
6	Day 6	6	PM	Study day =6
7	Day 7	7	AM	Study day =7
7	Day 7	7	PM	Study day =7
8	Day 8	8	AM	Study day =8
8	Day 8	8	PM	Study day =8
9	Day 9	9	AM	Study day =9
9	Day 9	9	PM	Study day =9
10	Day 10	10	AM	Study day =10
10	Day 10	10	PM	Study day =10
11	Day 11	11	AM	Study day =11

11	Day 11	11	PM	Study day =11
12	Day 12	12	AM	Study day =12
12	Day 12	12	PM	Study day =12
13	Day 13	13	AM	Study day =13
13	Day 13	13	PM	Study day =13
14	Day 14	14	AM	Study day =14
14	Day 14	14	PM	Study day =14

***** The ReSVinet assessments will be completed predose QD each day, by subjects' parent(s)/guardian(s), through Day 14 and at approximately the same time each day ±2 hours. The palatability question will be completed as soon as possible after each dose of study drug is administered. The RESOLVE-P assessments will be completed twice daily (AM and PM), approximately every 12 hours for 14 days. The D1 assessment must be completed pre-dose. Only one D1 assessment is expected if completed in the afternoon.

4.6 Subject 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 will be summarized using all subjects randomized. The denominator for the calculation of percentages will be from the number of subjects randomized.

The following categories will also be summarized by all randomized subjects:

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

The number of subjects excluded from analysis sets and reasons for exclusion will be summarized.

A separate listing will be also provided for subject disposition.

4.7 Protocol Deviations

All protocol deviations (PDs) will be entered and tracked in [redacted] Clinical Trial Management System (CTMS) by the study steam throughout the conduct of the study in accordance with [redacted] Protocol Deviation Guidance document. Protocol deviations that adversely affect the risk/benefit ratio of the study, the rights, safety, or welfare of the participants or others, or the integrity of the study must be reported to the medical monitoring team.

The PDs will be reviewed prior to closure of the database and unblinding the study to ensure all significant deviations (classified as "Important" in the PD Guidance document) are captured and categorised.

Significant protocol deviations will be summarized. Separate listings will also be provided for significant and non-significant protocol deviations. Summaries will be conducted on all subjects who were randomized.

4.8 Demographic and Baseline Characteristics

No statistical testing will be performed for the comparison between treatment groups on demographics and baseline characteristics. Subject demographics and baseline characteristics will be summarized descriptively using the Safety Population.

Age, Gestational Age, Body Length, Head Circumference, and Weight, RSV viral load measured by RT-qPCR (log10 copies/mL), professional and parent/guardian ReSVinet total scores, RESOLVE-P domain and composite scores, CaGI-S total score collected at baseline, and duration of RSV symptom onset (from the first sign of respiratory infection to randomization) will be summarized.

Qualitative variables such as sex, ethnicity, race, RSV type (RSV-A, RSV-B), and pathogen will be summarized using descriptive statistics. A by-subject listing will be provided.

4.9 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 or higher. The number and percentage of subjects with relevant medical history will be summarized by system organ class (SOC) and preferred term (PT). The percentage will be calculated based on the Safety Population. A by-subject listing will be provided.

4.10 Prior and Concomitant Medications

Medications used in this study will be coded using the latest available version of the World Health Organization Drug Dictionary Global B3 September 2020 or higher. Prior medications are defined as those medications with a start date prior to the first dose of study drug. Concomitant medications are defined as those medications with a start date on or after the first dose of study drug. A medication which started prior to dosing and continued after dosing will also be considered as concomitant medications. Concomitant medications will be summarized descriptively using frequency tables by Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup) and PT using the Safety Population. A by-subject listing will be provided for prior and concomitant medications. Details for imputing missing or partial start and/or stop dates of medication are described in *Section 4.3.1*.

4.11 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. Study drug exposure will be summarized using the Safety Population and the Efficacy Population. Only the summaries of Safety Population will be provided if the Safety Population and the Efficacy Population are identical.

4.12 Treatment Compliance

Study drug compliance based on the number of syringes taken will be calculated as: 100 x (total number of days dosed)/ (number of days of treatment planned per protocol) except for subjects who discontinued 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. Study drug compliance will be summarized using the Safety Population and the Efficacy Population. Only the summaries of Safety Population will be provided if the Safety Population and the Efficacy Population are identical.

4.13 Efficacy Analyses

All efficacy analyses will be based on the Efficacy Population. Selected efficacy endpoints will also be based on the mITT-3 and mITT-5 populations. Part 1 data and Part 2 data will be summarized separately using descriptive statistics. In addition, all secondary efficacy endpoints in Part 2 as well as all exploratory endpoints will be summarized based on pooled data from both Parts 1 and 2. Inferential statistical analysis will be performed to these pooled analyses, as appropriate.

4.13.1 Primary Efficacy Analysis Part 1

Not applicable because the primary endpoint for this part of the study is the PK analysis (please refer to *Section 4.15.1*)

4.13.2 Secondary Efficacy Analysis Part 1

The following secondary endpoints will be analyzed descriptively using the Efficacy, mITT-3, mITT-5 Populations.

- AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR)

  RSV RNA viral load will be measured in nasal swab samples by 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 the average of LOD (limit of detection) and LLOQ (lower limit of quantification). Viral load values reported as TND (Target Not Detected, below LOD) 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; 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 at baseline based on the RT-qPCR test. The baseline RSV viral load result is from the nasopharyngeal swab sample taken after randomization and prior to first dose on Day 1. After the imputation of TD, TND, and log10 transformation, if the baseline RSV A viral load is greater than RSV B viral load, the baseline

RSV type is classified as RSV A. Further, if the baseline RSV B viral load is greater than RSV A viral load, the baseline RSV type is classified as RSV B.

The RSV RNA viral load AUC will be calculated using the trapezoid rule [2]. 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. The AUC will be calculated based on all available assessments collected on Days 1/Baseline, 3, 5, 9, and 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 for 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 though Day 14.

Descriptive statistics for RSV RNA viral load AUC 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.

- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from baseline through the treatment phase
    - RSV RNA viral load observed and change from baseline will be summarized by visit (Baseline, Days 3, 5, 9 and 14). The summary statistics 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.

  Line graph of RSV RNA viral load will be produced:

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

- Time to RSV RNA viral load being undetectable

  Time to RSV RNA viral load being undetectable (TND) will be analyzed using two approaches as defined below:

    - Time to RSV RNA viral load being undetectable (days) is defined as the time between the date of first dose to the first date during post-dose period of achieving RSV RNA viral load TND after which no further samples have detectable RSV RNA viral load. Subjects with baseline RSV viral load TND will be excluded from the analysis.
    - Time to confirmed undetectable RSV RNA viral load (days) is defined as the time between the date of first dose to the first of 2 consecutive post-baseline time points of achieving RSV RNA viral load TND. Subjects with baseline RSV viral load TND will be excluded from the analysis.

- Proportion of subjects with RSV RNA viral load below the LOD in subjects receiving EDP-938 compared to placebo

- Frequency counts and percentages of subjects with RSV RNA viral load below the LOD will be summarized by Day 14. The respective 95% CIs will be reported using Clopper Pearson CI methods.

4.13.3 Primary Efficacy Analysis Part 2

- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from baseline through the treatment phase
  - RSV RNA viral load observed and change from baseline will be summarized descriptively by visit (Baseline, Days 3, 5, 9 and 14) using the efficacy, mIIT-3 and mITT-5 populations. The summary statistics 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.

    Line graph of RSV RNA viral load will be produced:

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

4.13.4 Secondary Efficacy Analysis Part 2

The following efficacy analyses will be summarized using the Efficacy, mITT-3, and mITT-5 populations.

- AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR)
  - The RSV RNA viral load AUC will be summarized as described in *Section 4.13.2*.
- Proportion of subjects with RSV RNA viral load below the LOD in subjects receiving EDP-938 compared to placebo
  - Frequency counts and percentages of subjects with RSV RNA viral load below LOD will be summarized by Day 14. The respective 95% CIs will be reported using Clopper Pearson CI methods.
- Time to RSV RNA viral load being undetectable

  Time to RSV RNA viral load being undetectable (TND) will be analyzed using two approaches as defined below:
  - Time to RSV RNA viral load being undetectable (days) is defined as the time between the date of first dose to the first date during the post-dose period of achieving viral load TND after which no further samples have detectable RSV RNA viral load. Subjects with baseline RSV viral load TND will be excluded from the analysis.
  - Time to confirmed undetectable RSV RNA viral load (days) is defined as the time between the date of first dose to the first 2 consecutive post-baseline time points of

achieving RSV RNA viral load TND. Subjects with baseline RSV viral load TND will be excluded from the analysis.

Frequency counts and percentages of subjects by end of study (Day 28 ±4), and their respective 95% CIs will be reported using Clopper Pearson CI methods for the following endpoints summarized using the Efficacy Population.

- Proportion of hospitalized subjects requiring oxygen supplementation or have an increased oxygen requirement.
    - Subjects who are hospitalized at randomization and/or during study are included. The proportion will be defined by the number of subjects who develop a new requirement for oxygen supplementation or new increase(s) in oxygen requirements after the first dose of study drug, based on the response of "yes" to the "is this an increase of oxygen supplementation compared to previous use?" question on the Oxygen Supplementation CRF.
- Proportion of hospitalized subjects requiring mechanical ventilation
    - Subjects who are hospitalized at randomization and/or during study are included. The proportion will be defined by the number of subjects who developed a new requirement for mechanical ventilation after the first dose of study drug. Subjects on mechanical ventilation prior to the first dose of study drug are excluded from analysis.
- Deaths among hospitalized subjects
    - Subjects who are hospitalized at randomization and/or during study are included.
- Proportion of outpatients who are subsequently hospitalized or died
    - Subjects who are not hospitalized at randomization are included.
- Proportion of outpatients who died
    - Subjects who are not hospitalized at randomization are included.

The following endpoints will be summarized using the Efficacy Population. The summary statistics will include, at a minimum, the number of non-missing measurements, mean, standard deviation, median, minimum, 25th percentile, 75th percentile, and maximum.

- Time to discharge for hospitalized subjects
    - Time to first hospital discharge for subjects who are hospitalized at randomization will be defined as the time between the first dose of study drug and the first date of discharge. For subjects with continuous hospitalization, the last date of discharge from the continuous hospitalization will be used.
- Time to use of oxygen for hospitalized subjects who are not receiving oxygen at the time they receive the first dose of study drug
    - For subjects who are hospitalized at randomization, time to use of oxygen for hospitalized subjects not receiving oxygen at the time they receive the first dose, is

defined as the time between the date/time of first dose of study drug to the first date/time of receiving oxygen.

