Statistical Analysis Plan for Interventional Studies

Sponsor Name: resTORbio, Inc.

Protocol Number: RTB-101-204
Protocol Title: A Multicenter, Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Determine if RTB101 Prevents Clinically Symptomatic Respiratory Illness in the Elderly

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I confirm that I have reviewed this document and agree with the content.

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Alanine Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
BDRM	Blind Data Review Meeting
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ER	Emergency Room
FAS	Full Analysis Set
GLM	Generalized Linear Model
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hMPV	Human Metapneumovirus
HRQoL	Health-Related Quality of Life
HRV	Human Rhinovirus
ICH	International Conference on Harmonization
IPF	Interstitial Pulmonary Fibrosis
IXRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMSE	Mini Mental Status Examination
N/A	Not Applicable

Abbreviation	Description
PCI	Percutaneous Coronary Intervention
PCR	Polymerase Chain Reaction
PKS	Pharmacokinetic Set
PPS	Per Protocol Set
PT	Preferred Term
RIDT	Rapid Influenza Diagnostic Test
RR	Rate Ratio
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract infections
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Screening Set
SD	Standard Deviation
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure and Listing
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

The study will be unblinded after all subjects complete the final clinic visit (Week 20 visit) or terminate early from the study and the database is locked.

Analysis of the primary efficacy endpoint, including 2 subgroup analyses (specifically, for subjects who are ≥85 years old and subjects who have a medical history of asthma) are planned after all subjects have completed their Week 16 visit to confirm efficacy of RTB101 prior to enrolling subjects in the second Phase 3 trial (Protector 2) during the northern hemisphere winter cold and flu season. The analysis will be done when all datasets required for determination of the primary endpoint have been cleaned, frozen and changes to the required data can no longer be made. The Syneos unblinded statistical team will prepare the analysis tables and will provide them only to the resTORbio Chief Executive Officer (CEO) and Chief Medical Officer (CMO), who are not involved in the RTB-101-204 study conduct. All resTORbio personnel will remain blinded on a subject-level, and only the resTORbio CEO and CMO will be unblinded at a treatment-group level at this time.

A final analysis of other safety and efficacy and/or pharmacokinetics endpoints is planned after all subjects complete the final clinic visit (Week 20 visit) or terminate early from the study.

An independent Data Monitoring Committee (DMC) will be established. The DMC will be responsible for the following:

- Providing ongoing assessments of safety data and the overall risk of the study conduct. This will include an ongoing unblinded analysis of GI SAEs and unexpected related SAE narratives, and a monthly analysis of unblinded listings of all other SAEs.
- Advising the Sponsor of the need for study stopping or protocol modification/amendments in order to minimize potential risk for subjects.
- Advising the Sponsor if study enrollment needs to be halted based on review within 48 hours of safety data outlined in Section 5.5.5 of the protocol.

Further details are provided in the DMC charter.

3. Study Objectives

3.1. Primary Objective

The primary objective is to determine if RTB101 as compared to placebo decreases the percentage of subjects with clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen) through Week 16.

3.2. Secondary Objectives

The secondary objectives are:

- To determine if RTB101 as compared to placebo decreases the percentage of subjects with clinically symptomatic respiratory illness associated with ≥1 laboratory-confirmed pathogen(s) through Week 16
- To determine the effect of RTB101 as compared to placebo on the rate of clinically symptomatic respiratory illnesses associated with specific laboratory confirmed viruses (coronaviruses, human metapneumovirus [hMPV], human rhinovirus [HRV]/enterovirus, adenovirus, influenza A and B virus, parainfluenza viruses, and respiratory syncytial virus [RSV]) through Week 16
- To determine if RTB101 as compared to placebo decreases the rate of clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen) through Week 16
- To determine if RTB101 as compared to placebo decreases the rate of clinically symptomatic respiratory illnesses associated with ≥1 laboratory-confirmed pathogen(s) through Week 16
- To determine if RTB101 as compared to placebo decreases time to alleviation of moderate and severe respiratory illness symptoms due to clinically symptomatic respiratory illness through Week 16
- To determine if RTB101 as compared to placebo decreases the percentage of subjects with severe symptoms due to clinically symptomatic respiratory illnesses through Week 16
- To assess the safety and tolerability of RTB101 through Week 20

3.3. Exploratory Objectives

The exploratory objectives are:

- To explore the effect of RTB101 as compared to placebo on the rate of all laboratory-confirmed viral respiratory infections with or without symptoms through Week 16
- To explore the effect of RTB101 as compared to placebo on the rate of all-cause hospitalizations through Week 16
- To explore the effect of RTB101 as compared to placebo on the rate of hospitalizations associated with RTIs through Week 16
- To explore the effect of RTB101 as compared to placebo on the rate of all-cause Emergency Room (ER) visits through Week 16

- To explore the effect of RTB101 as compared to placebo on the rate of ER visits associated with RTIs through Week 16
- To explore the effect of RTB101 as compared to placebo on the rate of all-cause urgent care clinic visits through Week 16
- To explore the effect of RTB101 as compared to placebo on the rate of all urgent care clinic visits for clinically symptomatic respiratory illness through Week 16
- To explore the effect of RTB101 as compared to placebo on the rate of all-cause admissions to skilled nursing facilities through Week 16
- To explore the effect of RTB101 as compared to placebo on hospital length of stay associated with RTIs through Week 16
- To explore the effect of RTB101 as compared to placebo on all-cause hospital length of stay through Week 16
- To explore the effect of RTB101 as compared to placebo on the percentage of subjects with clinically symptomatic respiratory illness and the percentage of subjects with clinically symptomatic respiratory illness associated with ≥1 laboratory-confirmed pathogen(s) through Week 20
- To explore the effect of RTB101 as compared to placebo on change from Baseline in health-related quality of life (HRQoL) as assessed by EQ-5D-5L scores during all clinically symptomatic respiratory illness episodes and at Week 16
- To explore the effect of RTB101 as compared to placebo on the percentage of subjects with clinically symptomatic respiratory illnesses and on the percentage of subjects with clinically symptomatic respiratory illnesses associated with ≥1 laboratory-confirmed pathogen(s) through Week 16 who are ≥85 years of age or subjects with a medical history of asthma
- To explore the effect of RTB101 as compared to placebo on the rate of clinically symptomatic respiratory illnesses and on the rate of clinically symptomatic respiratory illnesses associated with ≥1 laboratory-confirmed pathogen(s) through Week 16 in subjects who are ≥85 years of age or subjects with a medical history of asthma
- To explore the effect of RTB101 as compared to placebo on the incidence of asthma exacerbations through Week 16 in subjects with a medical history of asthma
- To explore the effect of RTB101 as compared to placebo on the incidence of urinary tract infections (UTIs) through Week 16
- To explore the effect of RTB101 on immunologic biomarkers and to explore biomarkers that may predict response (e.g. RNA expression in whole blood, serum biomarkers, genetic variation)

3.4. Brief Description

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, Phase 3 study to determine if RTB101 prevents clinically symptomatic respiratory illnesses (CSRI) in elderly subjects. Approximately 1066 subjects will be enrolled during cold and flu season. Subjects who meet the inclusion/exclusion criteria will be randomized 1:1 to receive RTB101 10 mg or matching placebo orally

once daily for 16 weeks. The study will be composed of: up to a 4-week screening period, a 16-week treatment period, and a 4-week short-term follow-up period off study drug through the Week 20 Visit. There will also be a long term follow-up by telephone at Week 48.

3.5. Subject Selection

3.5.1. Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill all of the criteria listed in section 4.1 of the protocol.

3.5.2. Exclusion Criteria

Subjects will not be eligible if they meet any of the criteria listed in section 4.2 of the protocol.

3.6. Determination of Sample Size

Sample size was determined based on a two-sided comparison between RTB101 and placebo. In parts 1 and 2 of the Phase 2b trial, 28.2% of subjects had a clinically symptomatic respiratory illness on placebo (excluding subjects with COPD and current smokers). With an assumed Week 16 clinically symptomatic respiratory illness incidence of 28.2% on placebo and 19.7% in the RTB101 arm, a total sample size of approximately 1066 subjects (equally randomized) will provide 90% power to detect a 30% reduction in the percentage of subjects with clinically symptomatic respiratory illness between RTB101 and placebo using a two-sided test of 0.05 significance. Power analysis was conducted using Likelihood Ratio Chi-square Test.

3.7. Treatment Assignment & Blinding

At the Baseline visit, all eligible subjects will be randomized via the IXRS to one of the treatment arms. The Investigator or his/her delegate will contact the IXRS after confirming that the subject fulfills all the inclusion/exclusion criteria. The IXRS will prompt the user to randomize the subject. The subject identifier number will be used to link the subject to a treatment arm and a unique medication number for the bottles of study drug to be dispensed to the subject.

