ENANTA Pharmaceuticals

Statistical Analysis Plan

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

Protocol Number: EDP 938-102

Protocol Version:	5.0 (Amendment 4.0)
Date:	20 May 2020
Study Sponsor:	Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472

Client:	Enanta Pharmaceuticals
Protocol Number:	EDP 938-102

Document Description:	Final Statistical Analysis Plan
SAP Title:	A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF EDP-938 ADMINISTERED ORALLY FOR THE TREATMENT OF ACUTE UPPER RESPIRATORY TRACT INFECTION WITH RESPIRATORY SYNCYTIAL VIRUS IN AMBULATORY ADULT SUBJECTS (RSVP)
SAP Version Number:	Final 1.0
Effective Date:	11MAR2022

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Approved by:

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[redacted] Date *(DD-MMM-YYYY)*

[redacted]

[redacted] Date *(DD-MMM-YYYY)*

LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
ANCOVA	analysis of covariance
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence intervals
COPD	chronic obstructive pulmonary disease
C_{trough}	trough concentration
DSMB	Data Safety Monitoring Board
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
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IWRS	Interactive Web Response System
LLN	lower limit of normal
mITT	Modified Intent-to-Treat
MCMC	Markov Chain Monte Carlo
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic(s)
PP	Per Protocol
QTcF	QT interval corrected for heart rate according to Fridericia
RSV	respiratory syncytial virus
SAE	serious adverse event
SAF	Safety (for the analysis population)
SAP	statistical analysis plan
SoA	Schedule of Assessments
TEAE	treatment-emergent adverse event

TSS	total symptom score
ULN	upper limit of normal
WHO	World Health Organization

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1. STUDY DESIGN

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

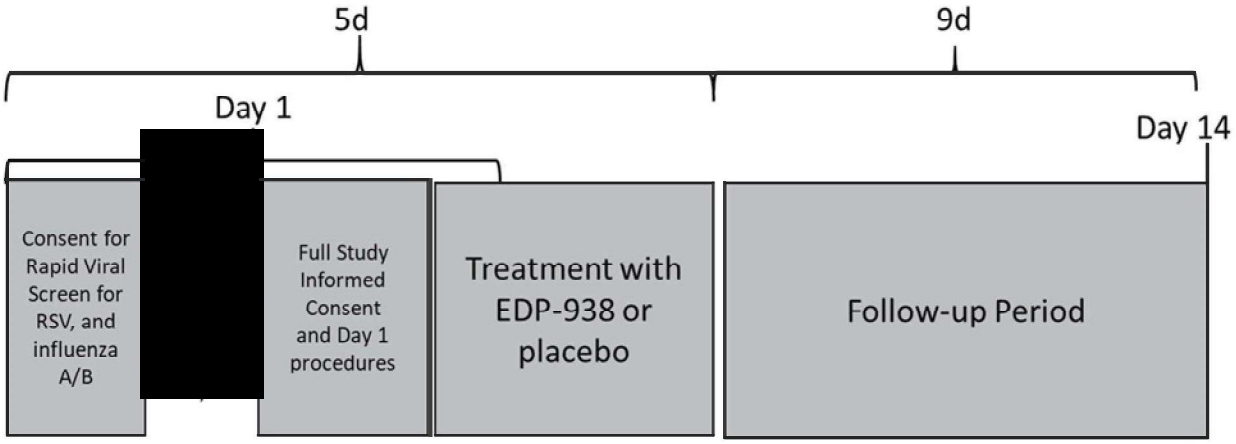
The study is composed of 3 periods:

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

1.1 Dose and Treatment Schedule

Subjects who meet all inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be randomized in a 1:1 ratio to receive 800 mg of EDP-938 or placebo once daily for a total of 5 days. An overview of the study design is shown in Figure 1. Study site visits and assessments are detailed in the Schedule of Assessments (SoA; Appendix 5.1).