- Duration of oxygen use for hospitalized subjects
    - This analysis will include subjects who are hospitalized at randomization and received oxygen supplementation at any time after the first dose of study drug. The duration of oxygen use (days) is defined as the sum of each duration of oxygen use (days) that occurred from the first dose of study drug to the end of study. The duration of oxygen use for the initial hospitalization is calculated as date/time of the end of oxygen use – date/time of first dose of study drug. The duration of oxygen use for subsequent rehospitalization(s) is calculated as date/time of the end of oxygen use – date/time of the start of oxygen use for the rehospitalization. Missing start times will be imputed to 00:01. Missing end times will be imputed to 23:59.
- Time to mechanical ventilation for hospitalized subjects
    - This analysis will include subjects who are hospitalized at randomization and required mechanical ventilation at any time after the first dose of study drug. Subjects on mechanical ventilation before their first dose of study drug are excluded from analysis. Time to mechanical ventilation is defined as the date/time from the first dose of study drug to the first use of mechanical ventilation.
- Duration of mechanical ventilation for hospitalized subjects
    - This analysis includes subjects who are hospitalized at randomization and required mechanical ventilation at any time after the first dose of study drug. The duration of mechanical ventilation (days) is defined as the sum of each duration of mechanical ventilation (days) that occurred from the first dose of study drug to the end of study. The duration of mechanical ventilation for the initial hospitalization is calculated as date/time of the end of mechanical ventilation – date/time of first dose of study drug. The duration of mechanical ventilation for subsequent rehospitalization(s) is calculated as date/time of the end of mechanical ventilation – date/time of the start of mechanical ventilation. Missing start times will be imputed to 00:01. Missing end times will be imputed to 23:59.
- Time to hospitalization for initial outpatients who are subsequently hospitalized
    - Time to hospitalization for initial outpatients who are subsequently hospitalized will be calculated, defined as the time between the date/time of first dose to the first date of hospitalization.
- Time to resolution of symptoms for outpatients who are not hospitalized
    - Time to resolution of symptoms for outpatients at randomization who are not hospitalized during study, is defined as the time between the date/time of first dose to the first of 2 consecutive time points where each of the seven symptoms assessed by the Parent/Caregiver ReSVinet clinical scoring is 0 or 1. If a subject meets the resolution

definition (0 or 1 score for 2 consecutive timepoints) at baseline and Day 2, then this subject will be excluded from the analysis.

4.13.5 Efficacy Analysis for Pooled Population

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

All secondary efficacy endpoints described in *Section 4.13.4*, as well as all exploratory endpoints described in Section 4.13.7 are also the secondary and exploratory endpoints for the pooled population and will be analyzed with the pooled data from both Parts 1 and 2.

All pooled efficacy data will be summarized descriptively by EDP 938 and Placebo for each age group and combined EDP 938 and Placebo, as described in *Section 4.13.4* and *Section 4.13.7*.

Inferential statistics analysis will be performed to detect treatment effects of EDP 938 and Placebo using the Efficacy Population, mITT-3 and mITT-5 for the following RSV RNA viral endpoints as well as RSV symptom related endpoints described in *Section 4.13.7* (except for RESOLVE-P where Efficacy Population is used)

- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from baseline through treatment phase
    - Absolute change from baseline in RSV RNA viral load (outcome variable) will also be analyzed using MMRM as described below.
    - AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR) will be estimated via MMRM.
- Time to RSV RNA viral load being undetectable

  Time to RSV RNA viral load being undetectable (TND) will be analyzed using two approaches as defined below:

    - Time to RSV RNA viral load being undetectable (days) is defined as the time between the date of first dose to the first date during post-dose period of achieving RSV RNA viral load TND after which no further samples have detectable RSV RNA viral load. Subjects with baseline RSV viral load TND will be excluded from the analysis.
    - Time to confirmed undetectable RSV RNA viral load (days) is defined as the time between the date of first dose to the first of 2 consecutive post-baseline time points of achieving RSV RNA viral load TND. Subjects with baseline RSV viral load TND will be excluded from the analysis.

Inferential statistics analysis approaches are as follows:

For continuous endpoints with multiple timepoints:

Absolute change from baseline in the outcome of interest (outcome variable) will be analyzed using a mixed-effect model for repeated measures (MMRM) to compare EDP-938 and Placebo.

The model includes treatment group (EDP-938, placebo) and Day (all scheduled post-baseline timepoints available) as fixed effect, associated baseline (as appropriate), and treatment group-by-Day interaction term as factors. Treatment groups will be compared at scheduled post-baseline timepoints of interest. An unstructured 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 of absolute change from baseline at each post-baseline timepoint will be presented for individual groups and the difference between groups. AUC of change from baseline will be derived via this model. The least-squares means and two-sided 95% CIs of AUC through Days 3, 5, 9 and 14 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.

For time to event endpoints:

Kaplan-Meier estimates will be provided including at least median survival and its 95% CI on the combined EDP-938 and placebo for Parts 1 and 2. Kaplan-Meier plots will also be provided. Generalized Wilcoxon test will be performed to compare the EDP-938 vs Placebo. If appropriate, log-rank test will be performed as well. If required, a Cox proportional hazards model, adjusting for associated baseline assessment (if appropriate), would be considered. Subjects who did not achieve the specified event will be censored as follows:

RSV RNA viral load:

- Subjects who have not been followed through the Day 14 visit (discontinued from the study or incomplete follow-up) or completed Day 14 visit will be censored at Day 14 visit date.

