CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Determine if RTB101 Prevents Clinically Symptomatic Respiratory Illness in the Elderly

Compound:	RTB101
Protocol Number:	RTB-101-204
Protocol Date:	16 September 2019
Version Number:	06 (Amendment 03)
Sponsor:	resTORbio, Inc. 500 Boylston Street 13th Floor Boston MA 02116 USA
Clinical Trial Phase:	3

Sponsor Protocol Signature Page

Protocol Title:	**A Multicenter, Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Determine if RTB101 Prevents Clinically Symptomatic Respiratory Illness in the Elderly**
Protocol Number:	**RTB-101-204, Version 06 (Amendment 03)**
Study Phase:	**3**
Sponsor:	**resTORbio, Inc.**

Sponsor Representatives

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

William Marshall, MD, VP, Medical Sciences — Date: 16 Sept 2019

Sarb Shergill, PhD, VP, Clinical Operations — Date: 16 SEPT 2019

Investigator Agreement

Protocol Title:	**A Multicenter, Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Determine if RTB101 Prevents Clinically Symptomatic Respiratory Illness in the Elderly**
Protocol Number:	**RTB-101-204, Version 06 (Amendment 03)**
Study Phase:	**3**
Sponsor:	**resTORbio, Inc.**

I confirm that I have read and that I understand this protocol amendment, the Investigator's Brochure, and other product information provided by the Sponsor.

I agree to conduct this study in accordance with the requirements of this protocol and protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization Guidance for Industry, Good Clinical Practice E6 (R2).
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Phone Number

_____

Full Address

Protocol Synopsis

Protocol Number	RTB-101-204
Title	A Multicenter, Randomized, Double Blind, Placebo-Controlled, Phase 3 Study to Determine if RTB101 Prevents Clinically Symptomatic Respiratory Illness in the Elderly
Brief Title	Phase 3 study to determine if RTB101 prevents respiratory illness associated with respiratory tract infections (RTIs) in the elderly
Sponsor	resTORbio, Inc.
Clinical Phase	3
Investigation Type	Drug
Study Type	Interventional
Purpose and Rationale	The purpose of this study is to determine if RTB101 prevents clinically symptomatic respiratory illness (CSRI) in subjects ≥65 years of age. Subjects with clinically symptomatic respiratory illness are defined as subjects with symptoms consistent with a RTI based on prespecified diagnostic criteria.
Primary Objective(s)	• 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
Secondary Objectives	• 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
Exploratory Objectives	• 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 urgent care 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)
Study Design	This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, Phase 3 study to determine if RTB101 prevents clinically symptomatic respiratory illness in elderly subjects. Subjects will be enrolled during cold and flu season. The study will be comprised of up to a 4-week Screening Period; a 16-week Primary Analysis Period (for evaluating efficacy) 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).
Population	The study population will be comprised of subjects ≥65 years of age without unstable underlying medical conditions including subjects in assisted-living or long-term care residential facilities that provide minimal assistance, such that the subject is primarily responsible for self-care and activities of daily living.
Number of Subjects	Approximately 1066 subjects are planned to be randomized in the study. Subjects will be randomized 1:1 to RTB101 10 mg or placebo taken orally once daily (approximately 533 subjects will be randomized to each arm).
Inclusion Criteria	Subjects eligible for inclusion in this study must fulfill all of the following criteria: 1. Written informed consent must be obtained before any assessment is performed.

	2. Male and female subjects who, in the clinical judgement of the Investigator, are without unstable medical conditions defined as conditions that require acute medical intervention or ongoing adjustments of concomitant medications (as determined by medical history, current concomitant medications and laboratory test results at Screening, and physical examination, electrocardiogram (ECG) and vital signs at Screening and Baseline). 3. Subjects must be ≥65 years of age. 4. Subjects should require no or minimal assistance with self-care and activities of daily living. Subjects in assisted-living or long-term care residential facilities that provide minimal assistance are eligible. 5. Females must be post-menopausal. Women are considered post-menopausal and not of child bearing potential if they have had: • 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) OR • surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to Screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment will she be considered not of child bearing potential. 6. Sexually active male subjects with a partner of child-bearing potential must be willing to wear a condom while on study drug and for 1 week after stopping study drug and should not father a child in this period. A condom is required to be used also by vasectomized men with a partner of child-bearing potential to prevent delivery of the drug via seminal fluid. 7. Subject must weigh at least 40 kg. 8. Subject must be able to communicate well with the Investigator, and to understand and comply with the requirements of the study including completing a daily eDiary at home.
Exclusion Criteria	Subjects will not be eligible if they meet any of the following criteria: 1. Any subject who: a. Is a current smoker as assessed by medical history or a positive serum cotinine test (or positive urine cotinine test if serum cotinine testing is unavailable) at Screening. b. Stopped smoking ≤1 year prior to Screening. c. Is a previous smoker with a ≥10 pack year smoking history. d. Has a household member who currently smokes in the house. 2. Subjects with a medical history of clinically significant lung diseases other than asthma (e.g., chronic obstructive pulmonary

	disease (COPD), emphysema, interstitial pulmonary fibrosis (IPF), bronchiectasis, etc.). 3. Subjects with a Mini Mental Status Examination (MMSE) score <24 at Screening. 4. Subjects with current evidence of a serious and/or unstable medical disorder including cardiovascular, respiratory, gastrointestinal, renal (including subjects with an estimated glomerular filtration rate (eGFR) as estimated by the modified diet in renal disease (MDRD) GFR equation that is ≤30 mL/min/1.73m2), or hematologic disorders. 5. The following cardiac conditions: a. Unstable angina pectoris or acute ischemic changes on ECG at Screening or Baseline b. History of myocardial infarction (MI), coronary bypass surgery, or any percutaneous coronary intervention (PCI) within 6 months prior to Screening c. New York Heart Association functional classification III-IV congestive heart failure d. Unstable or life-threatening cardiac arrhythmia i. Chronic stable atrial fibrillation is allowed. e. QTcF>480 msec at Screening or Baseline 6. Subjects with history of malignancy in any organ system within the past 5 years, EXCEPT for the following: a. Localized basal cell or squamous cell carcinoma of the skin. b. Prostate cancer confined to the gland (AJCC stage T2N0M0 or better). c. Cervical carcinoma in situ. d. Breast cancer localized to the breast. 7. Any RTI or acute significant illness (based on the subject's medical history and the clinical judgement of the Investigator) which has not resolved at least two (2) weeks prior to Baseline. 8. Subjects with a history of systemic autoimmune diseases (e.g., lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), or receiving immunosuppressive therapy (such as mycophenolate, tacrolimus, cyclosporine, azathioprine, infliximab) including chronic use of prednisone >10 mg daily (however, inhaled corticosteroids and the acute use of higher doses of prednisone to treat conditions such as exacerbation of asthma or other acute conditions are allowed). 9. Subjects with Type I diabetes mellitus. 10. Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further evaluation. 11. Subjects with any one of the following during Screening: a. white blood cell (WBC) count <2.0 x10^3/microL. b. neutrophil count <1.0 x 10^3/microL.

	c. platelet count <75 x 10^3/microL. 12. Subjects with a history of alcohol or drug abuse within 2 years of the Screening visit. 13. Subjects with any conditions affecting absorption, distribution, or metabolism of the study drug (e.g., inflammatory bowel disease, gastric or duodenal ulcers, or hepatic disease). For subjects with biochemical evidence of liver injury as indicated by abnormal liver function tests: • Any single parameter of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase or serum bilirubin must not exceed 1.5 x upper limit of normal (ULN) in subjects who do not have Gilbert's syndrome. If the subject has a history of Gilbert's syndrome, direct and indirect reacting bilirubin should be differentiated, and the direct bilirubin must be less than 1.5 x ULN. • Any elevation above ULN of more than one parameter of ALT, AST, alkaline phosphatase or serum bilirubin will exclude a subject from participation in the study. 14. Subjects with a history of immunodeficiency diseases, including a positive human immunodeficiency virus (HIV) test result. 15. Infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV). 16. Subjects who require treatment with strong CYP3A4 or CYP1A2 inhibitors or inducers, or subjects who require treatment with digoxin. 17. Use of any other investigational medication or participation in any other investigational study within 5 half-lives of the investigational medication, or within 30 days, whichever is longer; or longer if required by local regulations. 18. Subjects who have received an organ transplant. 19. Subjects who previously received treatment with RTB101 in another clinical study (e.g., CBEZ235Y2201, RTB-BEZ235-202, or RTB-101-203).
Drug Treatment	RTB101 (dactolisib, previously designated as BEZ235) Subjects will receive oral RTB101 10 mg or matched placebo capsule once daily for up to 16 weeks.
Efficacy Assessments	**Primary Endpoint:** • The percentage of subjects with clinically symptomatic respiratory illness (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

	Secondary Endpoints: • The percentage of subjects with 1 or more 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 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 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. • The rate of clinically symptomatic respiratory illness (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 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 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 clinically symptomatic respiratory illness symptoms due to clinically symptomatic respiratory illness beginning at least 3 days after the start of study drug treatment through Week 16 • The percentage of subjects with severe symptoms due to clinically symptomatic respiratory illnesses beginning at least 3 days after the start of study drug treatment through Week 16 • Safety and tolerability will be assessed by report of adverse events (AE)/serious adverse events (SAEs), physical exam and ECG findings, and safety laboratory values **Exploratory Endpoints:** • 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 symptomatic respiratory illnesses) and/or respiratory pathogen PCR of mid-turbinate swabs (obtained at scheduled study visits, even in the absence of symptoms) • The rate of all-cause hospitalizations through Week 16

	• The 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 ER visits through Week 16 • The rate of 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 clinically symptomatic respiratory illness 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 1 or more clinically symptomatic respiratory illnesses and the percentage of subjects with 1 or more 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 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 and at Week 16 • The percentage of subjects with one or more clinically symptomatic respiratory illnesses and the percentage of subjects with one or more 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 who are ≥85 years of age or subjects with a medical history of asthma • The rate of clinically symptomatic respiratory illnesses and 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 or subjects with a medical history of asthma • The rate of asthma exacerbations and the percentage of subjects with 1 or more 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 rate of UTIs and the percentage of subjects with one or more UTIs reported as adverse events.

	• Change from Baseline to Weeks 4 and 16 in biomarkers in whole blood and serum and potentially future pharmacogenomic analysis
Safety Assessments	• Physical examination • Body temperature • Blood pressure, heart rate • Respiratory rate • ECG • Hematology, blood chemistry, urinalysis • Adverse events (including SAEs) from time of start of study drug treatment until Week 20
Data Analysis	The percentage of subjects with clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen) beginning at least 3 days after the start of study drug treatment through Week 16 is the primary efficacy endpoint for this study. The primary analysis of the primary efficacy endpoint will be based on the intention-to-treat principle, comprising all subjects who are randomized and have received at least one dose of assigned study drug during the trial. The primary efficacy endpoint will be analyzed through a logistic regression model to obtain an estimate of the population odds ratio and associated confidence intervals between RTB101 and placebo. This primary efficacy model will be adjusted for factors that may influence response to treatment for clinically symptomatic respiratory illness, such as age, frailty score, receipt of current season influenza vaccination and medical history of asthma, CHF or Type 2 diabetes mellitus. 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 of 19.7% in the RTB101 arm, a total sample size of 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. 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 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. To investigate the impact of missing data assumptions on the primary efficacy results, a number of sensitivity analyses, including a tipping point analysis will be conducted. Details of the sensitivity analyses, will be provided in the statistical analysis plan (SAP). <u>Safety and Tolerability</u>: Safety evaluations will be based on actual treatment received. Continuous safety data will be summarized with descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum, and maximum) by treatment. Categorical safety data will be summarized with frequency counts and percentages by dose level. Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available. A by-subject AE data listing, including verbatim term, preferred term, system organ class, treatment, severity, and relationship to study drug will be provided. The number of subjects experiencing AEs and number of individual AEs will be summarized by treatment group, system organ class, and preferred term. AEs will also be summarized by severity and by relationship to study drug. Laboratory evaluations, vital signs and ECG assessments will be summarized by treatment group and protocol specified collection time point. A summary of change-from-baseline at each protocol specified time-point by treatment group will also be presented. Changes from baseline in continuous endpoints may be analyzed using repeated measures mixed analysis of covariance model adjusted for treatment, time point, treatment-by-time point interaction, and baseline values. Binomial endpoints may be summarized and compared between RTB101 and placebo via logistic regression. Rates per person will be summarized and compared between RTB101 and placebo via the Negative Binomial regression. Further details regarding presentation and analysis of safety data, including the approach for stratified data, will be detailed in the statistical analysis plan (SAP).

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List of Abbreviations

Abbreviation	Definition of Term
ADL	activities of daily living
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
AUC	area under the drug concentration versus time curve
AUC_{0-24}	area under the drug concentration versus time curve from 0 to 24 hours
b.i.d./BID	twice a day
BAL	bronchoalveolar lavage
BP	blood pressure
BUN	blood urea nitrogen
CHF	congestive heart failure
CFR	code of federal regulations
CI(s)	confidence interval(s)
C_{max}	maximum plasma concentration
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CT	Computerized tomography
CTC	Common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CXR	chest x-ray
DMC	data monitoring committee
DLCO	diffusing capacity of the lungs for carbon monoxide
ECG	electrocardiogram
EDC	electronic data capture
eDiary	electronic diary
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ER	emergency room
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal

Abbreviation	Definition of Term
HBV	hepatitis virus B
HCV	Hepatitis virus C
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
HRV	human rhinovirus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IEC	independent ethics committee
IPF	interstitial pulmonary fibrosis
IRB	independent review board
i.v.	intravenous
IXRS	interactive voice/web response system
LFT	liver function test
MDRO	multidrug-resistant organisms
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures model
MMSE	Mini Mental Status Examination
mRNA	Messenger ribonucleic acid
MI	myocardial infarction
MNAR	missing not at random
mTOR	mechanistic target of rapamycin
mTORC	mTOR-raptor signal transduction complex
OR	odds ratio
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PFT	pulmonary function test
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3'kinase
PK	pharmacokinetic(s)
PP	per protocol
PSD	premature subject discontinuation
q.d/QD	once a day
RIDT	rapid influenza diagnostic test

Abbreviation	Definition of Term
RNA	ribonucleic acid
RS	randomized set
RSV	respiratory syncytial virus
RTI(s)	respiratory tract infection(s)
S6K	S6 kinase
SAE(s)	serious adverse event(s)
SAF	safety
SAP	statistical analysis plan
SCR	screening
SD	standard deviation
SOM	study operations manual
T2DM	type 2 diabetes mellitus
TORC1	target of rapamycin complex 1
TORC2	target of rapamycin complex 2
ULN	upper limit of normal
U.S.	United States
WBC	white blood cell