Figure 1: Study Design



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

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

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

[redacted]

2.2 Endpoints

2.2.1 Primary Endpoint

- RSV infection clinical symptoms measured as the total symptom score (TSS) AUC from Day 1 through Day 14

2.2.2 Secondary Endpoints

- AUC from Day 1 through Day 14 for RSV RNA viral load measured in nasopharyngeal swab samples by quantitative reverse transcription polymerase chain reaction (RT-qPCR)

- Percentage of subjects with RSV RNA viral load below the limit of detection on Days 3, 5, 9 and 14 respectively
- Plasma PK concentrations of EDP-938 and its major metabolites ([redacted]024636, EP-024594, and EP-024595) on Days 1, 3 and 5
- Safety endpoints include, but are not limited to, AEs, vital sign measurements, pulse oximetry measurements, and clinical laboratory test results (including chemistry, hematology, and urinalysis)
- Time to RSV RNA viral load below the limit of detection
- RSV RNA viral load and change from baseline over time

[redacted]

3. STATISTICAL CONSIDERATIONS

3.1 General Considerations

Statistical analysis of this study will be the responsibility of Enanta Pharmaceuticals, Inc. or its designee. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. [redacted] The preparation of this SAP has been based on International Conference on Harmonization (ICH) E9 guidelines. The table of contents and shells for the tables, figures, and listings (TFLs) will be produced in a separate document.

All statistical procedures will be completed using SAS version 9.4 or higher. Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95% confidence intervals (CI) will be provided when relevant. P-values will be displayed in the following format, 0.999. Any p-value less than 0.001 will be displayed as <0.001. Any p-value greater than 0.999 will be displayed as >0.999.

All quantitative endpoints will be summarized using (n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum values). The mean and median and the percentiles will be rounded to one decimal place beyond the precision of the values being summarized, the standard deviation will be rounded to 2 additional decimal places beyond this precision and the minimum and maximum values will be displayed in the same precision. All qualitative endpoints will be summarized by the number of subjects meeting the endpoint and the percentage of subjects out of the appropriate population. The denominator will be displayed when needed and the percentage will be rounded to one decimal place.

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 only. All listings will be sorted by investigational site, 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. The randomized overall (totals) will only be presented for study disposition.

Unless otherwise specified, the baseline is defined as the last non-missing assessment value for a subject, for that particular parameter, that is prior to or on the date of first dose of study drug. For subjects who are randomized, but not treated, the baseline will be defined as the last non-missing assessment prior to or on the date of randomization. Percent change from baseline will be calculated as the [change divided by baseline] multiplied by 100. In the event change=0, then the percent change will be 0. In the event baseline=0, then the percent change will be missing.

The date of first dose and the date of last dose will be the date collected on the End of Treatment eCRF.

For the reporting of this study both CDISC SDTM (SDTM Implementation Guide version 3.2) and ADaM (ADaM Implementation Guide version 1.1) 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 14 ± 1 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.

Summary Tables and Figures will be presented by treatment group. Tables and Figures values for treatment group will be labelled as follows: • "EDP-938 800mg" • "Placebo". Models will include stratification factor for asthma/COPD status unless an insufficient amount of data exists where convergence or the analysis cannot be performed.

[redacted]

3.3 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. For some sensitivity analysis missing data imputation methods will be implemented. In particular, the methods of handling missing data for the efficacy endpoints (*Section 3.14.1.1*), incomplete dates for adverse events and concomitant medication use (*Section 3.3.1*) 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.

3.3.1 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.
    - 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 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.

Imputation rules for missing or partial medication 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.

3.4 Treatment Assignment/Randomization

Subjects will be randomized to a treatment group using an Interactive Web Response System (IWRS). Subjects will be randomized in a 1:1 ratio to the EDP-938 or placebo treatment group as shown below:

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

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

3.5 Analysis Populations

Subjects will be initially diagnosed using a local rapid antigen test. A central laboratory RT-PCR assay will be used to confirm the local results.

Safety (SAF) Population: All subjects who receive at least one dose of study drug. Subjects will be analyzed in the treatment group that corresponds to the study drug received during the study.

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

Per Protocol (PP) Population: All subjects in the mITT population who completed 5-day treatment period and do not have major protocol deviations that may unduly influence TSS. Protocol deviations that would exclude subjects from the PP population are defined in *Section 3.8* (Protocol Deviations). Subjects will be analyzed as randomized.

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

3.6 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 and safety laboratory tests:

Analysis Visit #	Analysis Visit Label	Target Day	Derivation
1	Day 1	1	Based on nominal visit

5	Day 5	5	Based on nominal visit
14	Day 14	14	Based on nominal visit

For RSV RNA quantitation of viral load:

Analysis Visit #	Analysis Visit Label	Target Day	Derivation
1	Day 1	1	Based on nominal visit
3	Day 3	3	Based on nominal visit
5	Day 5	5	Based on nominal visit
9	Day 9	9	Based on nominal visit
14	Day 14	14	Based on nominal visit

For RSV symptom diary:

Analysis Visit #	Analysis Visit Label	Target Day	Timepoint* Assessment	Derivation
1	Day1	1	1	Study day =1
1	Day1	1	2	Study day =1
2	Day 2	2	1	Study day =2
2	Day 2	2	2	Study day =2
3	Day 3	3	1	Study day =3
3	Day 3	3	2	Study day =3
4	Day 4	4	1	Study day =4
4	Day 4	4	2	Study day =4
5	Day 5	5	1	Study day =5
5	Day 5	5	2	Study day =5
6	Day 6	6	1	Study day =6
6	Day 6	6	2	Study day =6
7	Day 7	7	1	Study day =7

7	Day 7	7	2	Study day =7
8	Day 8	8	1	Study day =8
8	Day 8	8	2	Study day =8
9	Day 9	9	1	Study day =9
9	Day 9	9	2	Study day =9
10	Day 10	10	1	Study day =10
10	Day 10	10	2	Study day =10
11	Day 11	11	1	Study day =11
11	Day 11	11	2	Study day =11
12	Day 12	12	1	Study day =12
12	Day 12	12	2	Study day =12
13	Day 13	13	1	Study day =13
13	Day 13	13	2	Study day =13
14	Day 14	14	1	Study day =14
14	Day 14	14	2	Study day =14

* RSV symptom diary is completed twice daily by subjects and thus assigned as Timepoint 1 and 2. For Day 1, timepoint 1 corresponds to the pre-dose diary and timepoint 2 to the post-dose diary.

[redacted]

3.6.1 Data Handing for RSV Symptom Diary Data Issues

For a particular timepoint, if data is collected on both electronic and paper diary, then data from the electronic diary will be used for analysis.

[redacted]

3.7 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 by treatment group and overall. The denominator for the calculation of percentages will be from the number of subjects randomized.

The following categories will also be summarized for subject disposition by treatment group and overall:

- 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 denominator used for the calculation of percentages will be the number of subjects randomized. In addition, the number of subjects excluded from analysis sets and reasons for exclusion will be summarized by treatment group and overall.

3.8 Protocol Deviations

All protocol deviations (both significant and non-significant) 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. A significant deviation is any deviation that may affect primary efficacy and safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the trial.

Significant protocol deviations which may further result in exclusion of subjects from the Per Protocol population may include (but are not limited to) the following:

- Subjects missing significant number of RSV symptom diaries in the early days (Days 2-5)
- Subjects with poor compliance with study treatment (< 80%)
- Subjects taking prohibited medications that may potentially affect the RSV symptoms

Data will be reviewed prior to closure of the database and unblinding the study to ensure all significant deviations are captured and categorised. Particularly, a final list of significant protocol deviations leading to exclusion from the PP population (these were considered as major protocol deviations in the protocol) will also be determined by the study team.

Significant protocol deviations will be summarized by treatment group and overall. A separate listing will be also provided for significant protocol deviations with a flag for those excluded from the PP. Non-significant protocol deviations will be just listed. Summaries will be conducted on all subjects that were randomized.

3.9 Demographic and Baseline Characteristics

No statistical testing will be performed for the comparison between treatment groups on demographics and baseline characteristics. Subject demographics will be summarized by randomized treatment group for all subjects in the Safety Population. Age, height, weight and BMI collected at screening will be summarized (n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum values). Qualitative variables such as gender, ethnicity and race will be summarized using count and percentage. A by-subject listing will be provided.

Other baseline characteristics includes frailty scale scores at screening, stratification factors (asthma/COPD status [present or absent]), RSV type (RSVA or RSV B), RSV TSS, FLU-PRO Total Score and RSV viral load. These baseline characteristics will be summarized similarly as for subject demographics.

3.10 Medical History

A summary of past or present clinically significant medical conditions will be presented by system organ class (SOC) and referred term (PT) using Medical Dictionary for Regulatory Affairs® (MedDRA) using the latest version by counts and percentages. The summary will be based on the Safety Population. A by-subject listing will be provided.

3.11 Prior and Concomitant Medications

Medications used in this study will be coded by using the latest available version of the World Health Organization Drug Dictionary Enhanced (WHO-DDE). 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 and within 30 days after the last dose. 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-2) class and preferred term by treatment group on 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 3.3.1*.

3.12 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 by treatment group using the Safety Population and the Modified Intent-to-Treat Populations

3.13 Treatment Compliance

Study drug compliance based on the number of tablets taken will be calculated as: 100 x [(total number of tablets dispensed) – (total number of tablets returned)]/ (total number of tablets planned to be taken per day x duration of study drug in days). Study drug compliance will be summarized using the Safety Population and the Modified Intent-to-Treat Populations by treatment group.