Parent/Guardian ReSVinet, Professional ReSVinet, Parent/Guardian RESOLVE-P, Caregiver Global Impression of Severity (CaGI-S), Caregiver Global Impression of Change (CaGI-C):

- Subjects who have not been followed through the Day 14 visit (discontinued from the study or incomplete follow-up) or completed Day 14 questionnaire will be censored at Day 14.

4.13.6 Sensitivity Analysis

Sensitivity analyses will be based on the Efficacy Population.

Final dosing regimen:

Subjects who received the final selected doses (7.5 mg/kg in subjects in 12 to ≤36 months and 5 mg/kg in subjects <12 months) will be included in the following analyses.

- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from baseline through the treatment phase
    - Absolute change from baseline in RSV RNA viral load (outcome variable) will also be analyzed using MMRM as described in *Section 4.13.5*.
    - AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR) will be estimated via MMRM.
- Time to RSV RNA viral load being undetectable
    - The analyses are outlined in the time to event analyses as described in *Section 4.13.5*.

Steroid Use:

The populations for analysis of steroid use are defined as follows:

- Subjects who received systemic corticosteroids at any time between 21 days prior to randomization and the PT 2 visit (Day 14).
- Subjects who did not receive systemic corticosteroids at any time between 21 days prior to randomization and the PT 2 visit (Day 14).

The following analyses will be analyzed descriptively for each of the above populations.

- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from baseline through the treatment phase
- AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR)
- Time to RSV RNA viral load being undetectable

  Time to RSV RNA viral load being undetectable (TND) will be analyzed using two approaches as defined below:

    - Time to RSV RNA viral load being undetectable (days) is defined as the time between the date of first dose to the first date during post-dose period of achieving RSV RNA viral load TND after which no further samples have detectable RSV RNA viral load. Subjects with baseline RSV viral load TND will be excluded from the analysis.
    - Time to confirmed undetectable RSV RNA viral load (days) is defined as the time between the date of first dose to the first of 2 consecutive post-baseline time points of

achieving RSV RNA viral load TND. Subjects with baseline RSV viral load TND will be excluded from the analysis.

- Change from baseline of the Parent/Guardian ReSVinet total score which is defined as a sum of the score from each of the 7 parameters
- Parent/Guardian ReSVinet total score AUC will be calculated and summarized as described in *Section 4.13.2*.
- Time to resolution of RSV infection symptoms is defined as the time between the date of first dose to the first of 2 consecutive time points where each of the seven symptoms assessed by the Parent/Caregiver ReSVinet clinical scoring is 0 or 1. If a subject meets the resolution definition (0 or 1 score for 2 consecutive timepoints) at baseline and Day 2, then this subject will be excluded from the analysis.

Coinfection:

The populations for analysis of viral coinfection are defined as follows:

- Subjects who had a viral coinfection at baseline. Viral coinfection is defined as subjects who were infected with RSV and other pathogens at baseline.
- Subjects who were infected with RSV only (did not have a viral coinfection) at baseline.

The following analyses will be analyzed descriptively for each of the above populations.

- Daily change in RSV shedding in nasal swab samples determined using RT-qPCR from baseline through the treatment phase
- AUC for RSV RNA viral load measured in nasal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR)
- Time to RSV RNA viral load being undetectable

  Time to RSV RNA viral load being undetectable (TND) will be analyzed using two approaches as defined below:

  - Time to RSV RNA viral load being undetectable (days) is defined as the time between the date of first dose to the first date during post-dose period of achieving RSV RNA viral load TND after which no further samples have detectable RSV RNA viral load. Subjects with baseline RSV viral load TND will be excluded from the analysis.
  - Time to confirmed undetectable RSV RNA viral load (days) is defined as the time between the date of first dose to the first of 2 consecutive post-baseline time points of achieving RSV RNA viral load TND. Subjects with baseline RSV viral load TND will be excluded from the analysis.

- Change from baseline of the Parent/Guardian ReSVinet total score which is defined as a sum of the score from each of the 7 parameters.

- Parent/Guardian ReSVinet total score AUC will be calculated and summarized as described in *Section 4.13.2*.
- Time to resolution of RSV infection symptoms is defined as the time between the date of first dose to the first of 2 consecutive time points where each of the seven symptoms assessed by the Parent/Caregiver ReSVinet clinical scoring is 0 or 1. If a subject meets the resolution definition (0 or 1 score for 2 consecutive timepoints) at baseline and Day 2, then this subject will be excluded from the analysis.

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4.14 Safety Analyses

Statistical methods for the safety analyses will be primarily descriptive in nature. The SAF will be used for all safety analyses, unless stated otherwise. Part 1 and Part 2 will be summarized separately and pooled. In addition, pooling of Parts 1 and 2 will be summarized by age group.

4.14.1 Adverse Events

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 or higher, using the SOC and PT. 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 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 TEAEs: TEAE will be defined as related if causality is related or possibly related. TEAEs where the causality is missing will be assumed to be related for table summary. However, it is displayed as missing in the listing.
- Grade AEs: Grade AEs in accordance with the NCI/CTCAE Version 5.0 scale as follows: Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), Life-threatening (Grade 4), Fatal (Grade 5).