Randomization will be stratified based on the following factors that may influence the incidence and severity of RTIs and the response to treatment:

1. Age ≥ 85
2. Age ≥ 65 and <85 years with a medical history of asthma
3. Clinical Frailty Scale score ≥ 4

Therefore, the 6 randomization strata are as follows:

- Age ≥ 85 and Clinical Frailty Scale score ≥ 4
- Age ≥ 85 and Clinical Frailty Scale score < 4
- Age ≥ 65 and <85 years with a medical history of asthma and Clinical Frailty Scale score ≥ 4
- Age ≥ 65 and <85 years with a medical history of asthma and Clinical Frailty Scale score < 4

- Age ≥ 65 and <85 years with no medical history of asthma and Clinical Frailty Scale score ≥ 4

- Age ≥ 65 and <85 years with no medical history of asthma and Clinical Frailty Scale score < 4

The randomization scheme for subjects will be reviewed and approved by a member of the team responsible for Randomization schema.

This is a subject, Investigator and Sponsor-blinded study. Subjects, all study site staff, includingInvestigators and study nurses, will remain blinded until all subjects complete the Long-termFollow up Period (Study Week 48). The Sponsor will remain blinded to study treatment until allsubjects complete the Short-term Follow-up Period (Study Week 20). The only exception will be in the DMC. The DMC manager, coordinator, and statistician will have access to unblinded data and perform all work in a restricted and secured project folder. The unblinded files will be transferred to the unblinded DMC members by the unblinded DMC coordinator.

3.8. Administration of Study Medication

RTB101 10 mg or matching placebo will be dispensed at the Baseline visit, Week 4, Week 8, and Week 12. Subjects will be instructed to take one dose daily in the morning. Subjects participating in the PK assessments (per the IXRS randomization) will be asked not to take study drug on the morning of scheduled clinical visits of Week 4 (or alternatively Week 6 in case of logistical need) and Week 12 as the subject will be administered study drug with a light meal at the study site.

3.9. Study Procedures and Flowchart

The study will be comprised of up to a 4-week Screening Period; a 16-week Primary Analysis Period (for evaluating efficacy and safety) during which time subjects meeting study eligibility criteria will be randomized 1:1 to receive RTB101 10 mg or matching placebo once daily through the Week 16 Visit; a 4-week Short-term Follow-up Period (for evaluating safety and efficacy through the Week 20 Visit); and a 28-week Long-term Follow-up Period (for evaluating safety through Week 48 by follow-up questionnaire). The Blinded Treatment Period has clinical visits every 2 weeks for the first 8 weeks, and every 4 weeks thereafter (for a total of 7 visits including the Baseline visit).

Respiratory illness symptoms will be captured in an eDiary that subjects will complete daily (in the evening) at home after the Baseline visit. The eDiary will ask the subject to record their experience with a set of predefined respiratory illness symptoms at their worst during the past 24 hours. The subjects record whether each symptom was absent, mild, moderate or severe. If the subject experiences any symptom on a typical day even though they are not sick, they are instructed to record the symptom as “Absent”. The predefined symptoms include both respiratory symptoms (runny nose, sneezing, stuffy nose, sore throat, hoarseness, or cough) and general symptoms (headache, feverishness/chills, loss of appetite, body aches, or lack of energy).

The eDiary responses will be monitored by the Study Investigator or Study Coordinator. The Study Investigator or Study Coordinator at the site will contact subjects who miss completion of the daily eDiary questionnaires for >1 day and re-train the subject and explain the importance of completing the daily eDiary questionnaires.

Study sites will instruct subjects who report at least one respiratory symptom in 2 consecutive entries in their eDiary to come to the study site for evaluation, if possible, and for the collection of a nasopharyngeal swab. Subjects who are unable to come to the study site may also have the nasopharyngeal swab (and, if indicated, a sputum specimen and rapid influenza diagnostic test [RIDT]) obtained during a home visit by

trained personnel.

Details of assessments at each visit are provided in Table 6-1 of the protocol.

4. Endpoints

4.1. Primary Efficacy Endpoint

The primary endpoint is the percentage of subjects with CSRIs (with or without an associated laboratory confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria defined in 7.2.1 below.

4.2. Secondary Efficacy Endpoints

The secondary endpoints are:

- The percentage of subjects with 1 or more CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria, and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or Rapid Influenza Diagnostic Tests (RIDTs).
- The rate of CSRIs associated with specific laboratory-confirmed viruses (coronaviruses, hMPV, HRV/enterovirus, adenovirus, influenza A and B virus, parainfluenza viruses, and RSV) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs.
- The rate of CSRI (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria.
- The rate of CSRIs associated with ≥ 1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs.
- The time to alleviation of moderate and severe respiratory illness symptoms due to a CSRI beginning at least 3 days after the start of study drug treatment through Week 16.
- The percentage of subjects with severe symptoms due to CSRIs beginning at least 3 days after the start of study drug treatment through Week 16.
- Safety and tolerability will be assessed by report of AE/SAEs, physical exam and ECG findings, and safety laboratory values.

4.3. Exploratory Endpoints

The exploratory endpoints are:

- The rate of all laboratory-confirmed viral infections with or without symptoms beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by respiratory pathogen PCR of nasopharyngeal swabs and/or RIDTs (obtained during episodes of clinically

symptomatic respiratory illnesses) and/or respiratory pathogen PCR of mid-turbinate swabs (obtained at scheduled clinical visits even in the absence of symptoms). The rate of all-cause hospitalizations through Week 16.

- Rate of hospitalizations associated with RTIs beginning at least 3 days after the start of study drug treatment through Week 16.
- The rate of all-cause Emergency Room (ER) visits through Week 16.
- Rate of Emergency Room (ER) visits associated with RTIs beginning at least 3 days after the start of study drug treatment through Week 16.
- The rate of all-cause urgent care clinic visits through Week 16.
- The rate of urgent care clinic visits for CSRI beginning at least 3 days after the start of study drug treatment through Week 16.
- The rate of all-cause admissions to skilled nursing facilities through Week 16.
- Hospitalization length of stay associated with RTIs beginning at least 3 days after the start of study drug treatment through Week 16.
- All-cause hospitalization length of stay through Week 16.
- The percentage of subjects with one or more CSRIs (with or without an associated laboratory pathogen) beginning at least 3 days after the start of study drug treatment through Week 20
- The percentage of subjects with 1 or more CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 20 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs.
- The change from Baseline in HRQoL as assessed by EQ-5D-5L scores during all clinically symptomatic respiratory illness episodes beginning at least 3 days after the start of study drug treatment through Week 16 and at Week 16.
- The percentage of subjects who are ≥85 years of age with one or more CSRIs beginning at least 3 days after the start of study drug treatment through Week 16.
- The percentage of subjects who are ≥85 years of age with one or more CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16.
- The percentage of subjects who have a medical history of asthma with one or more CSRIs beginning at least 3 days after the start of study drug treatment through Week 16.
- The percentage of subjects who have a medical history of asthma with one or more associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16.

- The rate of clinically symptomatic respiratory illnesses beginning at least 3 days after the start of study drug treatment through Week 16 in subjects who are ≥85 years of age.
- The rate of clinically symptomatic respiratory illnesses associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 in subjects who are ≥85 years of age
- The rate of clinically symptomatic respiratory illnesses beginning at least 3 days after the start of study drug treatment through Week 16 in subjects with a medical history of asthma.
- The rate of clinically symptomatic respiratory illnesses associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 in subjects with a medical history of asthma..
- The rate of asthma exacerbations defined as deterioration of asthma symptoms that requires treatment with systemic steroids beginning at least 3 days after the start of study drug treatment through Week 16 in subjects with a medical history of asthma.
- The percentage of subjects with 1 or more asthma exacerbation defined as deterioration of asthma symptoms that requires treatment with systemic steroids beginning at least 3 days after the start of study drug treatment through Week 16 in subjects with a medical history of asthma
- The percentage of subjects with one or more UTIs reported as adverse events through Week 16.
- The rate of UTIs reported as adverse events through Week 16.
- Change from Baseline to Weeks 4 and 16 in biomarkers in whole blood and serum and potentially future pharmacogenomic analysis.

5. Analysis Sets

5.1. Screening / Randomized Sets

The Screening Set (SCR) will include all subjects, who provided informed consent, regardless of the subject's randomization and study treatment status in the study. Unless specified otherwise, this set will be used for summaries of subject disposition.

The Randomized Set (RS) will include all subjects randomized whether treated or not.

5.2. Safety Set

The Safety Set (SAF) will include all subjects who were administered any dose of any study drug. Subjects will be analyzed per the actual study treatment they received. The follow-up period will include the Week 20 visit which is 4 weeks after the end of the treatment period. The SAF will be used for all analyses and presentation of by-subject listings of all safety endpoints. Subjects will be analyzed according the actual treatment they received.

5.3. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who received at least 1 dose of trial medication. Subjects will be analyzed according to randomized treatment. The FAS will be used for all analyses and presentation of by-subject listings of all efficacy endpoints.