3.14 Efficacy Analyses

All efficacy analyses will be based on mITT population unless otherwise specified.

3.14.1 Primary Efficacy Analyses

The primary efficacy analysis will be performed on the total symptom score (TSS) AUC on the respiratory syncytial virus symptom diary (see Appendix 5.2) using the mITT population. The primary efficacy analysis will be repeated using the PP population. The TSS is measured twice daily using a 13-point symptom scale. Date and time of completion will be recorded. For Day 1,

the TSS is measured first pre-dose and then post-dose. Subjects have been instructed to complete the symptom scale either immediately before or 4 hours after using acetaminophen medication to avoid confounding results. From Day 1 through Day 14, subjects will electronically record the date and time of any acetaminophen use.

The TSS will be derived for each subject using the electronic data capture handheld device (ERT® electronic clinical outcome assessment [eCOA] Handheld eDiary) or paper diary. Baseline TSS will be collected once on Day 1 prior to first dose. If baseline TSS is missing, the assessment of TSS post-dose on Day 1 will used as baseline. The average daily TSS will be computed as part of the primary efficacy endpoint analysis.

The TSS will be derived for each subject, separately for each of the two assessments on each day (Day 1 to Day 14) as follows:

1) For each assessment, sum the 13 observed symptom grade values for a total symptom score. If *any* of the 13 observed values are missing the total symptom score will not be calculated for that assessment.

The TSS AUC from Day 1 through Day 14 will be calculated using the trapezoid rule (*Matthews et al., 1990*). The AUC will require at least 2 non-missing calculated total symptom scores. Missing total symptom score data will be reviewed for potential impact, and any decisions to include subjects that fail these criteria above will be documented. The AUC will be calculated based on available individual assessments of TSS collected twice per day from Day 1 through Day 14, and the actual date/time of each assessment will be used for the calculation. For the baseline TSS, the actual 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.

The AUC TSS from Day 1 through Day 14 will be compared between EDP-938 and placebo using an analysis of covariance (ANCOVA) model with treatment group, asthma/COPD status (present or absent) as factors and the baseline TSS as a covariate. The analysis will be performed using SAS procedure MIXED. Treatment groups will be compared using a type III sum-of-squares. The least-squares means, standard errors and two-sided 95% confidence intervals (CI) will be presented for individual groups and the difference between groups. The same ANCOVA analysis will be performed for the TSS AUC from Day 1 through Day 3, from Day 1 through Day 5 and from Day 1 through Day 9.

Descriptive statistics will be displayed for TSS and change from baseline by day and timepoint and also for average daily TSS by day and will include at a minimum the number of non-missing measurements, mean, standard deviation, median, minimum, maximum, and 95% CI for the mean.

Multiple line graphs of TSS will be produced:

(1) Observed mean TSS ± 95% confidence interval by days 1-14 and timepoint for each treatment group

(2) Observed mean TSS (average per day) ± 95% confidence interval by days 1-14 for each treatment group

3.14.1.1 Sensitivity Analysis of the Primary Endpoint

If acetaminophen use is within 4 hours before a TSS, then the TSS may have been impacted. Thus, TSS AUC for mITT analysis will be reproduced after excluding such TSS assessments post-baseline.

Time to resolution of TSS will be analyzed using a Cox Proportional Hazards model. This will be performed for the mITT population. Stratification factors, baseline TSS and asthma/COPD status (present or absent), will be included. Time to resolution of TSS will be defined as the time from first dose to first of two consecutive timepoints where TSS is zero (days). Consecutive timepoints is defined as two consecutive timepoints planned per protocol, e.g. Day 2 timepoint 2 and Day 3 Timepoint 1. A Kaplan-Meier curve will display the probability estimates with resolution. Descriptive statistics on the graph will include the median and 95% confidence interval at a minimum.

3.14.2 Secondary Efficacy Analyses

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 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.

There will be two readings for both RSV A and RSV B, one from each of the two wells (i.e. A1, A2, B1, and B2). In case of any technical failure, no readings will be reported for the standard test, but a re-test will be done using a different aliquot from the same sample to produce valid results. PPD's unblinded statistician will then review the data and identify samples meeting discrepancy criteria for RSV A or RSV B. For these samples, a re-test will be performed using a different aliquot from the same sample. The discrepancy criteria for RSV A (same for RSV B) are defined as the following:

- Both A1 and A2 are numeric, and A1/A2 is >10 or <1/10 (i.e., one log difference);
- One of A1 and A2 is numeric, and the other one is TD or TND
- One of A1 and A2 is TD, and the other one is TND

For each sample, the final data will contain one or two sets of results.