Where a subject has the same adverse event, based on PT, reported multiple times, the subject will only be counted once at the PT level in adverse event frequency tables. Where a subject has multiple adverse events within the same SOC, the subject will only be counted once at the SOC 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. Missing severity will be presented as severe for table summary. However, it is displayed as missing in the listing. All AEs will be presented in tables in descending order from the SOC with the highest total incidence (across all treatment groups) to the SOC with the lowest total incidence. Within each SOC, AEs will be sorted in alphabetical order of PT.

Summaries of TEAEs will include the following at a minimum:

- Overall summary of subjects with any TEAEs with a line for each of the following categories
    - TEAEs
    - Study Drug-Related TEAEs
    - TEAEs of Grade 3 or Higher
    - TEAEs by Maximum Severity (Grades 1 to 5)
    - TEAEs leading to study drug discontinuation
    - TEAEs leading to study discontinuation
    - AEs leading to death
    - Serious TEAEs
    - Study Drug-Related Serious TEAEs

The above categories will also be summarized by SOC and PT.

4.14.2 Clinical Laboratory Data

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

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

Laboratory assessment grading is to be based on National Institute of Allergy and Infectious Diseases Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1 dated July 2017. Lab grading will be coded as follows:

Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4=Potentially Life-threatening.

Shift from baseline by DAIDS Grading will be summarized for selected chemistry and hematology parameters. Also, DAIDS Grading will be included in the chemistry and hematology listings.

In addition to DAIDS grading, selected laboratory parameters that are not graded by DAIDS will be displayed using the following custom laboratory shift reports:

- 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 LLN, less than (½)× LLN and (1/3)× LLN.

4.14.3 Vital Sign Measurements

Vital signs will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), heart rate (beats/min), and body temperature (°C). Pulse oximetry (to measure peripheral capillary oxygen saturation [SpO_2] (%) will also be summarized. Vital sign observed and change from baseline will be summarized over scheduled visits.

4.14.4 Electrocardiograms

Screening and Day 5 ECG data will be provided in data listings.

4.14.5 Physical Examinations

Physical examination data will be provided in data listings.

4.15 Pharmacokinetic Analyses

During the study, PK samples will be collected for hospitalized subjects on Visit 1 (3 hours postdose), Visit 2 (predose), and Visit 5 (predose), and for non-hospitalized subjects on Visit 1 (3 hours postdose), Visit 3 (predose), and Visit 5 (predose). Predose samples will be collected at approximately the same time as the nasal swab sample(s). For the postdose collection on Day 1, a window of ±30 minutes for the sampling time is acceptable.

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

4.15.1 PK Analysis

Concentration-Time Data

For subjects in the PK population, descriptive statistics (number of subjects, arithmetic mean, geometric mean, standard deviation (SD), % coefficient of variation (%CV), %CV of the geometric mean (%GCV), median, min, and max) will be used to summarize the concentration data for EDP-938 and each metabolite by dose, age group, visit, and nominal time for Part 1 and Part 2 separately and pooled data from Parts 1 and 2. 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 BLQ, descriptive statistics will not be presented except for maximum (unless also BLQ, then BLQ will be presented), and BLQ will be displayed for mean and minimum.

Individual and 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.

PK Parameters

Plasma concentration of EDP-938 will be used to estimate the PK parameters of EDP-938 (including area under the curve (AUC, C_{trough}, and others as deemed appropriate) using a population PK model, as allowed by the data. The analysis will be described in a separate plan and results reported separately.

4.15.2 PKPD (Pharmacokinetic-Pharmacodynamic)

Scatter plots of EDP-938 plasma concentrations (Visit 5 predose for all subjects, Visit 2 predose for hospitalized subjects) in relation to RSV RNA viral load, clinical symptoms (ReSVinet [Parent/Guardian and Professional], RESOLVE-P), and AEs will be presented by Part 1 and Part 2 separately and pooled data from Parts 1 and 2.

PKPD will be presented as scatter plots using actual values. Both absolute change from baseline and percent change from baseline (for viral load and clinical symptoms) versus PK concentration on a linear scale figure will be presented as follows:

For all subjects:

- RSV RNA Viral Load and EDP-938 Plasma Concentration Predose at Visit 5
- RSV RNA Viral Load Change from Baseline and EDP-938 Plasma Concentration Predose at Visit 5
- RSV RNA Viral Load AUC Days 1-5 and EDP-938 Plasma Concentration Predose at Visit 5
- RSV RNA Viral Load AUC Days 1-14 and EDP-938 Plasma Concentration Predose at Visit 5
- Parent/Guardian ReSVinet Total Score and EDP-938 Plasma Concentration Predose at Visit 5
- Parent/Guardian ReSVinet Total Score Change from Baseline and EDP-938 Plasma Concentration Predose at Visit 5

- Professional ReSVinet Total Score and EDP-938 Plasma Concentration Predose at Visit 5
- Professional ReSVinet Total Score Change from Baseline and EDP-938 Plasma Concentration Predose at Visit 5
- Parent/Guardian RESOLVE-P Total Score and EDP-938 Plasma Concentration Predose at Visit 5
- Parent/Guardian RESOLVE-P Total Score Change from Baseline and EDP-938 Plasma Concentration Predose at Visit 5
- Total number of TEAEs and EDP-938 Plasma Concentration Predose at Visit 5 (by severity)

For hospitalized subjects:

- RSV RNA Viral Load at Day 5 and EDP-938 Plasma Concentration Predose at Visit 2
- RSV RNA Viral Load Change from Baseline at Day 5 and EDP-938 Plasma Concentration Predose at Visit 2

4.16 Respiratory Syncytial Virus Subgroup/Genotype Determination

A nasal swab sample at Baseline (Day 1) will be analyzed to determine the subgroup (A or B) and genotype of RSV. If data from Baseline (Day 1) are not available, then subgroup (A or B) will be determined from another nasal swab sample. Other subgroup analyses may be explored as allowed by data.