1. Introduction

1.1. Background

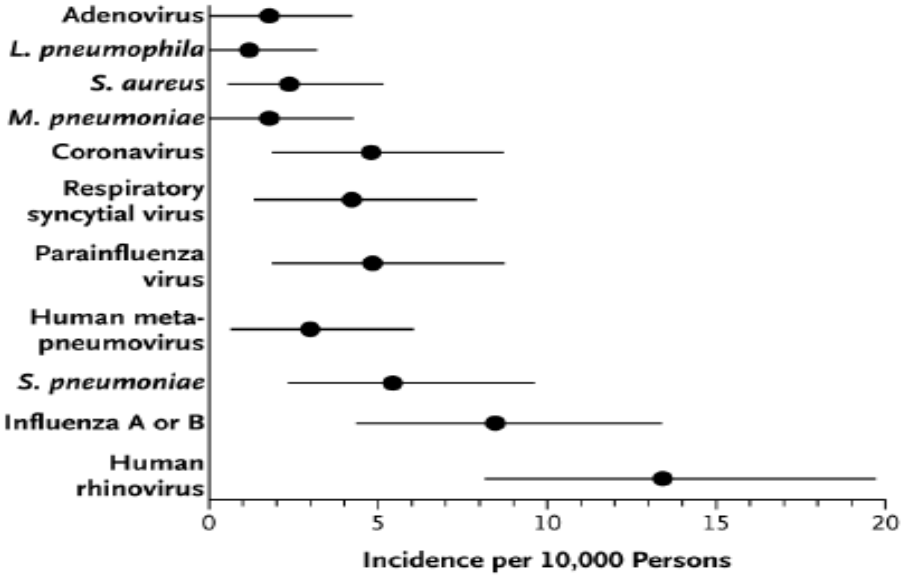
Aging is regulated in part by a discrete set of cellular signaling pathways including the mechanistic target of rapamycin (mTOR) pathway (Lopez-Otin et al., 2013). Inhibition of the mTOR pathway has extended lifespan in every species studied to date and improved the function of multiple aging organ systems in old mice including the immune, neurologic and cardiovascular systems (Johnson et al., 2013). These data raise the possibility that drugs that target the mTOR pathway will have therapeutic benefit in aging-related conditions in humans. One of the aging-related conditions that improves in old mice treated with mTOR inhibitors is immunosenescence which is the decline in both innate and adaptive immune function that occurs during aging. Immunosenescence leads to decreased response to vaccinations and increased rates of infections including respiratory tract infections (RTIs) in the elderly. In preclinical studies in aged mice, short-term (6-week) treatment with the mTOR inhibitor rapamycin rejuvenated hematopoietic stem cell function, increased naïve lymphocyte production, enhanced the immune response to influenza vaccination, and increased lifespan (Chen et al., 2009). In addition, the mTOR inhibitor RTB101 has been shown to protect mice from a lethal influenza virus challenge (Smallwood et al., 2017). These findings raise the possibility that mTOR inhibitors may enhance immune function and protect elderly subjects from infections, and in particular RTIs.

Unmet Medical Need

Decreasing the incidence of RTIs is a large unmet medical need in people age 65 and above who are also the fastest growing population globally (United Nations, 2005). RTIs are the fourth leading cause of hospitalization in people age 65 and over, and the second leading cause of hospitalization in people age 85 and over (Pfunter et al., 2013). Even upper RTIs, which are usually mild in younger adults, can cause significant morbidity in the elderly. A study of community dwelling subjects age 60-90 years of age found that 65% of subjects who developed upper respiratory tract infections also developed lower respiratory tract symptoms, 58% had systemic symptoms (headache, feverishness, chills, sweating, myalgias and rigors), 28% were confined to bed, and 35% were unable to cope with washing, shopping or cooking (Nicholson et al., 1997). The risk of cardiovascular events triples during episodes of RTIs, including upper RTIs, and the increased cardiovascular risk persists for weeks to months after a RTI episode (Musher et al., 2019). Finally, respiratory viruses cause the majority of RTIs, including community-acquired pneumonias requiring hospitalization in elderly subjects (Figure 1-1) (Jain et al., 2015). Unfortunately, there are currently no effective treatments for most respiratory viruses. RTB101 may offer an opportunity to enhance immune function in the elderly and

thereby decrease the incidence of RTIs, regardless of the specific pathogen, without inducing viral resistance.

Figure 1-1 Incidence of Specific Pathogens Detected in Subjects ≥ 80 Years of Age Hospitalized with Community-acquired Pneumonia (Jain et al., 2015)



Shown are the annual number of pathogen-specific pneumonia hospitalizations per 10,000 adults ≥80 years of age with 95% confidence intervals (CIs) (Jain et al., 2015).

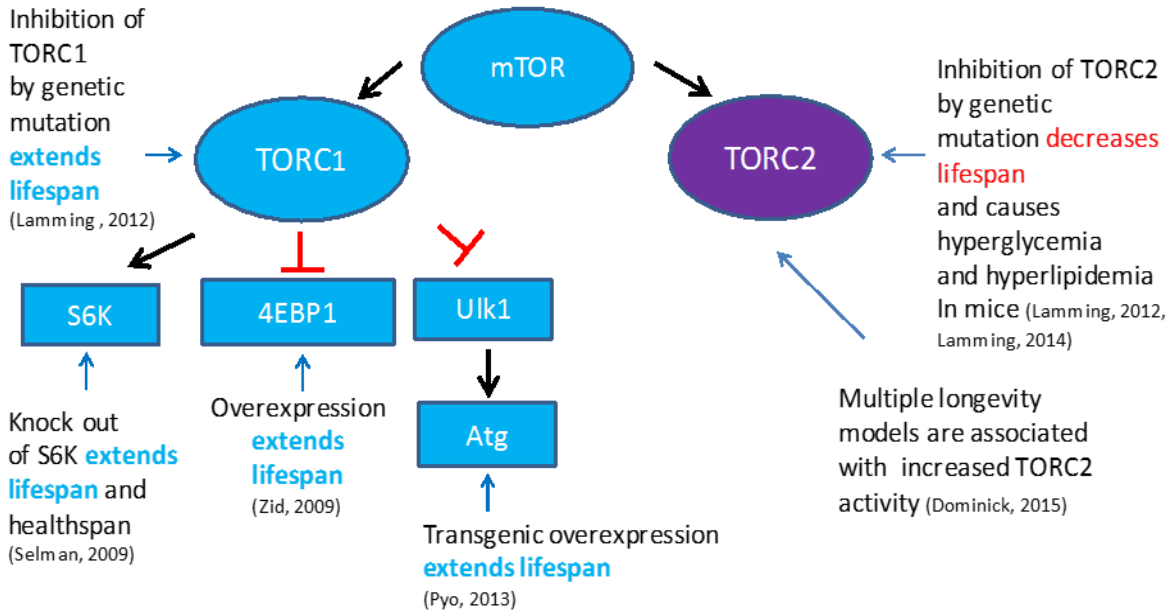
Since most respiratory infections in the elderly are caused by viruses for which there are currently no effective treatments, physicians are left with few therapeutic options for RTIs except antibiotics. This unnecessary use of antibiotics to treat RTIs contributes to the development of multidrug-resistant organisms (MDROs) that have become a major medical concern associated with high health care costs and patient morbidity and mortality. Therefore treatment with RTB101 may not only decrease RTI-associated morbidity and mortality in the elderly, but also limit the emergence of MDROs.

To address this significant unmet medical need, resTORbio is developing RTB101 to improve immune function and reduce the incidence of clinically symptomatic respiratory illness in elderly patients.

Scientific Background

mTOR signals via two complexes: target of rapamycin complex (TORC)1 and TORC2 (Figure 1-2). Many of the beneficial effects of mTOR inhibition on aging in preclinical models are mediated by inhibition of TORC1 (Laplante et al., 2012; Lamming et al., 2012). In contrast, TORC2 inhibition has been associated with adverse events (AEs) including hyperglycemia and hyperlipidemia, and with decreased lifespan in male mice (Lamming et al., 2012; Lamming et al., 2014). Therefore, optimal mTOR inhibition for the treatment of aging-related conditions such as immunosenescence may be a regimen that inhibits the activity of TORC1 and phosphorylation of its downstream targets without inhibiting the activity of TORC2.

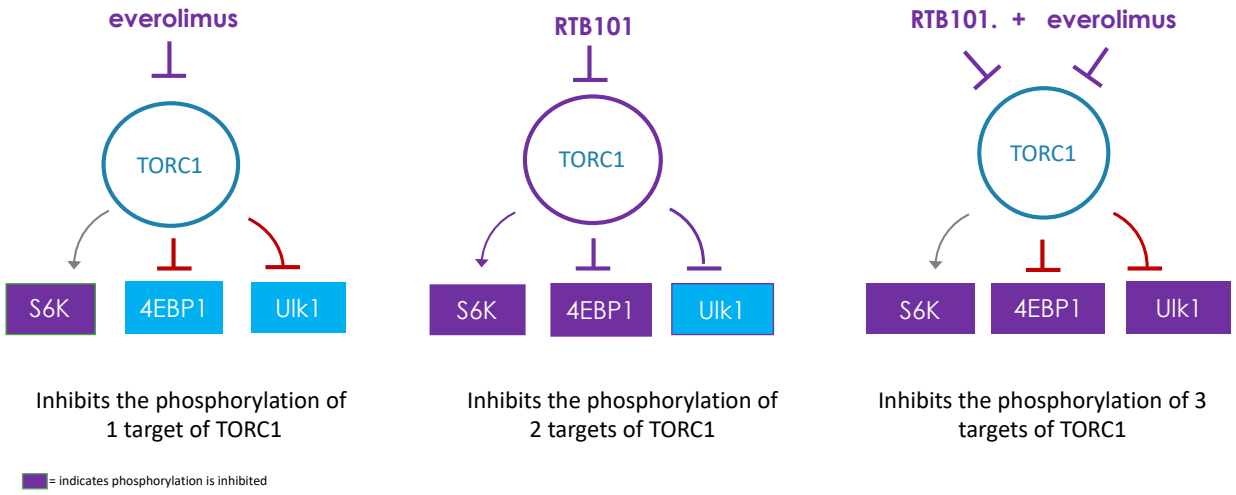
Figure 1-2 Inhibition of TORC1 but not TORC2 may be Optimal for Treating Aging Related Conditions in Humans



Rapalogs such as everolimus are a class of allosteric mTOR inhibitors that are derivatives of rapamycin and are partial TORC1 inhibitors. Rapalogs consistently inhibit only the phosphorylation of S6 kinase (S6K) downstream of TORC1 (Feldman et al., 2009). RTB101 is a dual-kinase inhibitor that inhibits both phosphatidylinositol 3'-kinase (PI3K) and mTOR. RTB101 is a more potent inhibitor of mTOR (IC_{50} <100 nM) than PI3K (IC_{50} ≅ 500 nM), and a more potent inhibitor of TORC1 (IC_{50} ≅ 12 nM) than TORC2 (IC_{50} ≅ 77 nM) (Serra et al., 2008). Therefore, at low concentrations, RTB101 is a TORC1-specific inhibitor and inhibits phosphorylation of S6K and eukaryotic translation initiation factor 4E binding protein 1 (4EPB1)

downstream of TORC1 (Serra et al., 2008; Maira et al., 2008; Baumann et al., 2008; Mannick et al., 2018). Moreover, low doses of RTB101 (and other catalytic mTOR inhibitors) in combination with low doses of everolimus synergistically inhibit all targets tested downstream of TORC1 without inhibiting TORC2 activity (Nyfeler et al., 2011; Nyfeler et al., 2012). Thus the least broad TORC1 inhibition is expected to be achieved with everolimus monotherapy, more broad inhibition is achieved with RTB101 monotherapy, and the most broad inhibition is achieved with a combination of low-dose RTB101 + everolimus therapy (Figure 1-3).

Figure 1-3 Spectrum of TORC1 Inhibition with Everolimus and RTB101



Two Phase 2 clinical studies in elderly subjects were conducted to determine if RTB101 or everolimus alone and in combination improved immune function and thereby decreased infection rates in the elderly. The two Phase 2 trials in over 900 elderly subjects demonstrated that treatment with 10 mg RTB101 once daily was safe and was associated with clinically meaningful reductions in the incidence of RTIs. Analysis of gene expression in whole blood suggested that upregulation of innate anti-viral immunity was one of the mechanisms underlying the decreased incidence of RTIs observed in elderly subjects treated with RTB101 (Mannick et al., 2018). Based on the results of the two Phase 2 clinical trials, resTORbio is proposing to develop RTB101 10 mg once daily to prevent clinically symptomatic respiratory illness in elderly subjects who are defined as ≥65 years of age.

1.2. Previous Human Safety and Efficacy Data

Exposure data

As of November 26, 2018, approximately 1088 subjects have been exposed to RTB101, alone or in combination with other compounds. RTB101 has been administered to more than 68 healthy

subjects in PK studies at doses up to 1000 mg/day. Four hundred and forty-two (442) oncology subjects have been exposed to RTB101 either as single agent once daily (q.d.) and twice daily (b.i.d.) in doses up to 1600 mg/day (160 times higher than the dose planned for Phase 3 trials to reduce the incidence of clinically symptomatic respiratory illness in elderly subjects), or in combination with everolimus, trastuzumab, paclitaxel, abiraterone, and MEK162. Development in oncology indications is no longer being pursued and there are no subjects enrolled in oncology studies. In trials in elderly subjects, 410 elderly subjects have been exposed to RTB101 alone at doses ranging from 5-20 mg/day for up to 6-16 consecutive weeks, and 168 elderly subjects have been exposed to 10 mg RTB101 in combination with 0.1 mg everolimus for 6-16 consecutive weeks. Of the 410 elderly subjects exposed to RTB101 alone, 176 of those subjects were exposed to 10 mg RTB101 daily for 16 consecutive weeks, the intended commercial dose. The most relevant data from the two Phase 2 studies in elderly subjects are summarized in sections below. For more detailed information, please refer to the RTB101 Investigator's Brochure (IB).

1.2.1. **Clinical Study CBEZ235Y2201**

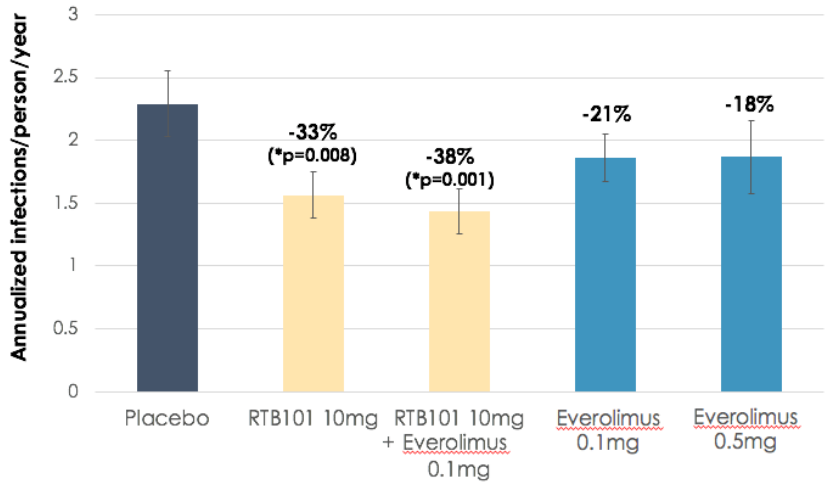
Study CBEZ235Y2201: Phase 2a clinical study in 264 elderly subjects demonstrating that TORC1 inhibition with RTB101 alone or in combination with everolimus enhanced immune function in the elderly

A total of 264 elderly subjects ≥65 years of age, without unstable medical conditions, were enrolled in the study and were randomly assigned to receive everolimus 0.1 mg, everolimus 0.5 mg, RTB101 10 mg, RTB101 10 mg + everolimus 0.1 mg, or placebo once daily. These doses were chosen based on results of a previous Phase 2a study that suggested that partial inhibition of S6K phosphorylation with everolimus 0.5 mg once daily was better than more complete inhibition of S6K phosphorylation with everolimus 20 mg once weekly for improving influenza vaccination responses in the elderly (Mannick et al., 2014). Therefore, study CBEZ235Y2201 included doses of RTB101 and everolimus predicted by modeling and simulation to partially inhibit the phosphorylation of S6K. Subjects were treated for 6 weeks with study drug and, after a 2-week drug-free interval, were given a seasonal influenza vaccine. Antibody titers to the three strains of influenza in the influenza vaccine were measured in serum collected at baseline and 4 weeks after influenza vaccination. The subjects were then followed for another 9 months off study drug. The type, onset, duration, and treatment of any infection experienced during the study was collected in patient diaries and in questionnaires administered by the study sites during phone calls with subjects that occurred once weekly during the 6 weeks subjects were on study drug, and then once monthly for the remainder of the study.