5.4. Per Protocol Set

The Per Protocol Set (PP) will include all subjects who complete the 16-week treatment period, missed < 20% of doses, and had no major protocol deviations impacting efficacy data. Subjects will be analyzed per the treatment group to which they were randomized.

Protocol deviations will be classified and reviewed for subject inclusion in the PP during a Blind Data Review Meeting (BDRM) as described in Syneos SOP 3911.00 (Blind) Data Review and Definition of Analysis Sets, prior to unblinding. Criteria for exclusion from the PP will be included in BDRM Preparation Plan.

6. Protocol Deviations

Protocol deviations will be collected throughout the study in the Medidata Clinical Trial Management System (CTMS). Protocol deviations will be reviewed during a BDRM. Details of selection criteria and documentation to be provided for review will be described in the BDRM Preparation Plan.

7. General Aspects for Statistical Analysis

7.1. General Methods

All analyses and outputs will be produced using SAS® version 9.4 or later. Unless otherwise specified, efficacy and safety summaries will be presented for each treatment. All other summaries will be presented for each treatment and overall. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency, and percentages of subjects.

All relevant subject data will be included in listings. All randomized subjects entered into the database will be included in subject data listings. All by visit summaries will use the nominal visit. Unscheduled visits will not be summarized but will be included in the listings.

7.2. Key Definitions

7.2.1. Clinically Symptomatic Respiratory Illness (CSRI)

A CSRI is defined as the occurrence of:

a. At least 2 respiratory symptoms (runny nose/sneezing [considered one symptom], stuffy nose, sore throat, hoarseness, or cough) OR 1 respiratory symptom and 1 of the following general symptoms (headache, feverishness/chills or loss of appetite),

   AND

b. at least 1 of these respiratory symptoms (runny nose, sneezing, stuffy nose, sore throat, hoarseness or cough) in (a) above being reported on 2 or more "consecutive entries" in the eDiary, and must
   i. overlap with another respiratory or general symptom for at least 1 day, or
   ii. be reported on a consecutive day to another respiratory or general symptom in the eDiary

   AND

c. any 2 or more symptoms (respiratory and/or general) reported during the CSRI event that are at least moderate in severity.

All CSRI-defining symptoms (i.e., runny nose, sneezing , stuffy nose, sore throat, hoarseness, cough, headache, feverishness/chills or loss of appetite) that occur after the start of a CSRI event will be included as part of a single CSRI event unless there is a period of ≥ 7 consecutive entries during which all CSRI-defining symptoms are reported as "Absent" in the eDiary.

"consecutive entries" include situations in which eDiary entries were missing for 1-6 days in between 2 days in which the symptom was reported. For example, if on Day 3 and Day 9 runny nose was reported but eDiary entries were missing from Days 4-8, then runny nose will be considered as reported for 2 consecutive entries. This definition of "consecutive entries" does not include situations in which subjects report all symptoms as "Absent". If ≥ 7 days of eDiary entries are missing, then symptoms reported before and after the ≥7 days of missing entries will not be considered consecutive eDiary entries.

The start date of the CSRI will be the start date of the first respiratory symptom reported as part of the CSRI. Note that the start date of a CSRI will always be based on the start date of the respiratory symptom and not a general symptom.

The end date of the CSRI will be defined as the latest date that any of the CSRI-defining symptoms for the same CSRI event were reported.

A separate CSRI event will not be diagnosed until a subject has ≥ 7 consecutive days during which all CSRI-defining symptoms are reported as "Absent" after the end date of the prior CSRI episode. If missing days of eDiary entries are sandwiched between 2 days of eDiary entries during which all CSRI-defining symptoms are reported as "Absent", then all symptoms will also be considered as "Absent" for the missing eDiary entries, and a separate CSRI event can be diagnosed if the ≥ 7 consecutive days criterion is met. For example, if on Day 4 and Day 10 all symptoms were reported as "Absent" in the eDiary, and on Days 5-9 the eDiary entries were missing, then all symptoms will be considered as "Absent" on Days 5-9. Therefore all symptoms will be considered as "Absent" for 7 consecutive days (Days 4-10), and a separate CSRI can be diagnosed.

Only CSRIs having a start date at least 3 days after the start of study drug and meet the definition of a CSRI by the specified time point (Week 16 or Week 20) will be included in the analysis. Only data recorded in the eDiary through the evening before the Week 16 visit will be included in all analyses of CSRIs for the Week 16 endpoint. Similarly, only data recorded in the eDiary through the evening before the Week 20 visit will be included in all analyses of CSRIs for the Week 20 endpoint.

7.2.2. First Dose Date

For any randomized subject, if there are any entries in the eDiary indicating the subject took study drug at any time during the study, then the first dose date will equal the randomization date because all subjects receive their first dose of study drug at the site during the Baseline (randomization) visit. However, if there are no entries in the eDiary indicating the subject took study drug at any time during the study (including at the Baseline visit), then the first dose date will be missing and the subject will be considered randomized but not treated.

7.2.3. Study Day

Study day 1 is defined as as the first dosing day of study drug. Subsequent days are numbered consecutively (Day 2, Day 3, etc.). Before the day of study drug administration, study days are numbered sequentially with negative values (i.e., Day -1, Day -2, etc.). There is no Day 0.

7.2.4. Baseline

Baseline is defined as the last measurement taken before the first dose of double-blind treatment on Day 1, unless otherwise specified.

7.3. Missing Data

Every effort will be made to collect all data at specified timepoints, according to the schedule of study events.

For the primary efficacy endpoint of occurrence of CSRI, subjects who did not meet the study definition for CSRI and discontinue the study prematurely due to a respiratory tract infection (RTI) adverse event (AE) or RTI serious adverse event (SAE) will be imputed to have experienced a CSRI; subjects who discontinue the study prematurely due to any reason aside from an RTI AE or RTI SAE and did not meet the CSRI definition will be imputed as having no CSRI; subjects who completed the study who did not meet the CSRI definition and have intermittent missing eDiary data will be imputed as having no CSRI.

Partial dates of medications will be imputed solely for the purpose of defining prior/concomitant status for medications. Dates will be defined using the hierarchy of derivations below.

- For missing start day where month and year are present, the start day will be set to the 1st of the month, unless the month and year are the same as the first dose month and year and the 1st of the month is before the first dose date, in which case, the start date will be set to the first dose date.

- For missing start day and month where year is present, the start day and month will be set to January 1st, unless the year is the same as the first dose year and January 1st is before the first dose date, in which case, the start date will be set to the first dose date.

- For missing end day where month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the trial termination month and year, in which case, the end date will be set to the trial termination date.

- For missing end day and month, where year is present, the end date will be set to the trial termination date if the years are the same. If the trial termination year is greater than the end year, the end day and month will be set to December 31st.

7.4. Visit Windows

Visit window will not be used in the summarization or analysis of data.

7.5. Pooling of Centres

Pooling of centers or countries will not be done. Center and country will not be included in the statistical model.

7.6. Subgroups

The analyses of the primary endpoint and selected secondary endpoints (listed below) will be repeated for the following subpopulations of the FAS:

- Age Group (≥85 years old vs. <85 years old)
- Clinical Frailty Scale score (≥4 vs. <4)
- History of asthma (Y/N)
- Congestive heart failure (CHF) (Y/N)
- Received a pneumococcal vaccination (Y/N)
- Received current season influenza vaccination (Y/N))
- Gender (Male vs. Female)

In each of the subgroup analyses, the independent variable relating to the subgroup will be dropped from the model, if applicable.

The selected secondary endpoints include

(1) The percentage of subjects with CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16

(2) The rate of CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16

(3) The rate of CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

Subject disposition will be presented for all subjects in the Screening Set, which include the following:

- Number of subjects enrolled (i.e. signed Informed Consent)
- Number of screened, screen failures and reason for screen failure
- Number (%) of subjects randomized

Among the randomized subjects, the following will be summarized

- Number (%) of subjects in the Safety Set
- Number (%) of subjects in the Full Analysis Set
- Number (%) of subjects in the Per-Protocol Set
- Number (%) of subjects who completed the study through Week 16
- Number (%) of subjects who completed the study through Week 20
- Number (%) of subjects who discontinued treatment and their reason
- Number (%) of subjects who discontinued study prematurely and their reason

A separate by-subject listing of subject disposition and withdrawal will also be provided for the Screening Set. Subjects who screen failed will be included in this listing along with the reason for the screen failure.

Reasons for exclusion from analysis sets will be summarized in the Randomized Set and listed.

8.2. Protocol Deviations

All protocol deviations will be listed in the Randomized Set. Major protocol deviations will be summarized in the Randomized Set.

8.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the Safety Set by actual treatment, for Randomized, Full Analysis, and Per Protocol Sets by randomized treatment and overall. Summary statistics and by-subject listings will be provided.