The final RSV value (for A and B separately) for each sample will be the simple mean of the readings in original scale based on the following:

- Two readings from the only set if the final data have only one set of results.
- Two readings from the set without discrepancy if the final data have two sets of results and one set has discrepancy while the other set has no discrepancy
- Four readings from both sets if the final data have two sets of results and both sets have discrepancy
- Four readings from both sets if the final data have two sets of results and both sets have no discrepancy

Note: The readings reported as TND (target not detected) will be replaced by zero and those reported as TD (target detected) will be replaced by the average of LOD and LLOQ in the calculation of the RSV value.

The RSV type of each subject will be determined based on the final RSV value at baseline. If the baseline of RSV A is bigger, then the RSV type is A; otherwise, it is B. The analysis of the viral load will be based on the log scale of the RSV.

The RSV RNA viral load AUC will be derived similarly as described in *Section 3.14.1*. 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 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 though Day 14.

An ANCOVA model with treatment group and asthma/COPD status (present or absent) 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 14. Treatment groups will be compared using a type III sum-of-squares. The least-squares means, standard errors and two-sided 95% confidence intervals (CI) will be presented for individual groups and the difference between groups. The same ANCOVA analysis will be performed for the AUC from Day 1 through Day 3, from Day 1 through Day 5, and from Day 1 through Day 9.

The proportion of subjects with RSV RNA viral load below the limit of detection (LOD) 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 factors of asthma/COPD status (present or absent). Additionally, the number and proportion of subjects with RSV RNA viral load below LOD 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 below LOD will be analyzed using a Cox Proportional Hazards model. Stratification factors, baseline RSV RNA viral load and asthma/COPD status (present or absent), will be included. For calculating time to RSV viral load below LOD it is required of at

least two consecutive timepoints (or end of study) with viral load below LOD. Time to RSV viral load below LOD will be defined as the time between the date of first dose to the first date of achieving viral load below LOD, of the two consecutive timepoints or end of study. Subjects who discontinue early and subject who do not achieve viral load below LOD will be censored at the end of study date reported on the End of Study CRF. A Kaplan-Meier curve will display the probability estimates of achieving RSV RNA viral load below LOD. Descriptive statistics on the graph will include the median and 95% confidence interval at a minimum.

Descriptive statistics will 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.

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

3.15 Safety Analyses

Statistical methods for the safety analyses will be primarily descriptive in nature. The SAF will be used for all analyses, unless stated otherwise.

3.15.1 Adverse Events

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) using the system organ class (SOC) and preferred term (PT) by 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 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.
- Grade AEs: Grade AEs (serious and non-serious) in accordance with the NCI/CTCAE scale as follows: Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), Life-threatening (Grade 4), Death (Grade 5).

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 at a minimum:

- Overall summary of AEs with a line for each of the following categories
- TEAEs
    - By PT and SOC
    - By PT
    - By SOC
- Study Drug-Related TEAEs - by PT and SOC
- TEAEs of Grade 3 or Higher - by PT and SOC
- TEAEs by Maximum Grade – by PT and SOC

- TEAEs leading to study drug discontinuation – by PT and SOC
- AEs leading to death – by PT and SOC
- Serious TEAEs – by PT and SOC
- Study Drug-Related Serious TEAEs – by PT and SOC

3.15.2 Clinical Laboratory Data

Laboratory assessments will be reported as the mean of 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 each treatment group for selected analytes. Laboratory shifts will be displayed as treatment-emergent abnormal, high, or low results. The following details the summary types where LLN = lower limit of normal and ULN = upper limit of normal.

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

For continuous tests:

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

  For all parameters except Glomerular Filtration Rate (GFR) 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 for GFR will be reported according to any value less than (½)× LLN and (¼)× LLN. All other results will be reported to any value less than the lower limit.

3.15.3 Vital Sign Measurements

Vital signs will include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), heart rate (beats/min), weight (kg), BMI (kg/m^2), and oral temperature (°C). The incidence rate of subjects with treatment-emergent vital sign changes at any post-baseline visit will be summarized. Specific criteria for the classification of treatment emergent are documented below. Vital sign observed and change from baseline will be summarized by treatment over scheduled visits.

Criteria for treatment-emergent changes in vital signs parameters are defined as follows.