Overall, all treatment regimens were well tolerated. There were no significant differences in the percentage of subjects experiencing serious adverse events (SAEs) between treatment groups and placebo. Only one SAE (syncope in a subject in the placebo cohort) was assessed by an Investigator to be related to study drug. Diarrhea was the most frequently reported AE that occurred more often in the TORC1 inhibitor than placebo treatment groups and in the majority of cases was mild or moderate in severity and self-limited.

The combination of low-dose everolimus (0.1 mg once daily) and RTB101 (10 mg once daily) significantly increased antibody titers to the 3 strains of influenza in the influenza vaccine. In addition, RTB101 10 mg once daily alone or in combination with everolimus (0.1 mg once daily) was associated with a statistically significant reduction in the annualized rate of all infections reported by subjects (Figure 1-4). There was a trend toward a reduction in infection rates in the everolimus monotherapy treatment groups, but the reductions were not statistically significant. The findings suggested that broader TORC1 inhibition with either RTB101 alone or in combination with everolimus was better than less broad TORC1 inhibition with everolimus monotherapy for reducing infection rates in elderly subjects.

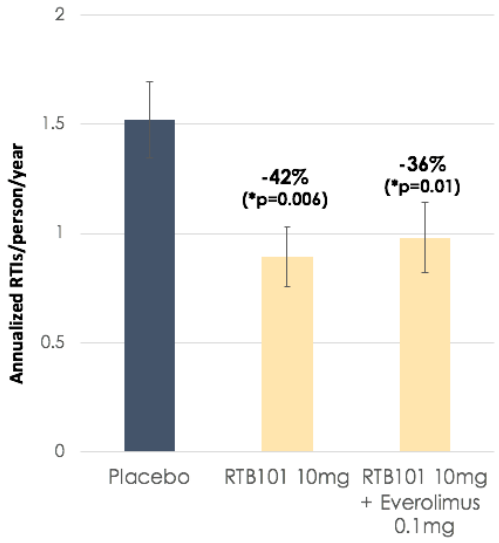
Figure 1-4 TORC1 Inhibition Decreases Infection Rates in the Elderly



Fitted annual rates of infections reported per person per year in each treatment group are shown. Error bars indicate 95% confidence intervals.

Most of the infections reported during the trial were RTIs. Both RTB101 monotherapy and RTB101 + everolimus combination therapy were associated with a significant reduction as compared to placebo in the annualized rate of RTIs reported by subjects (Figure 1-5).

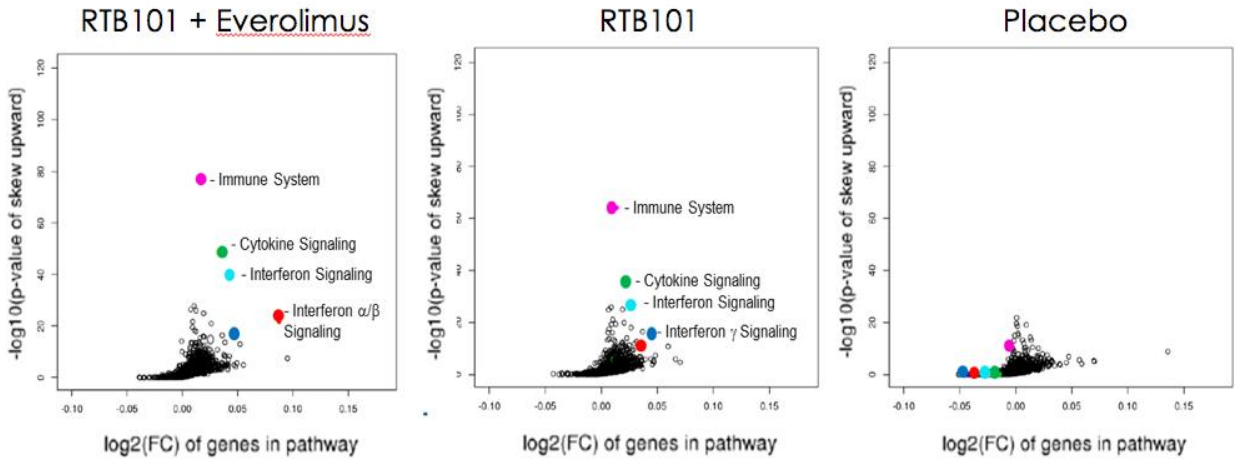
Figure 1-5 TORC1 Inhibition Decreases RTI Rates in the Elderly



Fitted annual rates of respiratory tract infections (RTIs) reported per person per year in the placebo, RTB101 monotherapy and RTB101+everolimus combination treatment groups are shown. Error bars indicate 95% confidence intervals.

To assess possible molecular mechanisms underlying the reduction in infection rates, messenger ribonucleic acid (mRNA) sequencing analysis was performed on whole blood obtained from subjects at baseline and after 6 weeks of either placebo or RTB101 alone or in combination with everolimus treatment. Whole-blood gene expression data revealed a highly statistically significant, low level up-regulation of pathways related to interferon signaling in the TORC1 inhibitor but not the placebo treatment group (Figure 1-6). The most highly upregulated genes were a subset of Type 1 interferon-induced genes that play a critical role in the innate immune response to viruses (Mannick et al., 2018). These findings raise the possibility that upregulation of antiviral genes may contribute to enhanced immune function and reduced infection rates in the elderly treated with TORC1 inhibitors. In particular, the upregulation of antiviral gene expression may be one of the mechanisms underlying the reduction in RTIs seen in elderly subjects treated with TORC1 inhibitors since most RTIs are viral in origin.

Figure 1-6 Treatment with RTB101 Alone and in Combination with Everolimus but not Placebo Treatment Leads to Upregulation of Interferon Pathway Gene Expression



Pathway enrichment analysis of gene expression changes in whole blood as measured 6 weeks after study drug treatment vs. baseline. This analysis revealed a highly significant enrichment of pathways related to interferon signaling after mTOR inhibitor but not placebo treatment. The x-axis indicates the mean log2-fold change in expression of genes in each pathway. The y-axis indicates the –log10 of the p value of pathway upregulation. Each circle represents a specific biological pathway. The most significantly upregulated pathways are those skewed toward the upper right in each figure.

1.2.2. Clinical Study RTB-BEZ235-202

Study RTB-BEZ235-202: Phase 2b clinical study in 652 elderly subjects demonstrating that TORC1 inhibition with RTB101 reduced the incidence of RTIs in elderly at increased risk of RTI-related morbidity and mortality.

Based on the results of the previous Phase 2a clinical trial, a Phase 2b dose-ranging trial was conducted to determine if RTB101 alone or in combination with everolimus decreased the incidence of RTIs in elderly subjects at increased risk of RTI-related morbidity and mortality.

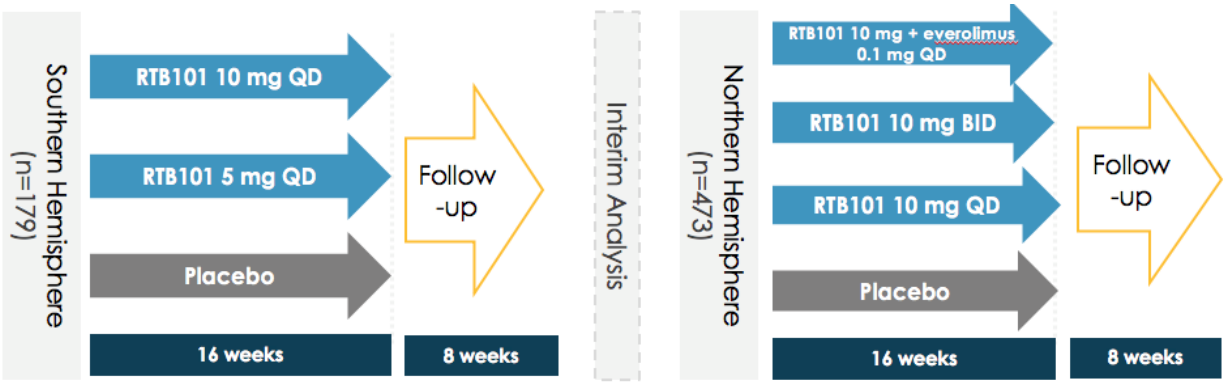
This was a 24-week multicenter, randomized, double-blinded, placebo-controlled, parallel group, dose-finding adaptive design study to assess the safety, tolerability, and efficacy of RTB101 alone or in combination with everolimus as compared to placebo in elderly subjects who were at increased risk of RTI-related morbidity and/or mortality. Subjects at increased risk for RTI-related morbidity and/or mortality included subjects who were:

- ≥85 years of age
- ≥65 years of age with one or more of the following co-morbidities:
  - Asthma
  - Chronic obstructive pulmonary disease (COPD)
  - Type 2 diabetes mellitus (T2DM)
  - Current smoker

The primary objective of the study was to determine if RTB101 alone or in combination with everolimus decreased the percentage of subjects who develop one or more laboratory-confirmed RTIs relative to placebo during the 16 weeks subjects were taking study drug. RTIs were defined as upper RTIs, influenza-like illness, lower RTIs (tracheobronchitis) and pneumonia. Prespecified clinical criteria were used to diagnose each type of RTI, and laboratory confirmation was obtained by respiratory pathogen polymerase chain reaction (PCR) of nasopharyngeal swabs, sputum gram stain and culture, and/or influenza rapid antigen tests.

Subjects were treated with study drug for 16 weeks during the winter cold and flu season and then followed for an additional 8 weeks off study drug. In Part 1 of the study conducted during winter cold and flu season in New Zealand, 179 subjects were randomized to RTB101 5 mg or 10 mg once daily or matching placebo. Following the 16-week treatment period in Part 1, an interim analysis was performed by an unblinded Data Monitoring Committee (DMC) who recommended RTB101 10 mg once daily as the best dose to move forward to Part 2 of the trial. The doses used in Part 2 were prespecified based on the RTB101 once daily dose chosen by the DMC from Part 1. In Part 2 conducted during winter cold and flu season in the United States (U.S.), 473 subjects were randomized to RTB101 10 mg once daily (QD), RTB101 10 mg twice daily (BID), RTB101 10 mg in combination with everolimus 0.1 mg once daily, or matching placebo.

Figure 1-7 Phase 2b Study Design



RTB-BEZ235-202 Efficacy:

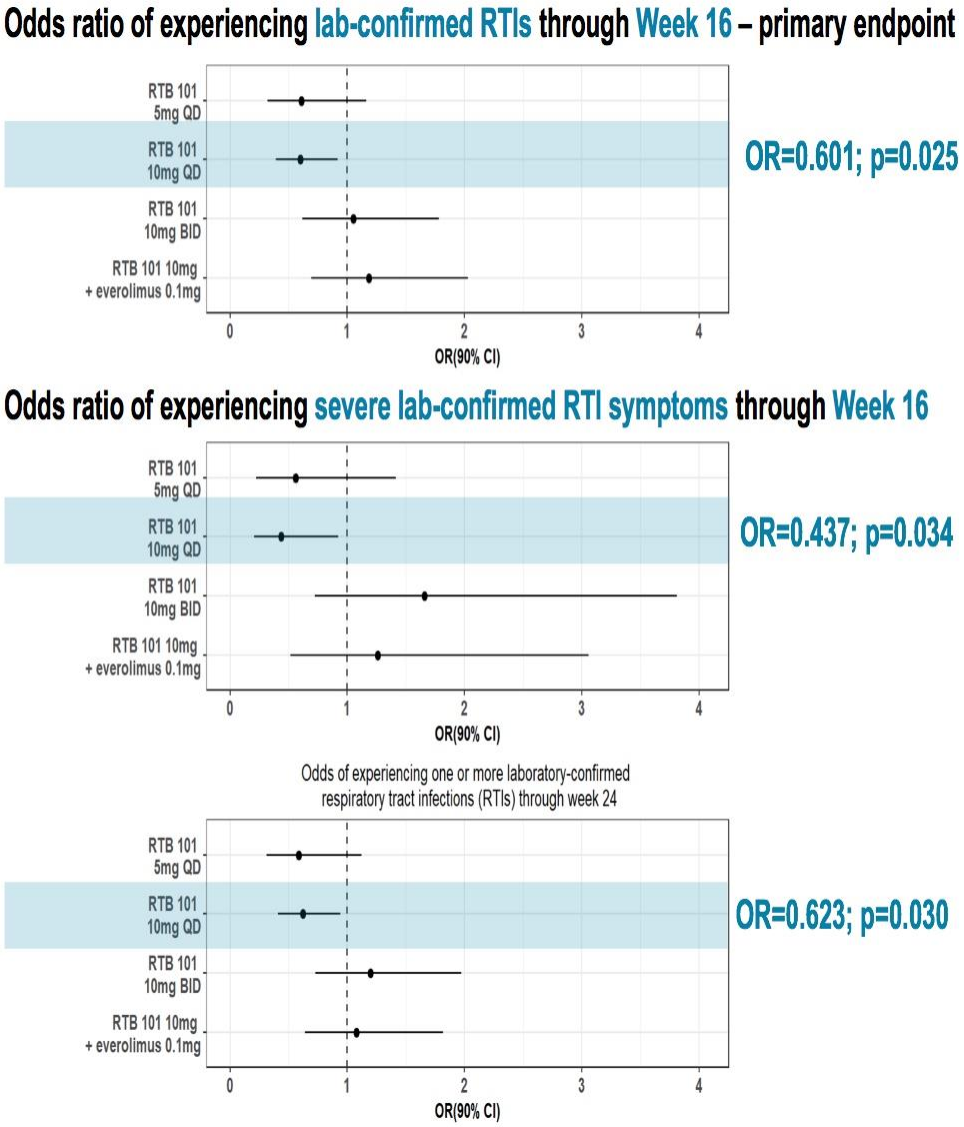
- The greatest reduction in laboratory-confirmed RTI incidence was observed in the RTB101 10 mg once daily treatment group. A 30.6% reduction in the percentage of subjects experiencing one or more laboratory-confirmed RTIs was seen in the pooled (Parts 1 and 2) RTB101 10 mg once daily treatment group compared with the pooled placebo group during 16 weeks of study drug treatment (odds ratio (OR) 0.600 [90% CI 0.391, 0.921]; nominal p-value=0.025) (Figure 1-8).