4.17 Interim Analyses

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

[redacted]

6. REFERENCES

[1] United States Food and Drug Administration Guidance Document. International Conference on Harmonization E9 Statistical Principles for Clinical Trials. September 1998.

[2] Matthews JN, Altman DG, Campbell MJ, et al. Analysis of serial measurements in medical research. BMJ. 1990; 300(6719): 230-5.

7. APPENDICES

7.1 Schedule of Assessments

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

Study Period	Screening[1,2]	Treatment					Follow-Up			For non-hospitalized subjects, V2 and V4 assessments will be done at home. (X) is for V2 and V4 assessments for hospitalized subjects.
Visit	Screening	V1	V2	V3	V4	V5	PT1	PT2	PT3[3]	
Day	Day-1 to Day 1	1	2	3 (±1)[4]	4	5 (±1) EOT[5]	9 (±1)	14 (±2)	28 (±4) EOS[5]	Notes[6]; Protocol Section
										assessment must be predose. Section 8.10.1
Parent/Guardian ReSVinet clinical scoring system and palatability question		Once daily from predose on D1 through D14								Caregiver(s) should complete the Parent/Guardian ReSVinet clinical scoring system using the eCOA handheld eDiary for both hospitalized and non-hospitalized subjects. The ReSVinet D1 assessment must be predose, and subsequent assessments should be completed predose at the same time **daily** (±2 hr) **for 14 days.** The palatability assessment should be completed after each dose of study drug is administered. If a caregiver is unable to use the eDiary, a paper diary may be used. Section 8.10.2
Parent/Guardian RESOLVE-P clinical scoring system)		Twice daily on D1 through D14								Caregiver(s) should complete the Parent/Guardian RESOLVE-P clinical scoring system on paper for both hospitalized and non-hospitalized subjects. The D1 assessment must be completed predose, and subsequent assessments should be completed twice daily, approximately every 12 hours, for 14 days. If D1 assessment is completed in the afternoon, only one assessment is expected for that day. RESOLVE-P will be completed in a subset of subjects. Section 8.10.3
Clinical Safety Evaluations										
Vital sign measurements (including SpO_2)	X	X		X		X	X	X		If Screening and V1 occur on the same calendar day, vital signs measurements do not need to be repeated and the Screening measurements will be used as baseline values. If Screening and V1 occur on different calendar days, V1 measurements should be taken pre-dose as baseline values. Starting on D1, vital signs should be performed QD on marked study site visit days. Section 8.4

Study Period	**Screening[1,2]**	**Treatment**					**Follow-Up**			**For non-hospitalized subjects, V2 and V4 assessments will be done at home. (X) is for V2 and V4 assessments for hospitalized subjects.**
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**PT1**	**PT2**	**PT3[3]**	
Day	**Day-1 to Day 1**	**1**	**2**	**3 (±1)[4]**	**4**	**5 (±1) EOT[5]**	**9 (±1)**	**14 (±2)**	**28 (±4) EOS[5]**	**Notes[6]; Protocol Section**
Physical examination	X			X		X	X	X		Full PE at Screening. Subsequent PEs done at discretion of Investigator will be targeted to new signs and symptoms, including specific assessments of changes from previous status. Section 8.6
ECG	X					X				12-lead ECG strongly preferred but where not possible, 6-lead ECG may be performed. If blood sampling and/or a nasal swab are scheduled for the same timepoint as ECG recording, those assessments should be done after the ECG. Section 8.5
Procedures										Residual samples from blood and/or nasal swab volume may be used for exploratory biomarker analyses. Section 8.14
Nasal swab		X		X		X	X	X		Swab samples should be taken at approx. same time before study drug administration. One swab will be collected at each visit. Section 8.12
Blood sampling for clinical laboratory tests	X	X*		X		X				Clinical laboratory tests include biochemistry, hematology, and cardiac biomarkers. All clinical laboratory tests that will be evaluated in the study are specified in Table 3. Evaluations will be conducted by local laboratories. *For subjects who have screening and randomization separated by more than 24 hours, blood sampling for clinical laboratory tests should be done predose on Day 1 for baseline values. This blood sampling does not need to be done for subjects who have randomization within 24 hours after screening because the screening clinical laboratory test results will be used as the baseline values. Section 8.11
Urinalysis	X					X				Urine will be collected only from subjects who are either toilet trained and able to provide a specimen or are already catheterized or fitted with a urine collection bag, Section 8.11