Heart Rate:

- Low: < 50 beats/min, > 30 beats/min decrease from baseline
- High: >120 beats/min, >30 beats/min increase from baseline

Systolic Blood Pressure:

- High: > 150 mmHg, > 200 mmHg

Diastolic Blood Pressure:

- High: > 100 mmHg, > 110 mmHg

Respiratory Rate:

- Low: < 8 breaths/min
- High: >40 breaths/min

Weight

- > 5% decrease from baseline
- > 5% increase from baseline

3.15.4 Electrocardiograms

Screening ECG data will be provided in data listings.

3.15.5 Pulse Oximetry

Pulse oximetry measurements should only be performed in subjects with asthma or COPD. Pulse oximetry measurements, oxygen level (%), will be summarized by visit and treatment.

3.15.6 Physical Examinations

Physical examination data will be provided in data listings.

3.16 Pharmacokinetic Analyses

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

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.

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

3.16.1 Analysis of PK samples

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. The number of observations, arithmetic mean, standard deviation (SD), % coefficient of variation (%CV), median, minimum, maximum, geometric mean, and %CV of the geometric mean (%GCV) will be displayed.

Individual data will be presented in listing.

3.17 Subgroup and Covariate Analyses

TSS AUC from Day 1 through Day 14 and RSV RNA viral load AUC from Day 1 through Day 14 will be analyzed by RSV type (A or B) using the same ANCOVA analysis as described in Section 3.14.1 and Section 3.14.2, except that RSV type and treatment by RSV type interaction are added to the model.

Other subgroup analyses may be explored as allowed by data.

[redacted]

3.19 Interim Analyses

No interim analysis will be performed in this study.

3.20 Multiplicity

No adjustment will be made for multiple comparisons.

3.21 Treatment by center interaction analysis

No analysis will be made to assess the treatment-by-center interaction.

4. REFERENCES

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5. APPENDICES

5.1 Schedule of Assessments

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

Adverse events	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; d = day; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; EOS = end-of-study; EOT = end-of-treatment; FLU-PRO = InFLUenza Patient-Reported Outcome; FSH – follicle-stimulating hormone; ICF – informed consent form; NP – nasopharyngeal; PK – pharmacokinetic; RSV – respiratory syncytial virus; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SPM = Study Procedures Manual.

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

[a] Day 1 assessments to be performed in randomized subjects.

[b] Subjects who discontinue treatment early (ie, prior to completing 5 days of dosing) or the study early (ie, prior to Day 14) should return to the study site within 24 hours and no more than 48 hours later to complete the EOS procedures.

[c] Visit assessments may be completed at the study site or by a study nurse via a home visit, if feasible; refer to the SPM for details. It is anticipated that every reasonable effort will be made to ensure that subjects return to the site for the Day 3 and Day 5 visits.

[d] Informed consent must be obtained prior to conducting any study-specific assessments. For this study, there will be two ICFs. Subjects will review and sign the Rapid Viral Screen ICF prior to RSV and influenza screening. Subjects whose swab sample tests positive for RSV and negative for influenza virus may proceed for further screening. Such subjects will be required to sign the full study ICF prior to performing any further study-specific assessments. After signing the full study ICF, subjects will undergo further screening procedures to determine study eligibility.

[e] A nasal (or NP) swab sample will be collected to obtain respiratory secretions for a rapid diagnostic screen for RSV and influenza A/B.

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

[g] Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Vital signs will be measured after the subject has been supine for a minimum of 5 minutes.

[h] A full physical examination will be performed at Screening. Any subsequent physical examinations performed at the discretion of the Investigator will be targeted to new signs and symptoms including specific assessments of any changes from previous status.

[i] Height will be documented at Screening only. Body mass index will be calculated at Screening (to assess eligibility) according to the following equation: BMI = weight (kg)/height $(m)^2$.

[j] Pulse oximetry measurements should only be performed in subjects with asthma or COPD.

[k] Pregnancy testing will be performed in female subjects of childbearing potential. A urine pregnancy test will be performed at Screening and at the EOS Visit. In addition, on Day 1, blood will be collected for a serum pregnancy test to be performed by the central laboratory. The screening urine pregnancy test results will be used to qualify subjects at study entry. Refer to Protocol Section Error! Reference source not found. for pregnancy testing requirements for postmenopausal females.

[l] Follicle-stimulating hormone should be tested in postmenopausal females. Refer to Protocol Section Error! Reference source not found..