Results of other prespecified exploratory endpoints supported the superiority of RTB101 10 mg once daily administration over placebo including:

- 52.1% reduction in the percentage of subjects with severe laboratory-confirmed RTI symptoms compared to placebo (OR=0.437, CI=(0.207, 0.923), nominal p-value=0.034) (Figure 1-8).

- 27.5% reduction in the percentage of subjects with laboratory-confirmed RTIs compared to placebo during 24 weeks (16 weeks of study drug treatment and 8 weeks of follow-up (OR=0.623, CI=(0.412, 0.942), nominal p-value=0.030). The persistent benefit observed at 24 weeks may have been driven by the benefit observed during the 16 weeks of study drug treatment because few laboratory-confirmed RTIs occurred in each treatment group between weeks 16 to 24 (Figure 1-8).

Figure 1-8 RTB101 10 mg QD Showed Consistent Benefit as Compared to Placebo in Multiple Pre-Specified Analyses of Laboratory (lab)-Confirmed RTIs



Odds ratios and 90% confidence intervals (CIs) for each study drug comparison versus placebo are shown. Odds ratio illustrate the odds of experiencing one or more laboratory-confirmed RTIs in the active dose(s) versus placebo. This was calculated by employing a logistic regression including a term for treatment, along with a term for each disease factor and age as separate covariates, where a nominal p-value for each dose versus placebo was computed based on the estimate of the treatment effect.

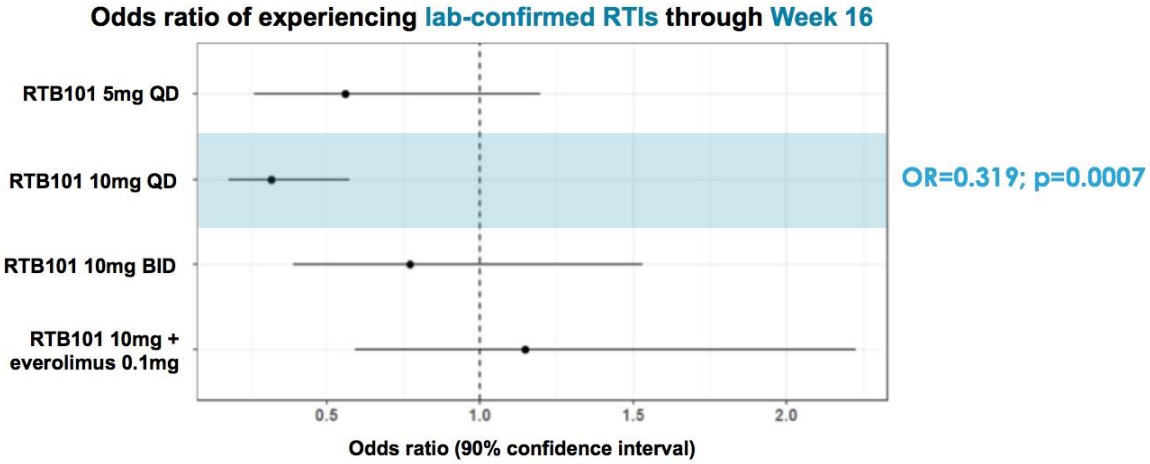
Pre-specified analyses evaluating the percentage of subjects with laboratory-confirmed RTIs in each of the 5 subgroups of subjects enrolled in the trial (subjects ≥85 years of age, or subjects ≥65 years of age with asthma, COPD, T2DM or current smoker) identified consistently higher responding subgroup populations receiving RTB101 10 mg once daily, including:

- Subjects ≥85 years of age
  - A 66.7% decrease relative to placebo, OR=0.184 (90% CI=[0.060, 0.568]), in the percentage of subjects experiencing one or more laboratory-confirmed RTIs during 16 weeks of study drug treatment, (nominal p-value=0.007).
- Subjects ≥65 years of age with asthma
  - A 68.9% decrease relative to placebo, OR=0.105 (90% CI=[0.038, 0.290]), in the percentage of subjects experiencing one or more laboratory-confirmed RTIs during 16 weeks of study drug treatment (nominal p-value= 0.0001).

A reduction in the percentage of subjects with laboratory-confirmed RTIs was also seen in subjects ≥65 years of age with T2DM who were treated with RTB101 10 mg once daily as compared to placebo (25.3% reduction, OR=0.362 (90% CI=[0.151, 0.867] nominal p-value=0.028). No reduction in the incidence of RTIs was seen in subjects who were ≥65 years of age with COPD, and a nominal increase in RTIs was observed in current smokers. The efficacy seen in asthmatics and lack of efficacy observed in current smokers and subjects with COPD is consistent with nonclinical data suggesting that mTOR inhibition alleviates lung allergen-induced inflammation in asthma models but exacerbates cigarette smoke-induced lung inflammation in COPD models (Mushaben et al., 2011; Wang et al., 2018).

When the non-responding subject populations (current smokers and subjects with COPD) were excluded from the analysis, RTB101 10 mg once daily was associated with a 56.9% reduction in the percentage of subjects with one or more laboratory-confirmed RTIs.

Figure 1-9 A Reduction in the Incidence of Laboratory-Confirmed RTIs was Observed in Subjects 65 Years of Age and Older (excluding current smokers and COPD subjects)



RTB-BEZ235-202 Safety:

Overall, all dosing regimens were well-tolerated in the elderly subjects evaluated in the Phase 2b study. There were no appreciable differences in AE profiles among treatment groups. For subjects in both active and placebo treatment groups, the majority of AEs were assessed as non-serious, mild or moderate in severity, and unrelated to study drug treatment. Subjects experiencing SAEs were also generally well-balanced between active and placebo treatment groups, with the exception of a slightly higher proportion of subjects experiencing SAEs in the placebo group relative to the RTB101 5 mg once daily treatment group in Part 1 of the study. Overall, the types of SAEs that occurred were consistent with the elderly population under evaluation in the study and none was assessed as related to study drug treatment.
Three of the 652 elderly subject enrolled in the study died (all in Part 2 of the study); one subject randomized to receive RTB101 10 mg once daily died from traumatic injuries sustained from being hit by a car while riding a bicycle during the 16-week treatment period of the study. Two subjects (one randomized to receive RTB101 10 mg twice daily and one randomized to receive placebo) died from unknown cause(s) after Week 24 of the study. None of the deaths that occurred was attributed to study drug treatment.

See the RTB101 IB for further details.

RTB-BEZ235-202 Overall Conclusion:

In summary, the results of the Phase 2a and 2b trials in over 900 elderly subjects identified a safe and efficacious dose (RTB101 10 mg once daily) and patient population (subjects ≥65 years of age who are non-smokers and do not have COPD) to study in Phase 3 trials.

1.2.3. **Human Pharmacokinetic Data**

The majority of pharmacokinetic data for low dose RTB101 was obtained in high risk elderly subjects in clinical study RTB-BEZ235-202. Values for area under the drug concentration versus time curve (AUC) and maximum plasma concentration (C_{max}) at the 10 mg daily oral dose of RTB101 revealed a mean area under the drug concentration versus time curve from 0 to 24 hours (AUC_{0-24}) (standard deviation [SD]) of 28.6 (35.9) ng.hr/mL and a C_{max} (SD) of 8.373 (7.853853) ng/mL, but there was substantial variability in PK as reflected by the magnitude of the SDs. Additional information about RTB101 pharmacokinetics is contained in the RTB101 IB.

1.3. Purpose

The purpose of this study is to determine if RTB101 prevents clinically symptomatic respiratory illness in elderly subjects ≥65 years of age. Subjects with clinically symptomatic respiratory illness are defined as subjects with symptoms consistent with a RTI based on prespecified diagnostic criteria.

2. Study Objectives and Endpoints

The primary, secondary and exploratory objectives and associated endpoints are summarized in Table 2-1 below.

Table 2-1 Summary of Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Endpoint for Primary Objective**
• 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	• The percentage of subjects with clinically symptomatic respiratory illness beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria
Secondary Objectives	**Endpoints for Secondary Objectives**
• 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	• The percentage of subjects with 1 or more 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 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs
• 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	• 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
• To determine if RTB101 as compared to placebo decreases the rate of clinically symptomatic respiratory illness (with or	• The rate of clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen)

Objectives	Endpoints
without an associated laboratory-confirmed pathogen) through Week 16	beginning at least 3 days after the start of study drug treatment through Week 16 as assessed by pre-specified clinical diagnostic criteria
• 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	• 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 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs
• 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	• The time to alleviation of moderate and severe respiratory illness symptoms due to clinically symptomatic respiratory illness beginning at least 3 days after the start of study drug treatment 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	• The percentage of subjects with severe symptoms due to clinically symptomatic respiratory illnesses beginning at least 3 days after the start of study drug treatment through Week 16
• To assess the safety and tolerability of RTB101 through Week 20	• Safety and tolerability will be assessed by report of AE/SAEs, physical exam and ECG findings, and safety laboratory values
Exploratory Objectives	**Endpoints for Exploratory Objectives**
• 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	• 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 symptomatic respiratory illnesses) and/or respiratory pathogen PCR of mid-turbinate swabs (obtained at scheduled study visits, even in the absence of symptoms)
• To explore the effect of RTB101 as compared to placebo on the rate of all-cause hospitalizations through Week 16	• 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	• Rate of hospitalizations associated with RTIs beginning at least 3 days after the

Objectives	Endpoints
respiratory tract infections (RTIs) through Week 16	start of study drug treatment 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	• The rate of all-cause 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	• Rate of ER visits associated with RTIs beginning at least 3 days after the start of study drug treatment 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	• 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 urgent care visits for clinically symptomatic respiratory illness through Week 16	• The rate of urgent care clinic visits for clinically symptomatic respiratory illness beginning at least 3 days after the start of study drug treatment 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	• 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	• Hospitalization length of stay associated with RTIs beginning at least 3 days after the start of study drug treatment through Week 16
• To explore the effect of RTB101 as compared to placebo on all-cause hospital length of stay through Week 16	• All-cause hospitalization 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	• The percentage of subjects with 1 or more clinically symptomatic respiratory illnesses and the percentage of subjects with 1 or more 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 20 as assessed by pre-specified clinical diagnostic criteria and respiratory pathogen PCR of nasopharyngeal swabs, sputum gram stain and culture, and/or RIDTs
• 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	• 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

Objectives	Endpoints
respiratory illness episodes and at Week 16	the start of study drug treatment 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	• The percentage of subjects with one or more clinically symptomatic respiratory illnesses and the percentage of subjects with one or more 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 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	• The rate of clinically symptomatic respiratory illnesses and 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 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	• The rate of asthma exacerbations and 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
• To explore the effect of RTB101 as compared to placebo on the incidence of UTIs	• The rate of UTIs and the percentage of subjects with one or more UTIs reported as adverse events
• 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)	• Change from Baseline to Weeks 4 and 16 in biomarkers in whole blood and serum and potentially future pharmacogenomic analysis

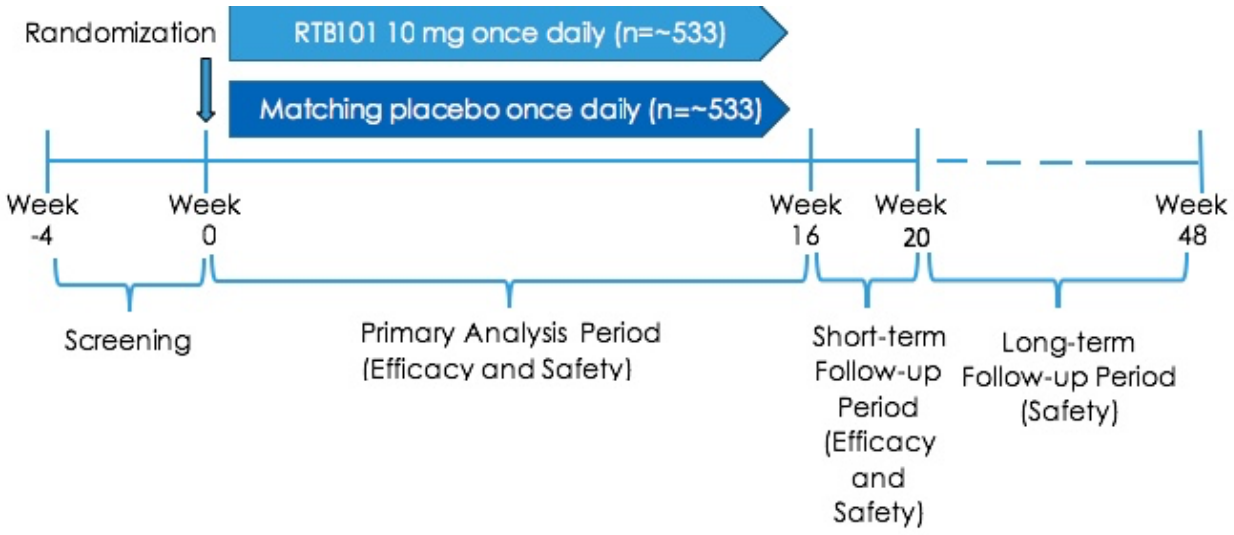
3. Investigational Plan

3.1. Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to assess the efficacy and safety of RTB101 for the prevention of clinically symptomatic respiratory illness in elderly (defined as ≥ 65 years of age) subjects. Subjects will be enrolled during winter cold and flu season. 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).

Figure 3-1 RTB-101-204 Study Design



Study Periods

Screening Period:

Screening Visit

Screening may occur prior to investigational product being available at the study site. During the Screening visit (maximum 4 weeks prior to Baseline/randomization), the study will be explained in detail to subjects and they will be asked to provide informed consent for participation. Subjects will be then assessed for eligibility to participate in the trial based on inclusion/exclusion criteria. The following assessments will be performed at this visit: Mini Mental Status Exam (MMSE); a review of subject demography and medical history (including current medical [including cardiac] conditions, prior and current medications); a complete physical exam (including height, weight, and vital signs [temperature, respiratory rate, heart rate and blood pressure]); and an electrocardiogram (ECG). In addition, a chest X-ray will be performed unless the subject has had a chest X-ray within the past 3 months and the film (or digital copy) and results of that CXR are available. Blood and urine will be collected for the following tests: hematology, chemistry, urinalysis, serum cotinine (or urine cotinine if serum

cotinine testing is unavailable), and HIV and hepatitis virus (B and C) screening. Details will be provided in the Study Operations Manual (SOM). In exceptional circumstances, when central laboratory testing is unavailable, local laboratory testing may occur with the Sponsors prior approval.

Blinded Treatment Phase:

Treatment Phase (16 weeks)

Subjects will be treated for 16 weeks with study drug. Approximately 533 subjects will be enrolled in each treatment group for a total enrollment of approximately 1066 subjects.