Study Period	**Screening[1,2]**	**Treatment**					**Follow-Up**			**For non-hospitalized subjects, V2 and V4 assessments will be done at home. (X) is for V2 and V4 assessments for hospitalized subjects.**
Visit	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5**	**PT1**	**PT2**	**PT3[3]**	
Day	**Day-1 to Day 1**	**1**	**2**	**3 (±1)[4]**	**4**	**5 (±1) EOT[5]**	**9 (±1)**	**14 (±2)**	**28 (±4) EOS[5]**	**Notes[6]; Protocol Section**
Blood sampling for PK		X	(X)	X		X				**Hospitalized subjects** • Visit 1: 3 hours postdose • Visit 2: predose • Visit 5: predose **Non-hospitalized subjects** • Visit 1: 3 hours postdose • Visit 3: predose • Visit 5: predose All subjects: Predose samples should be collected at approximately the same time as the nasal swab sample(s). For the postdose collection on Day 1, a window of ±30 minutes for the sampling time is acceptable. The time and date of PK sample collection will be recorded in source and eCRF. Section 8.13
Ongoing Subject Review										
Concomitant treatment	X	X	(X)	X	(X)	X	X	X	X	Section 8.3
Healthcare resource utilization		X	(X)	X	(X)	X	X	X	X	Evaluate level of care (e.g., ICU, translational care unit, ward floor, home), duration of hospitalization if hospitalized, incidence of MAARI, requirement for and duration of oxygen supplementation/noninvasive mechanical ventilation support and/or invasive mechanical ventilation support and requirement for hydration and feeding by IV catheter/nasogastric tube. Section 8.9
Adverse events	X	X	(X)	X	(X)	X	X	X	X	If V5 is conducted before D5 due to the visit window, caregivers should be contacted as soon as possible after D5 dosing to assess AEs, concomitant treatments, and healthcare utilization. Section 8.8

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

[1] Procedures performed as part of standard of care within 72 hours before the informed consent is signed may be used in determining study eligibility and/or as baseline values.

[2] Screening should be completed as soon as possible to ensure that subjects will be randomized and administered the first dose of study drug within 24 hours of signing the ICF.

[3] PT3 assessment may be conducted as a telephone call.

[4] If Visit 3 occurs on Day 4 due to the visit window, Visit 5 should occur on Day 5 or Day 6.

[5] Subjects who discontinue treatment early (before completing 5 days of dosing) should return to the study site within 24 hours following the last dose of study drug for an EOT visit. Follow-up visits will be scheduled 4 days (PT1, Day 9), 9 days (PT2, Day 14), and 23 days (PT3), Day 28 [EOS]) after the last dose of study drug was administered. Assessments should be performed as indicated, respectively for the Day 9 (PT1), Day 14 (PT2), and Day 28 (EOS/PT3) visit. Subjects who discontinue the study early (before Day 28) should return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.

[6] If multiple assessments are scheduled for the same timepoint, it is recommended that noninvasive procedures being done before more invasive procedures, e.g., first complete eCOA (parent/guardian and clinician eCOAs could be concurrent), then ECG, then vital signs/SpO2, then nasal swab and finally blood draw.

7.2 Professional ReSVinet Clinical Scoring System

To be completed by site investigator or designee

Assessment Period	Item	0 points	1 point	2 points	3 points
Over the last 24 hours	**1 Feeding intolerance**	**None**	**Mild** Decreased appetite and/or had isolated vomiting with coughing.	**Partial** Frequently vomits with coughing, rejected feeds but able to tolerate fluids sufficiently to ensure hydration.	**Total** Intolerance or absolute rejection of feeds, unable to maintain adequate hydration orally. Required nasogastric and/or intravenous fluids
Over the last 24 hours	**2 Medical intervention**	**None**	**Basic** Nasal secretion aspiration performed, trial of nebulized bronchodilators, antipyretics.	**Intermediate** Oxygen therapy required. Supplementary testing needed (eg, chest X-rays, blood gases). Ongoing nebulized bronchodilators.	**High** Required respiratory support with positive pressure (either non-invasive in continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or high-flow O2; or invasive through endotracheal tube).
As examined	**3 Respiratory difficulty**	**None**	**Mild** Not feeling as usual but does not look severely ill. Respiratory wheezing audible only with stethoscope, good air entry. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates mild severity.	**Moderate** Makes some extra respiratory effort (intercostal and/or tracheosternal retraction). Expiratory wheezing is audible even without stethoscope, and air entry may be decreased in localized areas with stethoscope. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates moderate severity.	**Severe** Respiratory effort is obvious. Inspiratory and expiratory wheezing and/or clearly decreased air entry with stethoscope. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates high severity.

To be completed by site investigator or designee

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

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

7.3 Parent/Guardian ReSVinet Clinical Scoring System and Palatability Question

To be completed by parent/caregiver

Assessment Period	Item	0 points	1 point	2 points	3 points
Over the last 24 hours	**1 Feeding intolerance**	**None**	**Mild** Decreased appetite (the child ate less than usual) and/or had isolated vomiting with coughing.	**Partial** Frequently vomits with coughing, but the child does not vomit with every feed. Feeding exhausts the child.	**Total** The child is unable to feed him/herself. The use of a nasogastric tube or parenteral nutrition was required.
Over the last 24 hours	**2 Medical intervention**	**None**	**Basic** The child's respiratory secretions needed to be removed, he or she was examined by a doctor or received occasional nebulized medication. Medication to treat fever was given.	**Intermediate** The child required oxygen therapy, underwent a chest X-ray, or a blood sample was taken. Treatment with nebulized medication was given regularly.	**High** The child required respiratory support with a machine. Respiratory support was given through a special mask applied to the nose or mouth or resting on the child's face, or through an endotracheal tube.
When the diary was completed	**3 Respiratory difficulty**	**None**	**Mild** The child was not breathing normally, but he/she does not seem to have any difficulty when breathing in.	**Moderate** The child finds breathing is an effort. Respiratory noises can be heard just by pressing your ear close to his or her chest (without a stethoscope)	**Severe** Respiratory effort is obvious. The child makes significant movements of his/her chest, the chest even collapses with every movement, and muscles of neck and belly were used. A lot of respiratory noise is heard without pressing the ear close to the child's chest.
Over the last 24 hours	**4 Respiratory frequency**	**Normal**	**Mild or occasional tachypnea** The child was breathing more rapidly but it was well tolerated, or the breathing became normal after removing secretions from the child's airways or administering nebulized medication.	**Prolonged or recurrent tachypnea** The child was breathing more rapidly and persistently, even after receiving nebulized medication or removing secretions from the child's airway.	**Severe alteration** The child breathed quickly and superficially, or really deeply. The child was agitated or drowsy. The child was severely short of breath.