[m] Clinical laboratory tests include chemistry, hematology, and urinalysis. See Protocol Section Error! Reference source not found. and Error! Reference source not found. for details regarding Day 1 sample collection and evaluations for the local and central laboratory(ies).

[n] Subjects who meet all inclusion criteria and none of the exclusion criteria to the satisfaction of the Investigator, including the screening ECG and the screening urine pregnancy test, will be eligible to enter the study and will be randomized 1:1 to receive 800 mg of EDP-938 or placebo. Subject randomization will be stratified by the presence or absence of asthma/COPD.

[o] Eligible subjects will receive an electronic data capture handheld device (ERT® eCOA Handheld eDiary) on Day 1 and will return the device to the study site at the EOS Visit. Refer to Protocol Section Error! Reference source not found. for additional details.

[p] The RSV symptom diary will be self-completed by subjects twice daily at the same times each day ±2 hours as an eCOA. If a subject plans to take acetaminophen within 2 hours of the scheduled RSV symptom diary completion, then the RSV symptom diary should be completed immediately before the subject takes acetaminophen or 4 hours after taking acetaminophen.

[redacted]

[s] Study drug (EDP-938 or placebo) should be administered at the study site on Days 1 and 5. On Day 5, the study site visit should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site. From Day 1, subjects will electronically record the time and date that each dose is taken. See Protocol Section Error! Reference source not found. for additional dosing details.

[t] Study drug accountability by tablet count and review of the electronic dosing record completed by the subjects.

[u] On Day 1, collect one postdose plasma PK sample, at least 1 hour after dosing or right before the subject leaves the site, whichever is later. On Day 3, collect one plasma PK sample at the same approximate time as that of the NP swab collection. On Day 5, collect one predose PK sample. If the subject takes the study drug prior to the study site visit, a PK sample should be taken at the same approximate time as that of the NP swab collection. See Protocol Section Error! Reference source not found. and Section Error! Reference source not found. for additional details.

[v] At the EOS Visit, a PK sample is only required for subjects who discontinue the study before the last dose of study drug is taken. The PK sample should be collected at the same approximate time as that of the NP swab collection.

[w] Acetaminophen use will be permitted only for the relief of fever or pain. Subjects will electronically record the date and time of any acetaminophen use. See Protocol Section Error! Reference source not found. for additional details on acetaminophen use.