Baseline Visit

At the Baseline visit, a review of any changes to the subject's medical (including cardiac) condition or current medications/other therapies will be performed. Subjects will then undergo clinical evaluation, including a targeted physical exam. This should include measurements of weight and vital signs, including orthostatic blood pressure, and an exam of the lungs, heart, oral cavity, and skin. The Clinical Frailty Scale (see Section 13.4 [Appendix 4]) score of each subject will also be determined. An ECG will be performed for Baseline safety assessment. Subjects will also have blood and urine samples obtained for Baseline safety assessments. In addition, blood samples will be obtained for biomarker analyses, including RNA expression and soluble biomarkers. Consent for Optional Blood Storage for Future Use and Consent for Optional Pharmacogenetic Analysis will be obtained at the Baseline Visit. A single blood sample will also be obtained at the Baseline Visit in those subjects who sign the option Pharmacogenetic Analysis consent form for the purposes of possible future Pharmacogenomic analysis. A mid-turbinate nasal swab specimen will be collected.

Prior to randomization, the inclusion and exclusion criteria will be reviewed again, and eligible subjects will be randomized via the IXRS system to 1 of 2 treatment groups in a ratio of 1:1.

- RTB101 10 mg once daily (QD)
- Matching placebo QD

Randomization will be stratified based on the following factors that may influence the incidence or severity of clinically symptomatic respiratory illness and/or the response to RTB101 treatment:

1. Age ≥85

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

Subjects will be given their first dose of study drug (and time of dosing recorded in the eDiary) at the study site and trained on use of the eDiary containing study assessments to be completed at home including:

- Study drug dosing information, to be completed daily through the Week 16 study visit
- Respiratory Illness Symptom Questionnaire, to be completed daily in the evening through the Week 20 study visit
- EQ-5D-5L, to be completed each day subjects report experiencing one or more respiratory illness symptoms through the Week 16 study visit

After randomization, all subjects will complete the Health-Related Quality of Life Questionnaire (EQ-5D-5L) and Respiratory Illness Symptom Questionnaire on their eDiary at the Baseline visit.

Subjects will then be sent home with study drug and the eDiary. Subjects will be instructed to take their study drug each day with breakfast and to complete the dosing diary in the eDiary at the time of study drug administration. Subjects will also be instructed to complete the Respiratory Illness Symptom Questionnaire in their eDiary each evening, and to complete the EQ-5D-5L in their eDiary each evening, if applicable (i.e., when the EQ-5D-5L appears in their eDiary on days they report experiencing one or more respiratory illness symptoms). Adverse events will be monitored and reported from the time of study drug administration at the Baseline Visit through Week 20.

Subject Contact/Follow up

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. The Study Investigator and Study Coordinator will also contact subjects who report at least one respiratory symptom (runny nose, sneezing, stuffy nose, sore throat, hoarseness, or cough) reported in 2 consecutive entries in their eDiary and instruct the subjects to come to the study site if they are able to within 48 hours for evaluation and for collection of a nasopharyngeal swab during the Clinically Symptomatic Respiratory Illness (Unscheduled) Visit (see below). Subjects who are unable to come to the study site may

also have the nasopharyngeal swab (and, if indicated, a sputum specimen and RIDT) obtained during a home visit by trained personnel.

To determine which subjects may need treatment for influenza, sites will contact subjects who record at least 1 respiratory and at least 1 general symptom, both of which are moderate or severe on 2 consecutive days in their eDiary. The sites will instruct the subjects to come to the study site if they are able to within 24 hours of the second day of eDiary symptom entry to have a nasopharyngeal swab and determine whether they require treatment for influenza per standard of care.

Clinically Symptomatic Respiratory Illness Visits (Unscheduled)

At the Clinically Symptomatic Respiratory Illness Unscheduled Visit, Study Investigators will evaluate the subject and perform a targeted physical exam based on the symptoms reported by the subject and including vital signs and temperature. Any medications used to treat the clinically symptomatic respiratory illness, including antibiotics and any change to current medications, will be recorded. In addition, a nasopharyngeal swab will be obtained. Subjects who have a productive cough that is changed from baseline should have a sputum specimen obtained for gram stain and culture. If clinically indicated, blood and urine samples needed to clinically evaluate the subject may be obtained at this visit. Subjects who have influenza-like illness signs and symptoms (such as 1 or more respiratory symptom (cough, sore throat or nasal symptoms) and 1 or more constitutional symptom (such as body aches or feverishness/chills) should have a rapid influenza diagnostic test (RIDT) done. Subjects with influenza-like illness who have influenza detected by RIDT or nasopharyngeal swab PCR should receive anti-influenza treatment per local standard of care, unless contraindicated, and/or other appropriate medical care. If subjects are unable or unwilling to return to the study site for the Clinically Symptomatic Respiratory Illness Unscheduled Visit, the nasopharyngeal swab and, if indicated, a sputum specimen and RIDT should be obtained at a home visit by trained personnel. Appropriate medical care (including referral to their healthcare provider or to a hospital, if indicated) should be provided for all clinically symptomatic respiratory illness episodes (including anti-influenza treatment, if indicated, in subjects diagnosed with influenza) per local standard of care. Study drug treatment can be continued in subjects who require antibiotics or anti-influenza medication for treatment of an RTI.

Weeks 2-12 Visits

Provided the study drug continues to be well tolerated, subjects will be treated with study drug for 16 weeks, during which time they will return to the clinic every 2 weeks (visits Week 2, 4, 6,

and 8) for the first 8 weeks, and then every 4 weeks (visit Week 12 and 16) for the final 8 weeks. At visit Weeks 2-12 of the study, the subject will have clinical evaluations, including a targeted physical exam, which will include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature, and an exam of the lungs, heart, oral cavity, and skin. A review of any changes to medical (including cardiac) conditions and medications/other therapies will also be performed. At all follow up visits, subjects will be queried by site staff regarding any visits to the ER, urgent care clinics, and any admission to a skilled nursing facility or hospital that may have occurred since their last study visit. Subjects will also have a mid-turbinate swab taken at each visit regardless of whether the subject reports respiratory illness symptoms. If subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) obtained as part of an unscheduled visit assessment. Blood and urine specimens will be collected at each visit for safety monitoring. An ECG will be performed at Week 4, 8 and 12 visits for safety monitoring. Only subjects participating in the PK assessments (per the Interactive Web or Telephone-based Response System (IXRS) randomization) will also have blood samples obtained for PK assessments at the Week 4 (or 6 if applicable), 8, and 12 visits, and have blood samples obtained for RNA expression and soluble biomarker assessments at the Week 4 visit. If PK sampling cannot be performed at the Week 4 visit for logistical reasons, it should be collected at the Week 6 visit instead, but according to the schedule described below for Week 4. This applies to the timing of the biomarker specimens originally scheduled for Week 4 as well.

Study drug will be dispensed at Day 0, Week 4, Week 8 and Week 12 visits (however, in the case of lost or damaged study drug, study drug can be dispensed at any study site visit). The subjects should bring their remaining study drug to each study visit. At Study Visits Week 4 (or Week 6 if applicable) and Week 12, subjects participating in the PK assessments should be instructed to not take their study drug dose at home (it will be administered at the site). At Weeks 4, 8, and 12, subjects will return study drug and will be dispensed new bottles. At Week 2 and 6, subjects will bring their drug supply to the study site to allow site personnel to perform a pill count; however, no new study drug will be dispensed at these visits.

Week 16 Visit

Subjects will take their last dose of study drug at home and come to the study site to undergo a clinical evaluation, including a review of any changes to medical (including cardiac) conditions and medications/other therapies, and a complete physical exam, which will include measurements of weight and vital signs. An ECG will also be performed for safety monitoring. In addition, subjects will have blood and urine samples obtained for safety labs. Blood samples will also be obtained for RNA expression and soluble serum biomarker assessments. In addition,

a mid-turbinate nasal swab will be obtained. Subjects will be queried by site staff regarding any visits to ER, urgent care clinics, any admission to a skilled nursing facility or hospital that may have occurred since their last study visit. All subjects will complete the EQ-5D-5L questionnaire at the Week 16 visit. All study drugs (RTB101 and placebo) should be returned to the study site.

Short-term Follow-up Period (Week 20)

All subjects will return to the study site 4 weeks after their last dose of study drug for a Week 20 (Short-term Follow-up Period) visit. At the Week 20 visit, subjects will undergo a complete physical exam, which will include measurements of weight and vital signs. A review of any changes to medical (including cardiac) conditions and medications or other therapies will also be performed. Blood and urine will be collected for safety lab evaluation. The eDiary should also be returned to site personnel at this visit.

Subjects who develop medically important laboratory abnormalities or medically important AEs should be referred for appropriate medical care, as per the local standard of medical care. If at the time of the completion of the Week 20 visit, all adverse events that are unresolved should be captured as "ongoing" in the database; however, they should continue to be followed until resolution or judged to be permanent by the Investigator (see Section 7.1).

Long-term Follow-up Period (Week 48)

After completion of the Short-term Follow-up Period (i.e., the Week 20 Visit), subjects will have long term follow-up by telephone questionnaire at Week 48 to collect information regarding any hospitalizations, skilled nursing facility admissions and death of subjects since the Week 20 Visit.

3.2. Study Design Rationale

The study is designed as a standard randomized, double-blinded, placebo-controlled study to obtain efficacy and safety data for RTB101 in an unbiased fashion. Subjects will be prompted to fill out a Respiratory Illness Symptoms questionnaire in the eDiary daily in order to rapidly and accurately capture the occurrence of symptoms consistent with an RTI and to enable collection of nasopharyngeal swabs if they are able to within 48 hours of symptom confirmation when viral detection rates are highest (Ginocchio et al., 2011). Sixteen weeks of treatment is considered a sufficient duration to achieve a clinically meaningful reduction in clinically symptomatic respiratory illness during winter cold and flu season when there is a peak in the circulation of multiple respiratory viruses. PK samples will be obtained in approximately 400 subjects (200 in

each treatment group) at weeks 4 (or 6), 8, and 12 to enable characterization of PK after the study drug has reached steady state levels.

Study Population

Prevention of clinically symptomatic respiratory illness is particularly important in people age 65 and older in whom RTIs are a leading cause of hospitalization. Data from the Phase 2b trial RTB-BEZ235-202 suggests that RTB101 10 mg given once daily for 16 weeks during winter cold and flu season was safe and reduced the incidence of laboratory-confirmed RTIs in people age ≥ 65. In addition, data from the RTB-BEZ235-202 study suggests that RTB101 had no benefit in elderly subjects who were current smokers or had a medical history of COPD. Therefore, the Phase 3 study will enroll subjects who are age ≥ 65 and who are not current smokers and do not have COPD. A Mini Mental Status Exam will be done at screening to ensure that subjects enrolled in the trial have the cognitive ability to understand the informed consent.

An effort will be made by monitoring screening to have at least 35% of the total subjects enrolled in the trial be from subgroups at increased risk of RTI-related morbidity and mortality (defined as age ≥ 85 or age ≥65 and <85 years with a medical history of asthma or congestive heart failure). Enhancing immune function and reducing the incidence of clinically symptomatic respiratory illness is of particular clinical relevance in these subgroups. RTIs are the second leading cause of hospitalization in people age ≥ 85 (Pfunter et al., 2013), the most common cause of asthma exacerbations (Nicholson et al., 1993), and the underlying cause of 16% of hospital admissions in patients with congestive heart failure (Chin and Goldman, 1997). Enrolling 35% of subjects from these subgroups is representative of the target ≥ 65 year old population since ~10% of those ≥65 have asthma (Gillman et al., 2012), 12% are ≥85 (U.S. Census 2010) and ~10% of individuals > 60 have congestive heart failure (Komanduri S et al., 2017).

Primary Endpoint

The primary endpoint of the study is the percentage of subjects who experience at least one clinically symptomatic respiratory illness beginning at least 3 days after the start of study drug treatment through Week 16. Clinically symptomatic respiratory illness is defined as respiratory illness symptoms that are consistent with a RTI based on prespecified diagnostic criteria and includes multiple types of RTIs (such as common cold, bronchitis, influenza-like illness, and pneumonia) caused by multiple different pathogens. Decreasing the incidence of clinically symptomatic respiratory illnesses is medically important in the elderly. Even respiratory illnesses such as upper RTIs that are normally mild in younger adults cause significant morbidity in the elderly (Nicholson et al., 1997) and significantly increase the risk of cardiovascular events (Musher et. al., 2019). The incidence of all clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen) was chosen as the primary endpoint

because some infectious pathogens may not be detected with the proposed laboratory detection methods. Data from Phase 2 studies suggest that RTB101 upregulates antiviral defenses and decreases the incidence of respiratory illness associated with multiple different viruses. Clinically symptomatic respiratory illnesses beginning at least 3 days after the start of study drug treatment will be analyzed because RTIs may have a 3-day incubation period. Therefore, RTIs occurring during the first 3 days of the study may have been acquired prior to initiation of study drug treatment. The clinical criteria that will be used in the Phase 3 trial to diagnose clinically symptomatic respiratory illnesses (see Section 6.7.1) capture RTI events that were also captured in the Phase 2b (RTB-BEZ235-202) trial. Prespecified clinical criteria will be used to diagnose clinically symptomatic respiratory illnesses to make sure that diagnosis is consistent across sites.

Secondary Endpoints

Secondary endpoints will include the incidence of clinically symptomatic respiratory illnesses associated with laboratory-confirmed pathogen(s). Assessment of clinically symptomatic respiratory illness that is associated with an infectious pathogen will allow assessment of the treatment effect of RTB101 on respiratory illness that is confirmed to be infectious in etiology. The incidence of clinically symptomatic respiratory illnesses associated with specific viruses (e.g., coronaviruses, hMPV, HRV/enterovirus, adenovirus, influenza A and B virus, parainfluenza viruses, and RSV) will also be assessed as a secondary endpoint to determine if RTB101 has consistent benefit across different viral infections, and to demonstrate no enhancement of any viral infection. Another secondary endpoint will be rate of clinically symptomatic respiratory illness because subjects may experience more than one respiratory illness during the 16-week treatment period, and RTB101 may decrease not just the percentage of subjects with clinically symptomatic respiratory illness but also the rate of clinically symptomatic respiratory illnesses. Additional secondary endpoints will determine if RTB101 decreases not only the incidence but also the severity and duration of respiratory illness symptoms. Decreasing the severity and duration of respiratory illness symptoms is a clinically important endpoint and will provide further evidence of the clinical benefit of RTB101.