Demographics and baseline characteristics will include age, sex, ethnicity, race, weight, height, body mass index (BMI), age ≥ 85 (Y/N), age ≥ 65 and <85 years, with a medical history of asthma (Y/N), medical history of congestive heart failure (Y/N), medical history of Type 2 Diabetes Mellitus (Y/N), Clinical Frailty Scale score ≥ 4 (Y/N), Clinical Frailty Score (ordinal), receipt of current season influenza vaccine (Y/N) and each of the stratification levels (age ≥ 85 and clinical frailty score ≥ 4; age ≥ 85 and clinical frailty score < 4; 65 ≤ age < 84, clinical frailty score ≥ 4 and medical history of asthma; 65 ≤ age

< 84, clinical frailty score ≥ 4 and no medical history of asthma; 65 ≤ age < 84, clinical frailty score < 4 and medical history of asthma; and 65 ≤ age < 84, clinical frailty score < 4 and no medical history of asthma).

Age at Screening = (Screening visit date - date of birth + 1) / 365.25 and truncated to complete years.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

Similarly, baseline disease characteristics will be summarized for the Safety Set, Randomized, Full Analysis, and Per Protocol Sets.

By-subject listing of all demographic and baseline disease characteristic data will be provided for the Full Analysis Set.

8.4. Medical History and Concomitant Diseases

A summary table of the number and percentage of subjects by medical history, system organ class (SOC) and preferred term will be produced from the Safety Set. Medical history will be sorted alphabetically by SOC and in descending order of subjects per preferred term within each SOC.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher.

A separate by-subject listing of medical history will also be provided.

8.5. Medication

All prior and concomitant medications will be summarized based on classification using the Anatomical Therapeutic Chemical (ATC) classification and preferred drug name from the World Health Organization Drug Dictionary, version Mar 2019, or later.

A separate by-subject listing of medications will also be provided for the Safey Set.

8.5.1. Prior Medication

Prior medications are defined as medications entered in the eCRF that either start, or end before the first dose of study medication. Prior medications will be summarized by ATC level 2 and preferred drug name for the Safety Population.

Prior medications which continue after first dose of study medication will also be classified as a concomitant medication.

8.5.2. Concomitant Medication

Concomitant medications are defined as medication on the eCRF that are taken on, after, or are ongoing at the start date of dosing. Concomitant medications will be summarized by ATC level 2 and preferred drug name for the Safety Population.

9. Efficacy

9.1. Multiple Testing Strategy

A fixed sequence gate-keeping strategy will be used to control the study-wise error rate at a 2-sided α-level of 0.05. The following primary, secondary and exploratory efficacy endpoints will be tested in the sequence specified below:

Order	
H_1	The percentage of subjects with 1 or more CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16.
H_2	The percentage of subjects with 1 or more CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria, and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs.
H_3	The rate of CSRI (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria.
H_4	The rate of CSRIs associated with ≥ 1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs.
H_5	The time to alleviation of moderate and severe respiratory illness symptoms due to CSRI beginning at least 3 days after the start of study drug treatment through Week 16.
H_6	The percentage of subjects with severe symptoms due to CSRIs beginning at least 3 days after the start of study drug treatment through Week 16.
H_7	The rate of all-cause hospitalizations beginning at least 3 days after the start of study drug treatment through Week 16.
H_8	The rate of UTIs beginning at least 3 days after the start of study drug treatment through Week 16 reported as adverse events
H_9	The percentage of subjects with 1 or more CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 20.

The primary endpoint, H_1, will be tested first at a 2-sided alpha level of 0.05. The subsequent endpoints will be tested in the order specified above also at a 2-sided 0.05 alpha-level of 0.05, if and only if the preceding endpoint was found to be statistically significant. If the preceding endpoint in the sequence fails to meet statistical significance, then testing of subsequent endpoints will be stopped and no further statistical conclusions will be made.

9.2. Estimands

This section presents a structured framework that link trial objectives with suitable and precise definition of how treatment effects are to be estimated. The estimand, which is the target of estimation to address

the scientific question of interest posed by the trial objective, with its 4 attributes as specified in the ICH E9(R1) Draft Addendum on Estimands and Sensitivity Analysis in Clinical Trials 2017, are provided below for the primary objective and key secondary objectives.

9.2.1. Primary Objective Estimand

The estimand used to address the primary objective "To determine if RTB101 as compared to placebo decreases the percentage of subjects with a CSRI (with or without an associated laboratory-confirmed pathogen) through Week 16" is defined by the following:

- Population:
  - Subjects in the FAS population
- Variable:
  - Occurrence of a CSRI, with or without an associated laboratory-confirmed pathogen, by the Week 16 visit
- Intercurrent events:
  - If a subject discontinues study prematurely due to an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI, impute the subject experienced a CSRI
  - If a subject discontinues study prematurely for any reason other than an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI, impute the subject did not have a CSRI
  - If a subject completed the study and has intermittent missing eDiary data and the subject did not meet the definition of a CSRI, impute the subject did not have a CSRI
- Population-level summary:
  - odds ratio, i.e. the ratio of the odds of having a CSRI in subjects treated with RTB101 compared to the odds of having a CSRI in subjects treated with placebo by the Week 16 visit

9.2.2. Secondary Objective Estimands

1. The estimand for the secondary objective "To determine if RTB101 as compared to placebo decreases the percentage of subjects with a CSRI associated with ≥1 laboratory-confirmed pathogen(s) through Week 16" is defined by the following:
   - Population:
     - Subjects in FAS population
   - Variable:
     - Occurrence of a CSRI with ≥1 laboratory-confirmed pathogen(s) by the Week 16 visit

- Intercurrent events:
    - If a subject discontinues study prematurely due to an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI associated with ≥1 laboratory-confirmed pathogen(s), assume the subject experienced a CSRI with ≥1 laboratory-confirmed pathogen(s)
    - If a subject discontinues study prematurely for any reason other than an RTI AE or RTI SAE , and the subject did not meet the definition of a CSRI associated with ≥1 laboratory-confirmed pathogen(s), impute the subject did not have a CSRI with ≥1 laboratory-confirmed pathogen(s)
    - If a subject completed the study and has intermittent missing eDiary data and the subject did not meet the definition of a CSRI associated with ≥1 laboratory-confirmed pathogen(s), impute the subject did not have a CSRI with ≥1 laboratory-confirmed pathogen(s)
- Population-level summary:
    - odds ratio, i.e. the ratio of the odds of having a CSRI with ≥1 laboratory-confirmed pathogen(s) in subjects treated with RTB101 compared to the odds of having a CSRI with ≥1 laboratory-confirmed pathogen(s) in subjects treated with placebo by the Week 16 visit

2. The estimand for the secondary objective “To determine if RTB101 as compared to placebo decreases the rate of CSRIs, with or without an associated laboratory-confirmed pathogen, through Week 16” is defined by the following:

    - Population:
        - Subjects in FAS population
    - Variable:
        - Number of CSRIs with or without an associated laboratory-confirmed pathogen through the Week 16 visit
    - Intercurrent events:
        - If a subject discontinues study prematurely due to an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI, assume the subject experienced one CSRI
        - If a subject discontinues study prematurely for any reason other than an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI, impute the subject did not have a CSRI
        - If a subject completed the study and has intermittent missing eDiary data and the subject did not meet the definition of a CSRI, impute the subject did not have a CSRI
    - Population-level summary:

- rate ratio, i.e. the ratio of the rate of having a CSRI (with or without an associated laboratory-confirmed pathogen) in subjects treated with RTB101 compared to the rate of having a CSRI (with or without an associated laboratory-confirmed pathogen) in subjects treated with placebo by the Week 16 visit

3. The estimand for the secondary objective "To determine if RTB101 as compared to placebo decreases the rate of CSRIs associated with ≥1 laboratory-confirmed pathogen(s) through Week 16" is defined by the following:

   - Population:
     - Subjects in FAS population
   - Variable:
     - Number of CSRIs with ≥1 laboratory-confirmed pathogen(s) through Week 16
   - Intercurrent events:
     - If a subject discontinues study prematurely due to an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI associated with ≥1 laboratory-confirmed pathogen(s) , assume the subject experienced one CSRI associated with ≥1 laboratory-confirmed pathogen(s)
     - If a subject discontinues study prematurely for any reason other than an RTI AE or RTI SAE, and the subject did not meet the definition of a CSRI associated with ≥1 laboratory-confirmed pathogen(s), impute the subject did not have a CSRI associated with ≥1 laboratory-confirmed pathogen(s)
     - If a subject completed the study and has intermittent missing eDiary data and the subject did not meet the definition of a CSRI associated with ≥1 laboratory-confirmed pathogen(s), impute the subject did not have a CSRI associated with ≥1 laboratory-confirmed pathogen(s)

- Population-level summary:
  - rate ratio, i.e. the ratio of the rate of having a CSRI with ≥1 laboratory-confirmed pathogen(s) in subjects treated with RTB101 compared to the rate of having a CSRI with ≥1 laboratory-confirmed pathogen(s) in subjects treated with placebo by the Week 16 visit