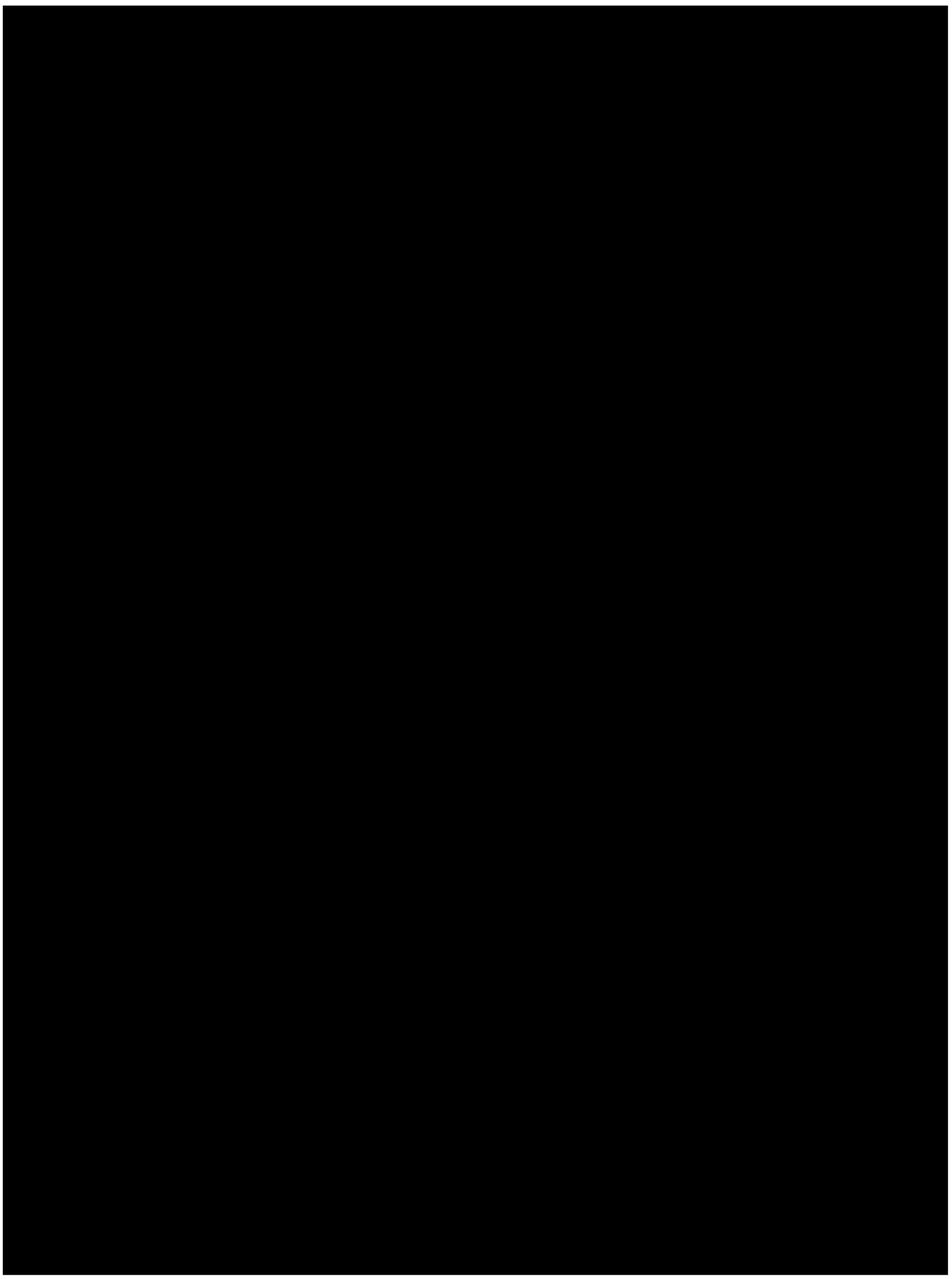
5.2 RSV Symptom Diary

The RSV Symptom Diary includes 13 items that assess the severity of RSV-related signs and symptoms. The 13 items are as follows: Nasal discharge, Nasal congestion (stuffy nose), Malaise/tiredness, Headache, Sinus congestion (sinus pressure), Sneezing, Sore throat, Hoarseness, Cough, Shortness of Breath, Respiratory wheeze, Earache, and Symptoms of fever. For each item, severity is rated using a 4-point scale: 0=absent, 1=noticeable, 2=Bothersome but does not interfere with activities, 3=Bothersome and interferes with activities. The total symptom score (TSS) is calculated as the sum of item scores across all 13 items. If *any* of the 13 observed values are missing the total symptom score will not be calculated for that assessment. The TSS ranges from 0 to 39 with higher scores indicating more severe symptoms.

The RSV Symptom Diary will be completed by subjects using a handheld device. Each subject will also be provided with a paper diary(ies) as a back-up, in case the subject is unable to complete the RSV symptom diary assessment for technical reasons. Diaries will be completed twice daily from Day 1 (date of first dose) through Day 14 at the same times each day ± 2 hours. Subjects are instructed to rate the severity of symptoms experienced in the last 12 hours for the morning diary on Day 1 then the maximum since the last completed diary for the subsequent diaries.

Throughout the study the subject may take acetaminophen for pain and fever relief. The subject should not take other pain relievers such as ibuprofen or naproxen. Each time the subject completes the diary acetaminophen use needs to be recorded. The time of the day the subject takes acetaminophen will be important to document due to the confounding effect on the primary analysis. If a subject plans to take acetaminophen within 2 hours of a scheduled RSV symptom diary completion, then the RSV symptom diary should be completed immediately before the subject takes acetaminophen or 4 hours after taking acetaminophen.

[redacted]



[redacted]

5.4 Statistical Methods – Sample SAS Codes

5.4.1 Example SAS code for analysis using ANCOVA

```
PROC MIXED DATA=ADTSS;
 CLASS ASTHCOPD TRT01P;
 MODEL AUCTSS= TSSBASE ASTHCOPD TRT01P;
 LSMEANS TRT01P/ DIFF CL;
RUN;
```

5.4.2 Example SAS code for subgroup analyses using ANCOVA

```
ODS OUTPUT SLICES=SUBGRPLSM SLICEDIFFS=SUBGRPDIFF;

PROC MIXED DATA=ADTSS;
 CLASS ASTHCOPD TRT01P SUBGRP;
 MODEL AUCTSS= TSSBASE ASTHCOPD SUBGRP TRT01P TRT01P*SUBGRP;
 SLICE  TRT01PN*SUBGRP/SLICEBY=SUBGRP  MEANS PDIFF CL;
RUN;
```