Exploratory Endpoints

An exploratory endpoint will be the rate of viral respiratory infection, irrespective of whether the infection is symptomatic, to better assess the antiviral effects of RTB101. As an additional exploratory endpoint, healthcare resource utilization will be assessed because an important benefit of decreasing the incidence of clinically symptomatic respiratory illness may be a decrease in healthcare resource utilization by elderly subjects. Since decreasing the incidence of clinically symptomatic respiratory illness may improve the quality of life of elderly subjects, an

additional exploratory endpoint will be health related quality of life in all subjects assessed with the EQ-5D-5L questionnaire. The incidence of clinically symptomatic respiratory illness in subjects with a medical history of asthma or who are ≥85 years of age will be assessed as exploratory endpoints because these subpopulations had the greatest reduction on the incidence of laboratory confirmed RTIs after treatment with 10 mg RTB101 once daily as compared with placebo in the previous Phase 2b (RTB-BEZ235-202) trial. The incidence of asthma exacerbations in subjects with a medical history of asthma will also be assessed since RTIs are common causes of asthma exacerbations. Another exploratory endpoint will be the incidence of clinically symptomatic respiratory illness and the incidence of symptomatic respiratory illness associated with laboratory-confirmed pathogen(s) through Week 20 to assess if the efficacy of RTB101 persists for 4 weeks after subjects discontinue study drug. To better understand if the incidence of other types of infections may be reduced, the incidence of UTIs will be assessed. Finally, RNA expression and soluble serum biomarkers and pharmacogenomics (also known as pharmacogenetics) (Note: pharmacogenomics will only be assessed in those subjects who sign a separate consent form to allow collection of a pharmacogenomic (also known as pharmacogenetic) sample) will be assessed as exploratory endpoints to assess the effects of RTB101 on relevant immunologic markers and to potentially assess the impact of mTOR pathway polymorphisms in a pharmacogenomic analysis.

3.2.1. **Rationale for Choice of Comparator**

A placebo will be used as a comparator since there is no available drug known to reduce the incidence of clinically symptomatic respiratory illness in the elderly. The placebo arm will provide data about baseline AE and clinically symptomatic respiratory illness incidence in the elderly to which responses in subjects receiving RTB101 can be compared.

3.3. **Risks and Benefits**

The potential benefit to subjects receiving RTB101 of reducing the incidence of clinically symptomatic respiratory illness is noted above. The potential risk to subjects in this study will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring, short study duration, and oversight by a DMC. The potential risks of RTB101 treatment are based on preclinical toxicology studies, and the observed safety of RTB101 in clinical trials to date. As noted above, the risk of AEs should also be minimized in this study by using very low doses of RTB101. The dose of RTB101 to be used in the proposed Phase 3 trial (10 mg once daily) is 120-fold lower than the maximum tolerated dose (1200 mg once daily) established in humans. The RTB101 10 mg once daily dose was also demonstrated to be safe and well tolerated in elderly subjects in 2 studies: 1) a previous Phase 2a study in which 53 elderly subjects were

treated with 10 mg once daily for up to 6 weeks, and 2) a previous Phase 2b study in which 176 elderly subjects were exposed to 10 mg once daily for up to 16 weeks. Thus, the nonclinical and clinical safety data supports the safety of the proposed Phase 3 clinical trial dose of RTB101 (10 mg once daily) in elderly subjects. However, RTB101-associated AEs seen when RTB101 has been used at significantly higher doses in oncology studies still represent potential risks as described below.

Stomatitis/Mucositis

Mouth ulcers/stomatitis similar to canker sores are common AEs following treatment with high doses of RTB101 in oncology studies. No increase in the incidence of mouth ulcers/stomatitis was observed in elderly subjects treated with RTB101 10 mg once daily as compared to placebo in the Phase 2a clinical trial CBEZ235Y2201 and the Phase 2b clinical trial RTB-BEZ235-202. However, in CBEZ235Y2201, one subject in the 10 mg RTB101 once daily dosing group discontinued study drug treatment due to mouth ulcers of moderate severity.

If needed, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

Gastrointestinal Symptoms

Gastrointestinal symptoms including nausea, vomiting, and diarrhea are common AEs following treatment with high doses of RTB101 in oncology studies.

During the one year of study follow-up of elderly subjects in the Phase 2a clinical trial CBEZ235Y2201, diarrhea occurred in:

- 8% of subjects in the placebo treatment group
- 19% of subjects in the RTB101 10 mg once daily treatment group

During the 24 weeks of study follow-up of elderly subjects in the Phase 2b clinical trial RTB-BEZ235-202, diarrhea occurred in:

- 4.4% of subjects in the placebo treatment group
- 4.5% of subjects in the RTB101 10 mg once daily treatment group

No increase in the incidence of nausea or vomiting was observed in elderly subjects treated with RTB101 10 mg once daily as compared to placebo in clinical trials CBEZ235Y2201 and RTB-

BEZ235-202, however in CBEZ235Y2201, one subject in the RTB101 10 mg treatment group discontinued study drug due to nausea.

In Study RTB-101-204, subjects must be monitored for signs of gastrointestinal irritation. Subjects experiencing nausea, vomiting, or diarrhea should receive appropriate medical treatment. Study drug should be permanently discontinued if a subject develops a gastrointestinal SAE, such as gastrointestinal bleeding or perforation. Study drug should also be permanently discontinued if a subject develops oral ulcers, stomatitis, or diarrhea that limits oral intake or is associated with dehydration or weight loss (>2% Baseline weight) over 2 or more consecutive study visits (see Section 5.5.2).

Fatigue

Fatigue/asthenia has been commonly reported following treatment with high doses of RTB101 in oncology studies. The incidence of fatigue was similar in the RTB101 10 mg once daily and placebo arms in elderly subjects in clinical trials CBEZ235Y2201 and RTB-BEZ235-202.

Rash

Rash has been frequently reported following treatment with high doses of RTB101 in oncology studies.

During the one year of study follow-up of elderly subjects in the Phase 2a clinical trial CBEZ25Y2201, rash occurred in:

- 3.8% of subjects in the placebo treatment group
- 3.8% of subjects in the RTB101 10 mg once daily treatment group

During the 24 weeks of study follow-up of elderly subjects in clinical trial RTB-BEZ235-202, rash occurred in:

- 2.2% of subjects in the placebo treatment group
- 0.6% of subjects in the RTB101 10 mg once daily treatment group

Subjects that experience rash while receiving RTB101 should receive appropriate symptomatic treatment.

Hyperglycemia

Hyperglycemia has commonly been seen following treatment with high dose RTB101 in oncology clinical trials. The incidence of hyperglycemia was similar in the RTB101 10 mg once daily and placebo arms in clinical trials CBEZ235Y2201 and RTB-BEZ235-202. Blood glucose levels will be closely monitored throughout the current trial.

Hematopoietic and Lymphopoietic Systems

Anemia, leukopenia and thrombocytopenia are common AEs following treatment with high doses of RTB101 in oncology studies. No increase in the incidence of anemia, leukopenia or thrombocytopenia was observed in elderly subjects treated with RTB101 10 mg once daily as compared to placebo in clinical trials CBEZ235Y2201 and RTB-BEZ235-202. Complete blood counts will be followed at each visit while subjects are on study drug.

Lipid Abnormalities

Lipid disturbances are common in clinical trials of the rapalog class of mTOR inhibitors but are uncommon in clinical trials of RTB101. The incidence of hyperlipidemia was similar in the RTB101 10 mg once daily and placebo arms in elderly subjects in clinical trials CBEZ235Y2201 and RTB-BEZ235-202. Cholesterol and triglyceride levels will be followed at each visit.

Cardiovascular Events

Preclinical findings did not indicate prominent cardiac risks of RTB101. In clinical studies with high doses of RTB101 in oncology subjects, only few cases of cardiac AEs were reported, and it is not clear if RTB101 increases the risk of cardiac events. A suspected case of myocardial infarction (MI) was reported in an oncology subject treated with high dose RTB101 (200 mg bid) in combination with everolimus, and a suspected case of acute coronary syndrome was reported in an oncology subject receiving high dose RTB101 in combination with paclitaxel. No increase in the incidence of cardiac events was observed in elderly subjects treated with RTB101 10 mg once daily as compared to placebo in clinical trial CBEZ235Y2201. In RTB-BEZ235-202, 3 elderly subjects with multiple cardiac risk factors had a MI in the RTB101 5 mg once daily treatment arm. No MIs occurred in the RTB101 10 mg once daily, RTB101 10 mg twice daily, RTB101 10 mg + everolimus or placebo treatment arms. Nevertheless, subjects with active severe, uncontrolled and/or unstable cardiac conditions (including subjects with unstable angina pectoris or acute ischemic changes on ECG at Screening or Baseline [see Section 4.2]) will be excluded from Study RTB-101-204. Central analysis of ECG data in oncology study CBEZ235A2101 did not show any evidence for QT prolongation. A preliminary exposure-QT analysis showed no significant impact of RTB101 plasma concentration on QT interval. Despite

these findings, as a conservative measure, subjects with a QTcF >480 msec at Screening or Baseline will also be excluded from study participation (see Section 4.2).

From the Baseline through the Week 20 Visit (i.e., completion of the Short-term Follow-up Period) in Study RTB-101-204, subjects will be queried with regard to any new cardiac symptoms (see SOM for details); a cardiac exam will be performed as part of required complete and targeted physical examinations (see Table 6-1 [Assessment Schedule]), and ECGs will be obtained at the Week 4, Week 8, Week 12, and Week 16 visits post-Baseline. Any QTcF >500 msec or >60 msec QTcF change from a subject's Baseline ECG, or any other clinically significant abnormal ECG change should be reported as an AE. As a safety precaution, subjects experiencing any cardiac-related SAEs (including, but not limited to, MI and unstable angina) must permanently discontinue study drug treatment (see Section 5.5.2).

Liver Toxicity

Elevated liver function tests (LFTs) have been reported in oncology subjects treated with high dose RTB101. No increase in the incidence of elevated LFTs was observed in elderly subjects treated with RTB101 10 mg once daily as compared to placebo in clinical trials CBEZ235Y2201 and RTB-BEZ235-202. However, subjects with active hepatitis or with significant LFT elevations should be excluded from this RTB101 trial. An elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin >3 x ULN should be reported as a severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3) AE.

Pneumonitis

Non-infectious pneumonitis is a class effect of mTOR inhibitors that are rapamycin-derivatives. However, it is unclear if RTB101 is associated with an increased risk of interstitial pneumonitis even when administered at high doses. In clinical trials of high dose RTB101 in 442 advanced cancer subjects, 5 cases of interstitial pneumonitis potentially related to RTB101 have been reported. However, 2 of these subjects were also receiving rapamycin-derivatives, and two had underlying pneumonia. No elderly subjects developed pneumonitis while receiving low dose RTB101 in clinical studies CBEZ235Y2201 or RTB-BEZ235-202.

Consider a diagnosis of non-infectious pneumonitis in subjects presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. The lung toxicity has been reported to be completely reversible in most of the cases upon drug interruption or discontinuation. The use of corticosteroids may be indicated. See Section 13.2 (Appendix 2) for an algorithm for treating interstitial pneumonitis.

4. Population

The study population will be comprised of elderly individuals ≥ 65 years of age without unstable underlying medical conditions defined as conditions that require acute medical intervention or ongoing adjustments of concomitant medications (as determined by medical history, ECG and laboratory tests at Screening, and physical examination, ECG and vital signs at Screening and Baseline). The goal is to randomize approximately 1066 subjects during winter cold and flu season.

The Investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the Investigator so that the study population will be representative of all eligible subjects. Subject selection is to be established by checking through inclusion/exclusion criteria at Screening and Baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site. Deviation from **any** entry criterion excludes a subject from enrollment into the study.

4.1. Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female subjects who, in the clinical judgement of the Investigator, are without unstable medical conditions defined as conditions that require acute medical intervention or ongoing adjustments of concomitant medications (as determined by medical history, concurrent concomitant medications and laboratory test results at Screening, and physical examination, ECG and vital signs at Screening and Baseline).
3. Subjects must be ≥65 years of age.
4. Subjects should require no or minimal assistance with self-care and activities of daily living. Subjects in assisted-living or long-term care residential facilities that provide minimal assistance are eligible.
5. Females must be post-menopausal. Women are considered post-menopausal and not of child bearing potential if they have had:
    - 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) OR
    - surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to Screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment will she be considered not of child bearing potential.
6. Sexually active male subjects with a partner of child-bearing potential must be willing to wear a condom while on study drug and for 1 week after stopping study drug and should not

father a child in this period. A condom is required to be used also by vasectomized men with a partner of child-bearing potential to prevent delivery of the drug via seminal fluid.

7. Subjects must weigh at least 40 kg.
8. Subject must be able to communicate well with the Investigator, and to understand and comply with the requirements of the study including completing an eDiary daily at home.

4.2. **Exclusion Criteria**

Subjects will not be eligible if they meet any of the following criteria:

1. Any of the following smoking criteria:
    a. Is a current smoker as assessed by medical history or a positive serum cotinine test (or positive urine cotinine test if serum cotinine testing is unavailable) at Screening.
    b. Stopped smoking ≤1 year prior to Screening.
    c. Is a previous smoker with a ≥10 pack year smoking history.
    d. Has a household member who currently smokes in the house.
2. Subjects with a medical history of clinically significant lung diseases other than asthma (e.g., chronic obstructive pulmonary disease (COPD), emphysema, interstitial pulmonary fibrosis (IPF), bronchiectasis, etc.).
3. Subjects with a Mini Mental Status Examination (MMSE) score <24 at Screening.
4. Subjects with current evidence of a serious and/or unstable medical disorder including cardiovascular, respiratory, gastrointestinal, renal (including subjects with an estimated glomerular filtration rate (eGFR) as estimated by the modified diet in renal disease (MDRD) GFR equation ≤30 mL/min/1.73m2), or hematologic disorders.
5. The following cardiac conditions:
    a. Unstable angina pectoris or acute ischemic changes on ECG at Screening or Baseline
    b. History of MI, coronary bypass surgery, or any percutaneous coronary intervention (PCI) within 6 months prior to Screening
    c. New York Heart Association functional classification III-IV congestive heart failure
    d. Unstable or life-threatening cardiac arrhythmia

        (Chronic stable atrial fibrillation is allowed)
    e. QTcF >480 msec at Screening or Baseline
6. Subjects with history of malignancy in any organ system within the past 5 years EXCEPT for the following:
    a. Localized basal cell or squamous cell carcinoma of the skin.

b. Prostate cancer confined to the gland (AJCC stage T2N0M0 or better).

c. Cervical carcinoma in situ.

d. Breast cancer localized to the breast

7. Any RTI or acute significant illness (based on the subject's medical history and the clinical judgement of the Investigator) which has not resolved at least two (2) weeks prior to Baseline.
8. Subjects with a history of systemic autoimmune diseases (e.g., lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), or receiving immunosuppressive therapy (such as mycophenolate, tacrolimus, cyclosporine, azathioprine, infliximab) including chronic use of prednisone >10 mg daily (however, inhaled corticosteroids and the acute use of higher doses of prednisone to treat conditions such as exacerbation of asthma or other acute conditions are allowed).
9. Subjects with Type I diabetes mellitus.
10. Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further evaluation.
11. Subjects with any one of the following during Screening:
    a. white blood cell (WBC) count <2.0 $x10^3$/microL.
    b. neutrophil count <1.0 x 10^3/microL.
    c. platelet count <75 x 10^3/microL.
12. Subjects with a history of alcohol or drug abuse within 2 years of the Screening visit.
13. Subjects with any conditions affecting absorption, distribution, or metabolism of the study drug (e.g., inflammatory bowel disease, gastric or duodenal ulcers, hepatic disease). For subjects with biochemical evidence of liver injury as indicated by abnormal liver function tests:

    • Any single parameter of ALT, AST, alkaline phosphatase or serum bilirubin must not exceed 1.5 x upper limit of normal (ULN) in subjects who do not have a history of Gilbert's syndrome. If the subject has a history of Gilbert's syndrome, direct and indirect reacting bilirubin should be differentiated, and the direct bilirubin must be less than 1.5 x ULN.