To be completed by parent/caregiver

Assessment Period	Item	0 points	1 point	2 points	3 points
Over the last 24 hours	**5 Apnea**	**No**			**Yes** The child stopped breathing. It may have been necessary to stimulate him/her to start normal breathing.
When the diary was completed	**6 General Condition**	**Normal**	**Mild** The child is not feeling as usual, but there does not seem to be anything to worry about.	**Moderate** Child looked ill, and medical examination was required, but it did not feel like a life-threatening situation.	**Severe** Child was agitated, apathetic and/or lethargic. He/she required urgent medical attention. There was no need to be a doctor to see that the condition of the child is worrying.
Over the last 24 hours	**7 Fever**	**No**	**Yes, Mild** Rectal or tympanic temperature <38.5°C, or axillar temperature <38°C	**Yes, Moderate** Rectal or tympanic temperature >38.5°C, or axillar temperature >38°C	

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

Palatability Question

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

Select all that apply:

- ☐ Successfully swallowed the medicine without vomiting within 2 minutes of swallowing;
- ☐ Took the study medication easily;
- ☐ The facial expression suggested that he/she did not like the taste;
- ☐ Cried after tasting it;
- ☐ Would not open mouth or turned head away to avoid it;
- ☐ Spit out or coughed it out;
- ☐ Gagged or vomited (within 2 minutes of swallowing medicine).

7.4 Respiratory Observable Reported Outcome -Pediatric (RESOLVE-P)

Instructions

Please answer the following questions thinking about the past 12 hours. Please complete this twice per day (once in the morning and once in the evening) around the same times each day. An [alarm/text] reminder will notify you when you can complete the survey.

Items

1. How bad was the child's difficulty breathing (e.g., shortness of breath, labored breathing, unable to breathe normally, rapid breathing) at its worst over the past 12 hours?

   ☐ 0 None
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe

2. How bad was the child's wheezing (a high-pitched whistling sound when breathing) at its worst over the past 12 hours?

   ☐ 0 None
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe

3. How bad was the child's cough at its worst over the past 12 hours?

   ☐ 0 None
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe

4. How bad was the child's stuffy nose at its worst over the past 12 hours?

   ☐ 0 None
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe

5. How bad was the child's runny nose at its worst over the past 12 hours?

☐ 0 None
☐ 1 Mild
☐ 2 Moderate
☐ 3 Severe

6. How bad was the child's sneezing at its worst over the past 12 hours?

☐ 0 None
☐ 1 Mild
☐ 2 Moderate
☐ 3 Severe

7. Did the child have a fever (a lot warmer to the touch) over the past 12 hours?

☐ 0 No
☐ 3 Yes

8. How was the child's appetite over the past 12 hours?

☐ 0 Usual appetite
☐ 1 Ate/nursed a little less than usual
☐ 2 Ate/nursed a lot less than usual
☐ 3 Did not eat/nurse at all

9. How was the child's activity level over the past 12 hours?

☐ 0 Usual activity level
☐ 1 A little less active than usual
☐ 2 A lot less active than usual
☐ 3 Not active at all

10. How was the child's alertness/responsiveness over the past 12 hours?

☐ 0 Usual alertness/responsiveness level
☐ 1 A little less alert/responsive than usual
☐ 2 A lot less alert/responsive than usual
☐ 3 Not alert/responsive at all

11. How was the child's crying over the past 12 hours?

☐ 0 Usual crying

☐ 1 A little more crying than usual
☐ 2 More crying than usual
☐ 3 A lot more crying than usual

7.5 Caregiver Global Impression of Severity (CaGI-S)

Please choose the response that best describes the severity of the child's Respiratory Syncytial Virus (RSV) symptoms in the past 12 hours.

☐ 0 None
☐ 1 Mild
☐ 2 Moderate
☐ 3 Severe

7.6 Caregiver Global Impression of Change (CaGI-C)

Compared to pre-treatment

Please choose the response that best describes the overall change in the child's Respiratory Syncytial Virus (RSV) symptoms since the child started taking the study medication.

☐ 2 Much better
☐ 1 A little better
☐ 0 No change
☐ -1 A little worse
☐ -2 Much worse

Compared to the previous assessment (continuation)

Please choose the response that best describes the overall change in the child's Respiratory Syncytial Virus (RSV) symptoms in the past 12 hours compared to the previous assessment.

☐ 2 Much better
☐ 1 A little better
☐ 0 No change
☐ 1 A little worse
☐ 2 Much worse