4. The estimand for the secondary objective "To determine if RTB101 as compared to placebo decreases the percentage of subjects with severe symptoms due to clinically symptomatic respiratory illnesses through Week 16" is defined by the following:

   - Population:
     - Subjects in FAS population
   - Variable:

- Occurrence a CSRI with severe symptoms by the Week 16 visit

- Intercurrent events:

  - If a subject discontinues study prematurely due to an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI with severe symptoms, assume the subject experienced a CSRI with severe symptoms

  - If a subject discontinues study prematurely for any reason other than an RTI AE or RTI SAE and the subject did not meet the definition of a CSRI with severe symptoms, impute the subject did not have a CSRI with severe symptoms

  - If a subject completed the study, has intermittent missing eDIary data and the subject did not meet the definition of a CSRI with severe symptoms, impute the subject did not have a CSRI with severe symptoms

- Population-level summary:

  - odds ratio, i.e. the ratio of the odds of having a CSRI with severe symptoms in subjects treated with RTB101 compared to the odds of having a CSRI with severe symptoms in subjects treated with placebo by the Week 16 visit

5. The estimand for the secondary objective “To determine if RTB101 as compared to placebo decreases time to alleviation of moderate and severe respiratory illness symptoms through Week 16” is defined by the following:

   - Population:

     - Subjects in FAS population

   - Variable:

     - Time to alleviation of moderate and severe CSRI symptoms

   - Intercurrent events:

     - If a subject discontinues study prematurely due to an RTI AE or RTI SAE and time to alleviation of moderate and severe respiratory illness symptoms has not been reached, subject is censored on the date of last eDiary entry

     - If a subject discontinues study prematurely for any other reason than an RTI AE or RTI SAE and time to alleviation of moderate and severe respiratory illness symptoms has not been reached, subject is censored on the date of last eDiary entry

     - If a subject completed the study and has intermittent missing eDiary data and time to alleviation of moderate and severe respiratory illness symptoms has not been reached, subject is censored on the date of last eDiary entry

   - Population-level summary:

- hazard ratio, i.e. the hazard rate of alleviation of moderate and severe respiratory illness symptoms in subjects treated with RTB101 divided by the hazard rate of alleviation of moderate and severe respiratory illness symptoms in subjects treated with placebo by the Week 16 visit

9.3. Primary Efficacy Endpoint Analysis

9.3.1. Primary Analysis of the Primary Endpoint

The primary efficacy endpoint is the percentage of subjects with at least one CSRI, with or without an associated laboratory-confirmed pathogen, beginning at least 3 days after the start of study drug treatment through Week 16 (H_1).

The primary efficacy endpoint will be analyzed through a logistic regression model to obtain an estimate of the population odds ratio, i.e. the odds of having a CSRI in subjects treated with RTB101 compared to the odds of having a CSRI in subjects treated with placebo and its associated confidence interval. The logistic regression model will be adjusted for factors that are known to be prognostic of outcome, specifically age (continuous covariate), clinical frailty score (ordinal covariate), medical history of diabetes mellitus type 2 (T2DM, Y/N), congestive heart failure (CHF, Y/N) asthma (Y/N), and receipt of current season influenza vaccination (Y/N). Presence or absence of asthma will be obtained from medical history records and not the stratification level entered at baseline.

Analysis of the primary efficacy endpoint will be based on the estimand for the primary objective described above.

Summary statistics will be presented along with a full data listing

9.3.2. Sensitivity and Supplemental Analyses of the Primary Endpoint

The following sensitivity analyses are planned to provide evidence in support of the strength of treatment of RTB 101 10 mg as compared to placebo.

9.3.2.1. *Sensitivity Analyses*

For placebo subjects who discontinue study prematurely for any reason other than an RTI AE or RTI SAE and/or had ≥7 consecutive days of missing eDiary entries, and did not meet the definition of a CSRI, impute with CSRI odds from the placebo group, adjusted for the duration of missing eDiary entries through Week 16 in the placebo arm (as described in (1) below). For RTB101 subjects who discontinue study prematurely for any reason other than an RTI AE or RTI SAE and/or had ≥7 consecutive days of missing eDiary entries, and did not meet the definition of a CSRI, impute with CSRI odds that vary between that of the RTB101 odds adjusted for the duration of missing eDiary entries in the RTB101 arm, and the placebo odds. Subjects who discontinued study prematurely due to an RTI AE or RTI SAE will continue to be imputed as having a CSRI.The maximum odds that yields statistically significant results will be computed and reported as the “tipping point”.

Adjustment for the duration of missing eDiary entries in each arm will be calculated as follows:

For each arm,

(1) Among subjects who have missing eDiary data through the Week 16 Visit, add the number of days in which subjects did not enter data in their eDiary, including only the periods that have ≥7

consecutive days of missing eDiary entries i.e. exclude days in which eDiary data was not entered between 1-6 days only. For subjects who discontinue study prematurely, the duration of missing eDiary entries will be calculated as the number of days from the last eDiary entry until 16 weeks after the start of study drug treatment.

(2) Add the number of days missed in (1) for all subjects.

(3) Calculate the total number of expected eDiary entry days for subjects with missing data, i.e. number of subjects with missing data multiplied by 111 days (16 weeks).

(4) Divide (2) by (3).
The result obtained in (4) provides the adjustment factor used to adjust for the duration of missing eDiary entries in each arm.

1. For placebo subjects who discontinue study prematurely for any reason other than an RTI AE or RTI SAE, and did not meet the definition of a CSRI, impute with CSRI odds from the placebo group, adjusted for the duration of missing eDiary entries in the placebo arm. For RTB101 subjects who discontinue study prematurely for any reason other than an RTI AE or RTI SAE, and did not meet the definition of a CSRI, impute with CSRI odds that vary between that of the RTB101 odds, adjusted for the duration of missing eDiary entries in the RTB101 arm, and the placebo odds . Subjects who discontinued study prematurely due to an RTI AE or RTI SAE will continue to be imputed as having a CSRI. The maximum odds that yields statistically significant results will be computed and reported as the "tipping point". Adjustment for the duration of missing eDiary entries for each arm will be calculated in the same manner as described under Sensitivity Analysis 1 above.

2. Conduct the same sensitivity analysis described in 1 above, for subjects with the following number of days with consecutive days of missing eDiary entries through the Week 16 visit:
   a. ≥14 consecutive days of missing eDiary
   b. ≥21 consecutive days of missing eDiary
   c. ≥28 consecutive days of missing eDiary
   d. ≥56 consecutive days of missing eDiary
   e. ≥84 consecutive days of missing eDiary

   Adjustment for the duration of missing eDiary entries for each arm will be calculated in the same manner as described under Sensitivity Analysis 1 above, with the following modifications:

   - for 3a, only count subjects that have ≥14 consecutive days of missing eDiary entries i.e. exclude days in which eDiary data was not entered for 1-13 days when calculating the number of missed days
   - for 3b, only count subjects that ≥21 consecutive days of missing eDiary entries i.e. exclude days in which eDiary data was not entered for 1-20 days when calculating the number of missed days.

   Modify criteria for 3c-3e in a similar fashion.

9.3.2.2. *Supplemental Analyses and Summaries*

1. The primary analysis described in 9.3.1 above will be conducted in the Per Protocol (PP) population.

2. The primary analysis described in 9.3.1 above9.3.1 above will be conducted in the subset of subjects who did not discontinue from the study prematurely and/or did not have ≥7 consecutive days of missing eDiary entries. (Completers Analysis 1)

3.. The primary analysis described in 9.3.1 above will be conducted in the subset of subjects who did not discontinue from the study prematurely. (Completers Analysis 2)

4.. Summary statistics (n, mean, SD, median, quartiles, minimum, maximum) and corresponding box plots by treatment group will be provided for the number of subjects with any missing data due to intermittent missed eDiary entries and premature discontinuation from the study. The number of subjects with ≥7, ≥14, ≥21, ≥28, ≥35, ≥42, ≥49, … ≥ 105 consecutive days of missing eDiary entries missing data will also be summarized in a similar manner.

9.4. Analyses of Secondary Efficacy Endpoints

9.4.1. Percentage of Subjects with One or More Clinically Symptomatic Respiratory Illnesses Associated with ≥1 Laboratory-confirmed Pathogen(s)

The percentage of subjects with CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 (**H_2**) as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 based on the estimand for the secondary objective corresponding to this endpoint described in 9.2.2 above.

Laboratory results from a specimen obtained within 3 days before the CSRI start date through the CSRI end date will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen. Laboratory confirmation includes a positive respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDT. If multiple specimens are obtained for a particular CSRI, then any positive result will be counted as laboratory confirmation if it occurs within 3 days before the CSRI start date through the CSRI end date. A laboratory-confirmed CSRI may be associated with multiple pathogens. Note that organisms considered to identify a positive sputum specimen should meet standard microbiological laboratory criteria of growing from a sputum specimen with > 25 WBC/hpf and < 10 Squamous cells/ hpf, and they have matching morphology on gram stain and culture.