    • Any elevation above ULN of more than one parameter of ALT, AST, alkaline phosphatase or serum bilirubin will exclude a subject from participation in the study.
14. Subjects with a history of immunodeficiency diseases, including a positive human immunodeficiency virus (HIV) test result.
15. Infection with Hepatitis B (HBV) or Hepatitis C (HCV).
16. Subjects who require treatment with strong CYP3A4 or CYP1A2 inhibitors or inducers, or subjects who require treatment with digoxin.

17. Use of any other investigational medication or participation in any other investigational study within 5 half-lives of the investigational medication, or within 30 days, whichever is longer; or longer if required by local regulations.
18. Subjects who have received an organ transplant.
19. Subjects who previously received treatment with RTB101 in another clinical study (e.g., CBEZ235Y2201, RTB-BEZ235-202, or RTB-101-203).

5. Treatment

5.1. Study Treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM.

Table 5-1 Investigational and Control Drugs

Study Drug Name	Formulation	Color	Unit Dose	Packaging
RTB101	Capsules	Pink	10 mg	Bulk supply bottles
Matching Placebo	Capsules	Pink	---	Bulk supply bottles

5.2. Treatment Arms

Subjects who meet study eligibility criteria will be randomized in a 1:1 ratio to one of the following 2 treatment arms.

- RTB101 10 mg (1 capsule of 10 mg) daily
- Matching Placebo (1 capsule of RTB101 matching placebo) daily

5.3. Treatment Assignment and Randomization

5.3.1. Subject Numbering

Each subject will be uniquely identified in the study by a combination of his/her study site number and a subject number. The study site number will be assigned by the Sponsor. Upon signing the informed consent form, the subject will be assigned a subject number by the IXRS system.

Details regarding the process and timing of treatment assignment and randomization of subjects are outlined in the IXRS System User Guide.

5.3.2. Treatment Assignment and Randomization

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 (see Section 4 above). 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.

Please reference the IXRS System User Guide for more information on treatment assignment and randomization instructions. 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

Randomization will be stratified to ensure that subjects in each of these subgroups are randomized equally between the treatment arms to minimize the risk of imbalance between the treatment arms.

The randomization scheme for subjects will be reviewed and approved by a member of the team responsible for Randomization schema. Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

Details regarding the process and timing of treatment assignment and randomization of subjects are outlined in the IXRS System User Guide.

5.3.3. Treatment Blinding and Study Site Staff

This is a subject, Investigator and Sponsor-blinded study. Subjects, all study site staff, including Investigators and study nurses, will remain blinded until all subjects complete the Long-term follow up Period (Study Week 48).

The Sponsor will remain blinded to study treatment until all subjects complete the Short-term Follow-up Period (Study Week 20). The identity of the treatments will be concealed by the use of active study drug that is identical to matched placebo in packaging, labeling, schedule of

administration, appearance, and odor. Unblinding a single subject at the study site for safety reasons (necessary for subject medical management) will occur via an emergency process in place at the study site (see Section 5.4.1 below). After all subjects complete the Short-term Follow-up Period (Study Week 20), the Sponsor and designee may be unblinded.

5.4. **Treating the Subject**

Study drug will be administered orally by the subject at home with breakfast. Exceptions will be at the Baseline Visit, when the study drug will be administered to all subjects at the study site, and at the Week 4 (or Week 6 if applicable) and 12 visits, when the study drug will be administered (with a light meal) at the site to those subjects identified per the IXRS randomization for PK assessments. See the Assessment Schedule of this protocol (Section 6) for further details, including dosing windows.

Treatment compliance will be assessed using 2 methods. First subjects will be instructed to enter the time they take their study drug daily in their eDiary. Second, subjects will be instructed to bring their remaining study drug to each study visit, and a pill count (study drug accountability) will be done at the site.

5.4.1. **Emergency Breaking of Assigned Treatment Code**

In order to meet International Conference on Harmonization (ICH) GCP requirements and ensure the integrity of the blind, and also to allow for those rare instances when the blind may need to be broken in emergency situations, emergency code breaks must only be undertaken when the information is essential to treat the subject safely and efficaciously. The Investigator should contact (in case of emergency the Investigator can unblind treatment and then contact the Sponsor) the Sponsor Medical Monitor prior to breaking the blind to promptly discuss and explain the planned or actual unblinding event. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IXRS System. When the Investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code. The Investigator will then receive details of the investigational drug treatment for the specified subject and a communication confirming this information.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IXRS System at any time in case of emergency. The Investigator will provide the protocol number, the study drug name and the subject identifier number.

In addition, the Investigator must provide oral and written information to the subject on how to contact the Investigator (or the Investigator's backup when the Investigator is unavailable) in case of emergency, to ensure that un-blinding can be performed at any time. Subjects whose treatment has been unblinded must be discontinued from the study treatment (see Section 5.5.2 below).

5.4.2. Permitted Dose Adjustments to Study Treatment

For subjects who are unable to tolerate the protocol-specified dosing scheme, the study drug treatment should be temporarily interrupted. If the subject is unable to tolerate restarting treatment, study drug should be permanently discontinued but the subject should continue to complete study assessments (as applicable) including completion of the daily eDiary. The AEs leading to study drug dose interruption or discontinuation must be recorded in the electronic case report form (eCRF).

5.4.3. Vaccinations

The date of the most recent pneumococcal and current seasonal influenza vaccinations of each subject should be captured at the Baseline Visit and entered into the Prior Vaccination eCRF page. For subjects who have not received their seasonal influenza or pneumococcal vaccination at the time of study entry, influenza and pneumococcal vaccinations per standard of care are recommended. It is recommended that other vaccinations such as herpes zoster (shingles), measles, mumps, or rubella virus vaccine, or yellow fever vaccine be administered at least 2 weeks before randomization or after the Week 20 Visit to avoid having vaccination-associated symptoms confound assessments of symptomatic respiratory illness.

5.4.4. Concomitant Medications

The site must instruct the subject to report any dosing changes of their concomitant medications, or any new medications that they start taking after being enrolled into the study. All medications (including vaccinations), procedures and significant nondrug therapies (including physical therapy, supplemental oxygen, and blood transfusions) administered after the subject is enrolled into the study must be recorded in the eCRF. Each prior and/or concomitant medication must be individually assessed against all exclusion criteria and prohibited medications. If in doubt, the Investigator should contact the Sponsor Medical Monitor or designee before randomizing a subject or any time a new medication needs to be started.

5.4.5. Prohibited Medications

Use of the treatments displayed in Table 5-2 is NOT allowed while subjects are taking study drug. Strong inhibitors and inducers of CYP3A4 and CYP1A2 are prohibited because they may substantially alter RTB101 blood levels. Immunosuppressive agents are prohibited because they may inhibit the immune response to infections and confound efficacy evaluations. Digoxin is prohibited because it is a narrow therapeutic index substrate of P-gp, and RTB101 may inhibit P-gp in the gut. Use of any prohibited concomitant medications including St. John's wort while on study drug should be documented as a protocol deviation.

Table 5-2 Prohibited Concomitant Medications

Medication	Prohibition Period	Action to be taken
Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, voriconazole, ritonavir).	While on study drug	Discontinue study treatment while taking prohibited medication and for 5 half-lives after discontinuation of the prohibited medication and document as a protocol deviation
Strong inducers of CYP3A4 (e.g., carbamazepine, phenytoin, rifampicin, rifabutin, St. John's wort).	While on study drug	Discontinue study treatment while taking prohibited medication and for 5 half-lives after discontinuation of the prohibited medication and document as a protocol deviation
Strong inhibitors of CYP1A2 (e.g., ciprofloxacin, enoxacin, fluvoxamine(a), zafirlukast).	While on study drug	Discontinue study treatment while taking prohibited medication and for 5 half-lives after discontinuation of the prohibited medication and document as a protocol deviation
Strong inducers of CYP1A2 (e.g., rifampicin).	While on study drug	Discontinue study treatment while taking prohibited medication and for 5 half-lives after discontinuation of the prohibited medication and document as a protocol deviation
Immunosuppressive therapy including prednisone > 10 mg daily except for acute treatment of conditions such as exacerbation of asthma	While on study drug	Discontinue study treatment while taking prohibited medication and for 5 half-lives after discontinuation of the prohibited medication and document as a protocol deviation
Digoxin	While on study drug	Discontinue study treatment while taking prohibited

		medication and for 5 half-lives after discontinuation of the prohibited medication and document as a protocol deviation

Subjects who require moderate CYP3A4 inhibitors such as (erythromycin, fluconazole, calcium channel blockers) should be followed closely for AEs known to be associated with RTB101 as outlined in Section 3.3.

A list of moderate and strong CYP3A4 and strong CYP1A2 inhibitors and inducers is included in Section 13.1 (Appendix 1).

5.5. Study Completion and Discontinuation

5.5.1. Completion and Post-Study Treatment

A subject will be considered to have completed the Primary Analysis Period of the study for efficacy and safety when the subject has completed the Week 16 Visit. The Short-term Follow-up Period of the study for efficacy and safety will be considered completed when a subject has completed the Week 20 visit or has withdrawn consent or discontinued the study prematurely.

After completion of the Short-term Follow-up Period of the study, subjects will enter the Long-term Follow-up Period of the study where a Long Term Follow-Up via questionnaire will be administered by telephone at Week 48. Information from this follow-up call on interim hospitalization(s), admission(s) to a skilled nursing facility, and/or death occurring since completion of the Short-term Follow-up Period of the study (i.e., Week 20) will be captured in the study database.

After completion of the Long-term Follow-up Period of the study, subject participation in the study will be considered concluded.

The Investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study for medical reasons or must refer them for appropriate ongoing care.

5.5.2. Discontinuation of Study Treatment

Premature discontinuation of study treatment for a subject occurs when study drug is permanently stopped earlier than the protocol planned duration, and can be initiated by either the subject, the Investigator, or the Sponsor.

Study treatment must be permanently discontinued under the following circumstances:

- Subject decision-subjects may choose to discontinue study drug treatment for any reason at any time.
- The Investigator believes that continuation of study treatment would negatively impact the safety of the subject or the risk/benefit ratio of trial participation. This includes any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the subject's overall status, prevents the subjects from continuing participation in the study.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Emergence of the following AEs:
    - Hypersensitivity reaction to study drug
    - Gastrointestinal SAE
    - Oral ulcers, stomatitis, or diarrhea that limits oral intake or is associated with dehydration or weight loss (>2% from Baseline weight) over two or more consecutive study visits
    - Cardiac SAE (including, but not limited to, MI and unstable angina)
    - Study drug-related non-infectious pneumonitis (see Section 13.2 [Appendix 2])
- Subject whose treatment has been unblinded.

If premature discontinuation of study treatment occurs, Investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the CRF. Subjects who permanently discontinue study drug due to an AE should return to the study site as soon as possible for an unscheduled visit to return all study drug for reconciliation and accountability and to have the following assessments: vital signs, complete physical exam, and blood and urine collection for safety labs. Subjects who discontinue treatment for reasons other than an AE should return all study drug for reconciliation and accountability at the next study visit. UNLESS subjects withdraw their consent (see Section 5.5.3), they should return for all remaining study visits (including completing the daily eDiary). If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, certified letter) should be made to contact the subject as specified in Section 5.5.4 (Lost to follow-up).

If subjects permanently discontinue study treatment early and DO NOT withdraw consent, study participation is expected to continue. At a minimum, attempts should be made to collect the following data via the eDiary, at abbreviated study site visits, and/or via telephone contact:

- Respiratory Illness Symptom Questionnaire completed daily in the eDiary

- AEs/SAEs
- New and/or concomitant treatments

5.5.3. **Withdrawal of Consent**

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when all of the following apply:

- A subject does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts, and
- Does not allow analysis of already obtained biologic material.

In this situation, the Investigator must make every effort (e.g., telephone, e-mail, certified letter) to determine the primary reason for the subject's decision to withdraw their consent and record this information in the eCRF. Study treatment must be discontinued (see Section 5.5.2) and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the subject in the context of the study are not allowed unless safety findings require communicating or follow-up.

5.5.4. **Lost to Follow-up**

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, certified letters, etc. Three (3) attempts to contact the subject should be performed by the study site staff and documented in the subject's source documentation.

Additionally, a registered/certified letter to the subject (with documentation of the registered letter in the subject's source documentation) should be sent to the subject (or caregiver).

A subject cannot be considered as lost to follow-up until the time point of their scheduled end of Short-term Follow-up Period (i.e., Week 20 Visit) has passed.

5.5.5. **Study Enrollment Stopping Criteria**

If the following criteria are met, an unblinded safety review will be completed by the DMC within 48 hours to determine if enrollment needs to be halted:

- Three or more subjects develop the same or a clinically similar SAE
- Three or more subjects experience a Grade 3 or higher AE or laboratory abnormality of the same type considered at least possibly related to study drug
- QTcF >500 msec or >60 msec change from pre-dose Baseline ECG, or any other clinically significant abnormal ECG change in any 3 or more subjects
- Two or more subjects develop ALT, AST or total bilirubin > 3x ULN

5.5.6. **Early Study Termination by the Sponsor**

The study can be terminated by resTORbio at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory, medical or operational reasons (including slow enrollment). Should this be necessary, any remaining subjects enrolled in the study must be seen as soon as possible, treated as a prematurely withdrawn subject and an End of Study Visit must be completed. The Investigator will be responsible for informing the institutional review board (IRB)/independent ethics committee (IEC) of the early termination of the study.

6. **Visit Schedule and Assessments**

Screening Visit:

Screening may occur prior to investigational product being available at the study site. During the Screening Visit (maximum 4 weeks prior to Baseline/randomization), subjects will be assessed for eligibility to participate in the trial based on inclusion/exclusion criteria. Subjects will have the following assessments/evaluations:

- Informed Consent (Main Study)
- Review of medical history and current medical (including cardiac) conditions.
- Review of prior and concomitant medications.
- Clinical evaluation, including a complete physical exam to include measurements of weight, height, blood pressure, heart rate, respiratory rate, and temperature.
- Electrocardiogram (ECG)
- Blood and urine drawn for safety assessments and testing for HIV, Hepatitis B and C virus.
- Serum cotinine test (or urine cotinine test if serum cotinine testing is unavailable) to exclude current smokers.

- Chest X-ray, unless one was completed in the last three months.
- Mini Mental Status Examination (MMSE)

If necessary to address an abnormal laboratory value during the screening period, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error.