Summary statistics will be presented along with a full data listing by treatment group.

9.4.2. Rate of Clinically Symptomatic Respiratory Illnesses (with or without an Associated Laboratory-confirmed Pathogen)

The rate of CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16 (**H_3**) will be analyzed based on the negative binomial distribution. The first 3 days of study drug treatment will not be included in determining the denominator of rate.

A generalized linear model analysis will be conducted using the number of CSRIs per 16-week period (illnesses/16 weeks) as the dependent variable and will include treatment group, age (continuous covariate), Clinical Frailty Scale score (ordinal covariate), medical history of diabetes mellitus type 2 (Y/N), medical history of asthma (Y/N) medical history of CHF (Y/N), and receipt of current season influenza vaccination (Y/N) as fixed effects.

The rate ratio (RR) (RTB101 dose group to placebo) of the treatment effect will be derived from the model along with the 95% 2-sided confidence interval (CI). Model-adjusted mean rates for each treatment group and their corresponding 95% 2-sided CI will also be calculated.

The "log" link function will be used in the model and an offset term will be included to account for variable lengths of treatment exposure across the subjects. The unadjusted rate of CSRI per subject through Week 16 will be calculated by summing the number of total CSRIs per subject through Week 16 within each treatment group.

Analysis of this endpoint will be based on the estimand for the secondary objective corresponding to this endpoint described in 9.2.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.4.3. Rate of Clinically Symptomatic Respiratory Illness Associated with ≥1 Laboratory-confirmed Pathogen(s)

The rate of CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 (**H_4**) as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs will be analyzed in the same manner as described in 9.4.2 above, based on the estimand for the secondary objective corresponding to this endpoint described in 9.2.2 above. Section 9.4.1 describes which laboratory result will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen.

Summary statistics will be presented along with a full data listing by treatment group.

9.4.4. Time to Alleviation of Moderate and Severe Respiratory Illness Symptoms

The time to alleviation of moderate and severe symptoms due to a CSRIs beginning at least 3 days after the start of study drug treatment through Week 16 (**H_5**) will be analyzed as a secondary endpoint.

The time to alleviation of moderate or severe symptoms is defined as the time when all of 6 respiratory symptoms (runny nose, sneezing, stuffy nose, sore throat, hoarseness, or cough) and 3 general symptoms (headache, feverishness/chills or loss of appetite) have been assessed by the patient as Absent or Mild in the patient eDiary from the earliest start date of any moderate or severe symptoms associated with the CSRI among all subjects with ≥1 CSRI through the Week 16 visit. For subjects with >1 CSRI, the longest time to alleviation of moderate or severe symptoms among the CSRIs will be used for the analysis.

The time to alleviation of moderate and severe symptoms (days) = (earliest date all symptoms due to a CSRI are Absent or Mild – earliest start date among all moderate or severe symptoms) +1

Risk set: Subjects who have a ≥1 CSRI.

Time origin: Earliest start date of moderate or severe symptom associated with a CSRI.

For subjects who were not observed to have an alleviation of their moderate or severe symptoms, time to alleviation of moderate or severe symptoms will be censored on the date of last eDiary entry.

The point estimate of the hazard ratios and the associated 95% confidence intervals for RTB101 versus placebo will be obtained using the Cox proportional hazards regression model with fixed effects for treatment group, age (continuous covariate), Clinical Frailty Scale score (ordinal covariate), medical history of diabetes mellitus type 2 (Y/N), medical history of asthma (Y/N) and medical history of CHF (Y/N) as covariates. An approximate Chi-square test based on Wald statistic will be used to compare treatment groups.

Summary statistics and associated survival curves (Kaplan-Meier estimates) will be presented along with a full data listing by treatment group.

9.4.5. Percentage of Subjects with Severe Symptoms due to Clinically Symptomatic Respiratory Illnesses

The percentage of subjects with severe symptoms due to CSRIs beginning at least 3 days after the start of study drug treatment through Week 16 ($\mathbf{H_6}$) will be analyzed in the same manner as the primary efficacy endpoint, as described in 9.3.1 above based on the estimand for the secondary objective corresponding to this secondary endpoint as described in 9.2.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.4.6. Rate of Clinically Symptomatic Respiratory Illnesses Associated with Specific Laboratory-confirmed Viruses

A comparison of the rate of clinically symptomatic respiratory illnesses associated with specific laboratory-confirmed viruses (coronaviruses, hMPV, HRV/enterovirus, adenovirus, influenza A and B virus, parainfluenza viruses, and RSV) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by respiratory pathogen PCR of nasopharyngeal swabs and/or RIDTs is not powered to demonstrate a pre-specified treatment effect. This endpoint will be analyzed in the same manner as described in 9.4.2 above. However, there will be no formal statistical tests conducted and no p-values will be presented. To demonstrate trends consistent with the primary endpoint for the pre-specified laboratory-confirmed viruses, the estimated rate of the laboratory-confirmed viruses and associated CIs will be presented by treatment arm.

9.5. Analyses of Exploratory Efficacy Endpoints

9.5.1. Rate of All Laboratory-confirmed Viral Infections with or without Symptoms

The rate of all laboratory-confirmed viral infections with or without symptoms beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by respiratory pathogen PCR of nasopharyngeal swabs and/or RIDTs (obtained during episodes of clinically symptomatic respiratory illnesses) and/or respiratory pathogen PCR of mid-turbinate swabs (obtained at required clinical visits even in the absence of symptoms) will be analyzed in the same manner as described in 9.4.2 above.

All positive results from specimens (respiratory pathogen PCR of nasopharyngeal swabs or midturbinate swabs and/or RIDT) collected at least 3 days after the start of study drug treatment through Week 16, which may or may not be associated with a CSRI, will count as laboratory-confirmed viral infections (both symptomatic and asymptomatic).

Summary statistics will be presented along with a full data listing by treatment group.

9.5.2. Rate of All-cause Hospitalizations

The rate of all-cause hospitalizations beginning at least 3 days after the start of study drug through Week 16 **(H_7)** will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.3. Rate of Hospitalizations Associated with RTIs

The rate of hospitalizations associated with RTIs beginning at least 3 days after the start of study drug through Week 16 will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.4. Rate of All-cause Emergency Room Visits

The rate of all-cause Emergency Room (ER) visits beginning at least 3 days after the start of study drug through Week 16 will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.5. Rate of Emergency Room Visits with RTIs

The rate of ER visits associated with RTIs beginning at least 3 days after the start of study drug treatment through Week 16 will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.6. Rate of All-cause Urgent Care Clinic Visits for Clinically Symptomatic Respiratory Illness

The rate of all-cause urgent care clinic for clinically symptomatic respiratory illness visits beginning at least 3 days after the start of study drug treatment through Week 16 will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.7. Rate of All-cause Urgent Care Clinic Visits

The rate of all-cause urgent care clinic visits beginning at least 3 days after the start of study drug through Week 16 will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.8. Rate of All-cause Admissions to Skilled Nursing Facilities

The rate of all-cause admissions to skilled nursing facilities beginning at least 3 days after the start of study drug through Week 16 will be analyzed in the same manner as described in 9.4.2 above

Summary statistics will be presented along with a full data listing by treatment group.

9.5.9. Hospitalization Length of Stay Associated with RTIs

Total hospitalization length of stay associated with RTIs beginning at least 3 days after the start of study drug treatment through Week 16 will be analyzed as an exploratory endpoint.

Total hospitalization length of stay associated with RTIs will consist of the total duration of hospitalizations associated with RTIs for each subject starting between 3 days after the start of study drug and prior to Week 16. Duration of a hospital stay is defined as (hospital discharge date –hospital admission date) +1.

The analysis will be performed using the Analysis of Covariance model (PROC MIXED) with fixed effects for treatment group, age (continuous covariate), Clinical Frailty Scale score (ordinal covariate), medical history of diabetes mellitus type 2 (Y/N), medical history of asthma (Y/N), medical history of CHF (Y/N), and receipt of current season influenza vaccination (Y/N) as covariates. The least squares (LS) means, differences between LS means, a 95% 2-sided CLs for the difference and the p-values from model effects will be reported for overall treatment to evaluate the treatment effect.

Summary statistics, including Least Squares Mean and standard error for each treatment and the treatment difference will be presented along with a full data listing by treatment group.

9.5.10. Percentage of Subjects with 1 or more Clinically Symptomatic Respiratory Illnesses (with or without an Associated Laboratory-confirmed Pathogen) through Week 20

The percentage of subjects with 1 or more CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 20 **(H_9)** will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.11. Percentage of Subjects with 1 or more Clinically Symptomatic Respiratory Illnesses Associated with ≥1 Laboratory-confirmed Pathogen(s) through Week 20

The percentage of subjects with 1 or more CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 20 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above. Section 9.4.1 describes which laboratory result will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.12. All-cause Hospitalization Length of Stay

All-cause hospitalization total length of stay beginning at least 3 days after the start of study drug through Week 16 will be analyzed in the same manner described in 9.5.9 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.13. Change from Baseline in EQ-5D-5L Scores during All Clinically Symptomatic Respiratory Illness Episodes and at Week 16

The change from Baseline in HRQoL as assessed by EQ-5D-5L Visual Analog Scale (VAS) scores during all CSRI episodes beginning at least 3 days after the start of study drug treatment through Week 16 and at Week 16 will be analyzed using a Mixed Model Repeated Measure model (PROC MIXED). The model will include the change from Baseline in EQ-5D-5L (measured each day during a CSRI event and at the Week 16 visit) as the dependent variable and will include patient as a random effect, and fixed effects of treatment group, Baseline EQ-5D-5L, time (study day the measure was taken), and a treatment-by-time interaction.

The Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. An unstructured (general) covariance structure will be assumed initially to model the within-subject errors; however, other covariance structures will be tested and may be used in the final model if a better fit is evident. The least squares (LS) means, differences between LS means, a 95% 2-sided CLs for the difference and the p-values from model effects will be reported for overall treatment to evaluate the treatment effect.

Summary statistics for the VAS and individual items and associated boxplot for VAS will be presented along with a full data listing of EQ-5D-5L data by treatment group.

9.5.14. Percentage of Subjects with One or More Clinically Symptomatic Respiratory Illnesses (with or without an Associated Laboratory-confirmed Pathogen) through Week 16 who are ≥85 years of age

The percentage of subjects with one or more CSRIs beginning at least 3 days after the start of study drug treatment through Week 16 who are ≥85 years of age will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.15. Rate of Clinically Symptomatic Respiratory Illnesses (with or without an Associated Laboratory-confirmed Pathogen) through Week 16 in Subjects who are ≥85 years of age

The rate of CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16 in subjects who are ≥85 years of age will be analyzed in the same manner as described in 9.4.2 above. Summary statistics will be presented along with a full data listing by treatment group.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.16. Percentage of Subjects with One or More Clinically Symptomatic Respiratory Illnesses (with or without an Associated Laboratory-confirmed Pathogen) through Week 16 who have a Medical History of Asthma

The percentage of subjects with one or more CSRIs at least 3 days after the start of study drug treatment through Week 16 who have a medical history of asthma will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.17. Rate of Clinically Symptomatic Respiratory Illnesses (with or without an Associated Laboratory-confirmed Pathogen) through Week 16 in Subjects who have a Medical Hstory of Asthma

The rate of CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16 in subjects who have a medical history of asthma will be analyzed in the same manner as described in 9.4.2 above. Summary statistics will be presented along with a full data listing by treatment group.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.18. Percentage of Subjects with One or More Clinically Symptomatic Respiratory Illnesses Associated with ≥1 Laboratory-confirmed Pathogen(s) through Week 16 who are ≥85 years of age

The percentage of subjects with one or more CSRIs associated with ≥1 laboratory-confirmed pathogen(s) at least 3 days after the start of study drug treatment through Week 16 who are ≥85 years of age will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above. Section 9.4.1 describes which laboratory result will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.19. Percentage of Subjects with One or More Clinically Symptomatic Respiratory Illnesses Associated with ≥1 Laboratory-confirmed Pathogen(s) through Week 16 who have a Medical History of Asthma

The percentage of subjects with one or more CSRIs associated with ≥1 laboratory-confirmed pathogen(s) at least 3 days after the start of study drug treatment through Week 16 who have a medical history of asthma will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above. Summary statistics will be presented along with a full data listing by treatment group. Section 9.4.1 describes which laboratory result will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen.

9.5.20. Rate of Clinically Symptomatic Respiratory Illnesses Associated with ≥1 Laboratory-confirmed Pathogen(s) through Week 16 in Subjects who are ≥85 years of age

The rate of CSRIs associated with ≥1 laboratory-confirmed pathogen(s) in subjects who are ≥85 years of age beginning at least 3 days after the start of study drug treatment through Week 16 will be analyzed in the same manner as described in 9.4.2 above. Section 9.4.1 describes which laboratory result will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.21. Rate of Clinically Symptomatic Respiratory Illnesses Associated with ≥1 Laboratory-confirmed Pathogen(s) through Week 16 in Subjects with a Medical History of Asthma

The rate of CSRIs associated with ≥1 laboratory-confirmed pathogen(s) in subjects with a medical history of asthma beginning at least 3 days after the start of study drug treatment through Week 16 will be

analyzed in the same manner as described in 9.4.2 above. Section 9.4.1 describes which laboratory result will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.22. Rate of Asthma Exacerbations through Week 16 in Subjects with a Medical History of Asthma

The rate of asthma exacerbations, defined as deterioration of asthma symptoms that requires treatment with systemic steroids, beginning at least 3 days after the start of study drug treatment through Week 16 in subjects with a medical history of asthma will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.23. Percentage of Subjects with 1 or more Asthma Exacerbation through Week 16 in Subjects with a Medical History of Asthma

The percentage of subjects with 1 or more asthma exacerbation defined as deterioration of asthma symptoms that requires treatment with systemic steroids beginning at least 3 days after the start of study drug treatment through Week 16 in subjects with a medical history of asthma will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.24. Change from Baseline to Weeks 4 and 16 in Biomarkers in Whole Blood

Blood samples will be obtained for exploratory biomarker analyses, including RNA expression in whole blood and soluble biomarkers in serum, in all subjects at the Baseline and Week 16 visit, and for subjects in the pharmacokinetic analysis subset (approximately 400 subjects) at the Week 4 or Week 6 visit (4 hours after study drug administration). The RNA expression to be measured may include:

- IFNG
- IFI44L
- IFIT5
- IFIH1
- MSR1
- IFIT1
- IFIT2
- HERC5
- MX1
- IFITM3
- OAS2
- IFIT3
- RSAD2
- ISG15
- IFI27
- IFI6
- STAT2

- STAT1
- SOCS3
- IRF7
- OASL
- OAS3

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study.

Summary statistics of the biomarkers by clinical visit and their associated change from baseline values will be presented along with a full data listing by treatment group.

9.5.25. Rate of Urinary Tract Infections (UTIs) Reported as Adverse Events

The rate of UTIs beginning at least 3 days after the start of study drug treatment through Week 16 **(H_8)** reported as adverse events will be analyzed in the same manner as described in 9.4.2 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.26. Percentage of Subjects with One or more UTIs Reported as Adverse Events.

The percentage of subjects with 1 or more UTIs reported as adverse events beginning at least 3 days after the start of study drug treatmentthrough Week 16 will be analyzed in the same manner as the primary efficacy endpoint analysis described in 9.3.1 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.5.27. Percentage of Subjects with Expanded-Definition Clinically Symptomatic Respiratory Illness (with or without an associated laboratory-confirmed pathogen) by Week 16

Percentage of subjects with expanded-definition clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment by Week 16 will be analyzed as an exploratory analysis. Expanded-definition clinically symptomatic respiratory illness is defined similarly to the primary endpoint except the general symptoms of body aches and lack of energy will be included in the list of general symptoms for the purpose of identifying a case of an expanded CSRI.

The analysis method will be the same as the primary endpoint efficacy analysis as described in 9.3.1 above.

Summary statistics will be presented along with a full data listing by treatment group.

9.6. Additional Sensitivity/Exploratory Analyses

9.6.1. Percentage of Subjects with One or More Clinically Symptomatic Respiratory Illnesses Associated with ≥1 Laboratory-confirmed Pathogen(s) Including Assessment using Midturbinate Swabs

The percentage of subjects with CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs or midturbinate swabs,

sputum gram stain and culture and/or RIDTs will be analyzed in the same manner as the primary efficacy analysis as described in 9.3.1 above.

Laboratory results from a specimen obtained within 3 days before the CSRI start date through the CSRI end date will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen. Laboratory confirmation includes a positive respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, RIDT, and/or respiratory pathogen PCR of midturbinate swabs. If multiple specimens are obtained for a particular CSRI, then any positive result will be counted as laboratory confirmation if it occurs within 3 days before the CSRI start date through the CSRI end date. A laboratory-confirmed CSRI may be associated with multiple pathogens.

9.6.2. Rate of Clinically Symptomatic Respiratory Illness Associated with ≥1 Laboratory-confirmed Pathogen(s) Including Assessment using Midturbinate Swabs

The rate of CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs or midturbinate swabs, sputum gram stain and culture and/or RIDTs will be analyzed in the same manner as described in 9.4.2 above. 9.6.1 describes which laboratory result will be used to determine if the CSRI is associated with ≥1 laboratory-confirmed pathogen.

Summary statistics will be presented along with a full data listing by treatment group.

10. Safety

Safety analyses will be conducted on the Safety Set (SAF) and will be assessed on the basis of adverse event (AE), clinical laboratory data, ECG parameters, physical examinations, and vital signs.

10.1. Extent of Exposure

Duration of exposure is defined as (Date of Last Dose – Date of First Dose) +1. If date of last dose is unknown then the date of last clinical visit no later than the Week 16 Visit will be used to impute the date of last dose. If there are temporary dose interruptions based on the data from the eCRF, then only the periods of time when study drug interruption did not occur will be used to calculate the duration of exposure. Duration of exposure will be summarized using descriptive statistics by treatment group. The duration of exposure (in days) will also be categorized as follows: <7, 7-<14, 14-<28, 28-<42, 42-<46, 56-<70, 70-<84, 84-<98, 98-<112, ≥112, and tabulated by treatment group..

A listing including study drug administration information from the eDiary will be presented.

10.2. Treatment Compliance

Treatment compliance will be summarized as the number (%) of subjects indicated as compliant (>=80%) on the eCRF by treatment group.

Subjects are expected to take 1 tablet of study medication once per day through the Week 16 visit.

10.3. Adverse Events

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. All adverse events (AEs) will be coded using the MedDRA version 22.0 or higher. Only treatment-emergent adverse events, defined as any adverse events that start or increase in intensity on or after the first dose of double-blind treatment (Study Day 1), were collected in this study. The following listings of AEs will be provided by subjects:

- All AEs,
- Serious adverse events (SAEs)
- AEs leading to death
- AEs leading to study withdrawal
- AEs leading to study drug discontinuation
- Severe AEs
- Study drug related AEs
- Study drug related SAEs

Adverse Events will be included in summary tables by treatment received. An overall summary table of AEs through Week 20 will be produced for the following categories:

- Any AE
- Grade 1 (Mild) AEs, Grade 2 (Moderate) AEs, Grade 3 (Severe) AEs, Grade 4 (Severe and Life Threatening), and Grade 5 (Fatal) AEs
- Study drug-related AEs
- Serious AEs
- Study drug-related Serious AEs
- AEs leading to permanent study drug discontinuation
- AEs leading to study discontinuation
- AEs leading to death

All AEs will be classified by SOC and PT. Frequency count of AEs, the number of unique subjects experiencing an AE, percentage of unique subjects experiencing an AE and total number of events will be tabulated by treatment. For the number of unique subjects reporting, if a subject reported more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT.

The following summaries of AEs will also be provided:

- AEs by SOC and PT
- Treatment-related AEs by SOC and PT
- AEs by SOC, PT and maximum severity
- AEs by SOC, PT and causality relationship
- Serious AEs by SOC and PT
- Serious treatment-related AEs by SOC and PT
- AEs leading to study withdrawal by SOC and PT
- TEAEs leading to study drug discontimuation by SOC and PT
- AEs leading to death by SOC and PT

For AEs presented by relationship to study treatment, the strongest relationship to study treatment(s) during the clinical trial will be presented for each subject if coded to the same SOC or PT. For AEs presented by severity, the worst severity during the clinical trial will be presented for each subject if coded to the same SOC or PT. If either relationship or severity is missing, then the strongest relationship (related) or worst severity (severe) will be assigned.

10.4. Laboratory Evaluations

Blood samples for hematology, chemistry, and urine samples for urinalysis are to be collected at screening, Baseline, Weeks 2, 4, 6, 8, 12, 16, and 20 visits. All results will be provided using International System of Units (SI).

Descriptive statistics for hematology, chemistry, and urine will be provided for each test parameter and for change from baseline summarized by visit and treatment grou. Shift tables (i.e., low-normal-high at Baseline versus low-normal-high at each post-baseline visit in a 3-by-3 contingency table) will be provided for hematology, biochemistry, and urine to assess changes from Baseline in laboratory values by visit and by treatment group. Listings of abnormal laboratory values, defined as values that are either <0.5x lower limit of normal (LLN) or >2x upper limit of normal (ULN) for each hematology and chemistry test parameter will be provided.

Boxplots for the change from baseline values for each post-baseline visit for hematology, chemistry and urinalysis (numerical results only) test parameters will be generated by treatment group, with LLN, ULN, 0.5x LLN and 2x ULN values plotted for each test parameter.

Separate listings of all laboratory data will be provided for all laboratory evaluations (hematology, biochemistry, and urinalysis).

10.5. Vital Signs

Vital signs consist of temperature; respiratory rate; heart rate, and seated Blood Pressure. Vital signs are collected at Screening, Baseline, Weeks 2, 4, 6, 8, 12, 16, and 20 visits.

Observed values at each visit and changes from Baseline to each post-baseline visit in vital signs will be summarized by visit and treatment group using descriptive statistics. Shift tables (i.e., low-normal-high at Baseline versus low-normal-high at each post-baseline visit in a 3-by-3 contingency table) will be provided to assess changes from Baseline in each vital sign value by visit and treatment group.

All vital signs will be provided in subject data listings.

10.6. ECG

A 12-lead ECG will be performed during the study at Screening, Baseline, Week 4, Week 8, Week 12, and Week 16.

Observed values at each visit and changes from Baseline to each post-baseline visit in ECG parameter will be summarized by visit and treatment group using descriptive statistics. A summary of abnormal results for QTc, QTcB, and QTcF. Abnormal values will be categorized as >450 msec, >480 msec, >500 msec, change from baseline >30 msec, and/or change from baseline >60 msec.

Listings will be provided for all ECG parameters and interpretive results.

10.7. Physical Examination

A complete physical examination will be done at Screening, Week 16, and Week 20. A targeted physical exam of at least oral cavity, skin, heart and lungs will be done at all other visits. Listings will be provided for all physical exams.

11. Interim Analyses

There is no planned interim analysis.

12. Changes from Analysis Planned in Protocol

The following changes from the analyses planned in the protocol were included in this SAP:

(1) The subgroup analysis by gender was added (see Section 7.6 above) to the list of subpopulations specified in Section 9.4.4.2 of the protocol.
(2) In Section 9.4 of the protocol, it was stated that no imputation for missing data will be done for the primary analysis of the primary efficacy endpoint. This was modified such that subjects who discontinued study prematurely due to an RTI AE or RTI SAE will be imputed to have experienced a CSRI (see Section 7.3 above),
(3) An additional factor, i.e. receipt of current season influenza vaccination (Y/N), was added (see Section 9.3.1 above) to the logistic regression model specified for the primary analysis of the primary efficacy endpoint specified in Section 9.4.1 the protocol.
(4) In Section 9.4.1 of the protocol, a gate-keeping strategy for testing multiple endpoints for a primary family (F_1), secondary family (F_2) and exploratory family (F_3) of endpoints was specified. The testing strategy was modified such that families of endpoints will no longer be defined; instead a set of 9 endpoints will be tested using a fixed sequence gate-keeping strategy, as specified in Section 9.1 above.
(5) Supplemental analyses for the Completers 1 and Completers 2 populations described in Section 9.3.2.2 above were added.
(6) Analyses of 4 endpoints not specified in the protocol were included here (see Sections 9.5.26, 9.5.27, 9.6.1 and 9.6.2 above) as exploratory and/or sensitivity analyses, specifically the analyses of
    a. the percentage of subjects with expanded-definition CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment by Week 16,
    b. the rate of expanded-definition CSRIs (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment by Week 16,
    c. the percentage of subjects with CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 which includes assessment by respiratory pathogen PCR of midturbniate swabs, aside from the assessments based on the respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture and/or RIDTs, to determine laboratory confirmation of pathogens, and
    d. the rate of CSRIs associated with ≥1 laboratory-confirmed pathogen(s) beginning at least 3 days after the start of study drug treatment through Week 16 which includes assessment by respiratory pathogen PCR of midturbniate swabs, aside from the assessments based on the respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture and/or RIDTs, to determine laboratory confirmation of pathogens.

13. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output.
- One output file can contain several outputs or each output will be stored in a separate file.
- Output files will be delivered in Word format or portable document format pdf.
- Numbering of TFLs will follow ICH E3 guidance

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TFLs will be produced in landscape format on American letter size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

- resTORbio, Inc. Protocol RTB-101-204 (Syneos Health study number 7001371)
- Draft/Final Run *<date>*
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont.)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.

- Dates are printed in SAS DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as “N/A”, unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, clinical visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output."

15. Index of Tables

Table Number	Name	Analysis Set
14.1.1	Subject Disposition	Screening Set
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14.1.2.2	Reasons for Exclusion from Analysis Sets	Randomized Set
14.1.3.1.1	Subject Demographic and Baseline Characteristics	Randomized Set
14.1.3.1.2	Subject Demographic and Baseline Characteristics	Safety Set
14.1.3.1.3	Subject Demographic and Baseline Characteristics	Full Analysis Set
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