Baseline (Day 0) Visit:

At the Baseline visit, subjects will undergo the following evaluations:

- Complete informed consent for Optional Blood Storage for Future use and Consent for Optional Pharmacogenetic Analysis of Pharmacogenomic Blood Specimens (if applicable).
- Review of inclusion/exclusion criteria.
- Review of medical history and current medical (including cardiac) conditions.
- Review of prior and concomitant medications including dates of the most recent administration (if applicable) of the pneumococcal and the current seasonal influenza vaccinations.
- Clinical evaluation, including a targeted physical exam to include measurements of weight, orthostatic blood pressure, heart rate, respiratory rate, and temperature, and an exam of the lungs, heart, oral cavity, and skin.
- Clinical frailty index score assessment (see Section 13.4 [Appendix 4]).
- ECG for Baseline safety assessment.
- A mid-turbinate swab will be obtained.
- Blood and urine samples obtained for Baseline safety assessments.
- Blood samples will be obtained for biomarker (including RNA expression and soluble serum biomarker) analysis.
- Blood samples will be obtained for potential future pharmacogenomic assessments (for consenting subjects only).
- Once randomized via IXRS, subjects will be administered their first dose of study drug at the study site. Subjects will be instructed on how to complete the dosing and the Respiratory Illness Symptom Questionnaire in the eDiary daily at home. Subjects will then complete the Health Related Quality of Life (EQ-5D-5L; see Section 13.3

[Appendix 3]) and Respiratory Illness Symptom Questionnaire on their eDiary at the Baseline visit.

After assessment for adverse events, subjects will then be sent home with study drug and the eDiary. Subjects will be instructed to take study drug at home daily with breakfast and to bring remaining study drug to all study visits.

Provided the study drug continues to be well tolerated, subjects will be treated with study drug through the Week 16 Visit, during which time they will return to the clinic every 2 weeks (Visits Week 2, 4, 6, and 8) for the first 8 weeks, and then every 4 weeks (Visits Week 12 and 16).

Week 2 Visit:

Subjects will return to the study site 2 weeks after starting study drug. The following evaluations will be performed:

- Review of interim and current medical (including cardiac) conditions (see SOM for details).
- Clinical evaluation, including a targeted physical exam to include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature, and an exam of the lungs, heart, oral cavity, and skin.
- Assessments for safety including any adverse/serious adverse events and any concomitant medications taken since the last study visit.
- Obtain information about whether subjects have been evaluated in an ER or urgent care facility or been admitted to a hospital or skilled nursing facility since their last visit.
- Blood and urine samples will be obtained for safety assessments.
- A mid-turbinate swab will be obtained. If a subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) obtained as outlined in the unscheduled visit assessments.
- Remaining study drug brought back by the subject to the study visit will be counted to ensure compliance and subject will be retrained if compliance is not 100%. Subject will be re-dispensed the same study drug that they brought to the visit.
- Those subjects participating in the PK assessments (per the IXRS randomization) will be asked to not take study drug on the morning of their next scheduled study visit (Week 4 [or Week 6 if applicable]) as the subject will be administered study drug together with a light meal at the study site.

Week 4 Visit:

The following evaluations will be performed:

- Review of interim and current medical (including cardiac) conditions (see SOM for details).
- Clinical evaluation, including a targeted physical exam to include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature, and an exam of the lungs, heart, oral cavity, and skin.
- ECG for safety monitoring.
- Assessments for safety including any adverse/serious adverse events and any concomitant medications taken since the last study visit.
- Obtain information about whether subjects have been evaluated in an ER or urgent care facility or been admitted to a hospital or skilled nursing facility since their last visit.
- Blood and urine will be obtained for safety assessments.
- A mid-turbinate swab will be obtained. If a subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) obtained as outlined in the unscheduled visit assessments.
- PK and biomarker assessments (only for those subjects identified per the IXRS randomization for PK assessments):
    - A pre-dose PK sample will be taken after which study drug will be administered at the study site together with a light meal.
    - The remaining PK samples will be drawn at the following timepoints post study drug administration:
        - 30 minutes (±10 minutes)
        - 1 hour (±15 minutes)
        - 2 hour (±30 minutes)
        - 4 hour (±30 minutes) – After obtaining a PK blood sample, blood samples for biomarker assessments will also be obtained at the 4 hour time point (see SOM and Lab Manual for instructions).
        - If PK sampling cannot be performed at the Week 4 visit for logistical reasons, it should be collected at the Week 6 visit instead, but according to the schedule described above for Week 4. This applies to timing of biomarker samples originally scheduled for Week 4 as well.

- Remaining study drug brought back by the subject to the study visit will be counted to ensure compliance and subject will be retrained if compliance is not 100%. Subject will be dispensed new study drug at this visit.

Week 6 Visit:

The following evaluations will be performed:

- Review of interim and current medical (including cardiac) conditions (see SOM for details).
- Clinical evaluation, including a targeted physical exam to include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature, and an exam of the lungs, heart, oral cavity, and skin.
- Assessments for safety including any adverse/serious adverse events and any concomitant medications taken since the last study visit.
- Obtain information about whether subjects have been evaluated in an ER or urgent care facility or been admitted to a hospital or skilled nursing facility since their last visit.
- Blood and urine samples will be obtained for safety assessments.
- If PK sampling could not be performed at the Week 4 visit for logistical reasons, it should be collected at the Week 6 visit instead, but according to the schedule described above for Week 4. This applies to timing of biomarker samples originally scheduled for Week 4 as well.
- A mid-turbinate swab will be obtained. If a subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) obtained as outlined in the unscheduled visit assessments.
- Remaining study drug brought back by the subject to the study visit will be counted to ensure compliance and subject will be retrained if compliance is not 100%. Subject will be re-dispensed the study drug that the subject brought to the visit.

Preparation for Week 8 Visit (PK subjects only): Those subjects participating in the PK assessments (per the IXRS randomization) will be instructed to take their study drug at home with breakfast and to record the time of dosing in the eDiary on the morning of their next scheduled visit (Week 8 Visit). The Week 8 visit should be scheduled approximately 7 hours after the subject plans to take their morning dose of medication to enable an 8 hour post-dose PK blood draw.

Week 8 Visit:

The following evaluations will be performed:

- Review of interim and current medical (including cardiac) conditions (see SOM for details).
- Clinical evaluation, including a targeted physical exam to include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature, and an exam of the lungs, heart, oral cavity, and skin.
- ECG for safety monitoring
- Assessments for safety including any adverse/serious adverse events and any concomitant medications taken since the last study visit.
- Obtain information about whether subjects have been evaluated in an ER or urgent care facility or been admitted to a hospital or skilled nursing facility since their last visit.
- Blood and urine will be obtained for safety assessments.
- A mid-turbinate swab will be obtained. If a subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) obtained as outlined in the unscheduled visit assessments.
- For those subjects participating in the PK assessments (identified per the IXRS randomization), a post-dose 8 hour (±1 hour) PK sample will be taken.

Remaining study drug brought back by the subject to the study visit will be counted to ensure compliance and subject will be retrained if compliance is not 100%. Subject will be dispensed new study drug at this visit.

- **Preparation for Week 12 Visit (PK subjects only):** Those subjects participating in the PK assessments (per the IXRS randomization) will be asked to not take study drug on the morning of their next scheduled study visit (Week 12) as the subject will be administered study drug together with a light meal at the study site.

Week 12 Visit:

The following evaluations will be performed:

- Review of interim and current medical (including cardiac) conditions (see SOM for details).
- Clinical evaluation, including a targeted physical exam to include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature, and an exam of the lungs, heart, oral cavity, and skin.
- ECG for safety monitoring

- Assessments for safety including any adverse/serious adverse events and any concomitant medications taken since the last study visit
- Obtain information about whether subjects have been evaluated in an ER or urgent care facility, or been admitted to a hospital or skilled nursing facility since their last visit
- Blood and urine samples will be obtained for safety assessments.
- A mid-turbinate swab will be obtained. If a subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) obtained as outlined in the unscheduled visit assessments.
- PK assessments (only for those subjects identified per the IXRS randomization):
    - A pre-dose PK sample will be taken after which study drug will be administered at the study site together with a light meal.
    - The remaining PK samples will be drawn at the following timepoints post study drug administration:
        - 30 minutes (±10 minutes)
        - 1 hour (±15 minutes)
        - 2 hour (±30 minutes)
- Remaining study drug brought back by the subject to the study visit will be counted to ensure compliance and subject will be retrained if compliance is not 100%. Subject will be dispensed new study drug at this visit.

Week 16 Visit:

The following evaluations will be performed:

- Review of interim and current medical (including cardiac) conditions (see SOM for details).
- Clinical evaluation, including a complete physical exam to include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature.
- ECG for safety monitoring.
- Assessments for safety including any adverse/serious adverse events and any concomitant medications taken since the last study visit.
- Obtain information about whether subjects have been evaluated in an ER or urgent care facility or been admitted to a hospital or skilled nursing facility since their last visit.
- Blood and urine will be obtained for safety assessments.

- Blood will be obtained for biomarker analysis.
- Subjects will have a mid-turbinate swab taken. If a subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) as outlined in the unscheduled visit assessments.
- Subjects will complete the Health Related Quality of Life (EQ-5D-5L).
- Remaining study drug will be returned. No study drug will be dispensed as this will be end of treatment.

Week 20 Visit: End of the Short-term Follow-up Period of the Study

All subjects will be followed up for 4 weeks after their last dose of study drug. The following evaluations will be performed:

- Review of interim and current medical (including cardiac) conditions (see SOM for details).
- Clinical evaluation, including a complete physical exam to include measurements of weight, blood pressure, heart rate, respiratory rate, and temperature.
- If a subject presents with respiratory illness symptoms at this visit they may also have a nasopharyngeal swab, RIDT and sputum sample (if applicable) obtained as outlined in the unscheduled visit assessments (section 3.1).
- Assessments for safety including any adverse/serious adverse events and any concomitant medications taken since the last study visit.
- Obtain information about whether subjects have been evaluated in an ER or urgent care facility or been admitted to a hospital or skilled nursing facility since their last visit.
- Blood and urine samples will be obtained for safety assessments.
- eDiaries will be returned.

Subject who have AEs that are continuing at the end of the Short-term Follow-up Period (i.e., Week 20 Visit) will be captured as “ongoing” in the database; however, the AEs should continue to be followed until resolution or judged to be permanent by the Investigator (see Section 7.1).

Clinically Symptomatic Respiratory Illness Unscheduled Visits

Refer to Section 3.1.

Week 48: End of the Long-term Follow-up Period of the Study

As part of extended long-term safety follow-up post-treatment, sites will contact subjects by telephone at Week 48 to capture information on a questionnaire concerning hospitalization(s), skilled nursing facility admission(s) and deaths that have occurred since the Week 20 visit.

Table 6-1 lists all of the visits and assessments and indicates with an "X" when the assessments are performed. Visit windows are provided to ease scheduling of subject visits. Visits that occur outside these visit windows will be considered a protocol deviation. Below are some highlights of specific activities by visit. More details regarding specific tests and procedures can be found below in this section and in the SOM. Adverse events should be monitored throughout the study and recorded as described in Section 7, Safety Monitoring.

Table 6-1 Assessment Schedule

	Screening	Baseline	Primary Analysis (and Study Drug Administration) Period						Clinically Symptomatic Respiratory Illness Visit (Unscheduled)	Short-term Follow-up Period	Long Term Follow-Up Period
Day/Week	**Day -28 to -1**	**Day 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**---**	**Week 20**	**Week 48**
Visit Window	**---**	**---**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**---**	**±5 days**	**±4 weeks**
Main Informed Consent	X										
Mini Mental Status Exam (MMSE)	X										
Inclusion/Exclusion Criteria	X	X[1]									
Influenza and pneumococcal vaccination history		X									
Demography	X										
Medical History/Interim/Current Medical (including cardiac) Conditions	X	X	X	X	X	X	X	X	X	X	
Prior & Concomitant Medications/Therapies	X	X	X	X	X	X	X	X	X	X	
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	
Vital signs: Temperature; Respiratory Rate; Heart Rate & Blood Pressure[2]	X	X	X	X	X	X	X	X	X	X	
Orthostatic Blood Pressure		X									
Complete Physical Exam	X							X		X	
Targeted Physical Exam (including: oral, lungs, heart, skin)		X	X	X	X	X	X		X[3]		
ECG Evaluation	X[4]	X[4]		X		X	X	X			
Chest X-Ray[5]	X										
Hematology, Blood Chemistry, Urinalysis	X	X	X	X	X	X	X	X	X[19]	X	
Serum Cotinine Test[21]	X										
HIV/Hepatitis Screen[6]	X										
Clinical Frailty Scale Scoring[7]		X									

	Screening	Baseline	Primary Analysis (and Study Drug Administration) Period						Clinically Symptomatic Respiratory Illness Visit (Unscheduled)	Short-term Follow-up Period	Long Term Follow-Up Period
Day/Week	**Day -28 to -1**	**Day 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**---**	**Week 20**	**Week 48**
Visit Window	**---**	**---**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**---**	**±5 days**	**±4 weeks**
Randomization		X									
Study Drug Administration/ Dispensation/Return[8,9]		X[9,11]	X[10a]	X[9,11]	X[10a]	X[9]	X[9,11]	X[10b]			
Dispensation/Return of eDiary		X[12a]								X[12b]	
Record Time of Study Drug Administration in eDiary		Daily									
Respiratory Symptom Questionnaire		Daily through Week 20							X		
Health-related Quality of Life (HRQoL) EQ-5D-5L[13]		X	X[13]					X	X[13]		
Any visits to ER/urgent care or admission to hospital or skilled nursing facility since last study visit?			X	X	X	X	X	X	X	X	
Adverse Events[8]		X	X	X	X	X	X	X	X	X	
Mid-Turbinate Nasal Swab		X	X	X	X	X	X	X			
Nasopharyngeal Swab for Respiratory Pathogen PCR									X[14]		
Rapid Influenza Diagnostic Test (RIDT) (if clinically indicated)									X[15]		
Sputum Gram Stain and Culture (if clinically indicated)									X[16]		
Consent for Optional Blood Storage for Future Use and Consent for Optional Pharmacogenetic Analysis of Pharmacogenomics Blood Specimen (for consenting subjects only)		X									

	Screening	Baseline	Primary Analysis (and Study Drug Administration) Period						Clinically Symptomatic Respiratory Illness Visit (Unscheduled)	Short-term Follow-up Period	Long Term Follow-Up Period
Day/Week	**Day -28 to -1**	**Day 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**---**	**Week 20**	**Week 48**
Visit Window	**---**	**---**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±5 days**	**---**	**±5 days**	**±4 weeks**
Blood Collection for RNA Expression in Whole Blood and Soluble Biomarkers		X		X[17]				X			
PK Blood (Plasma) Collection				X[18a]		X[18b]	X[18a]				
Long Term Follow-Up Questions by Telephone[20]											X

HIV = human immunodeficiency virus; MMSE = mini mental state examination; PCR = polymerase chain reaction; PK = pharmacokinetics; PSD= Premature subject discontinuation from study; RNA = ribonucleic acid; ER = emergency room.

[1] Review of inclusion / exclusion criteria is required at the Baseline evaluation.

[2] Seated blood pressure and heart rate measurements are required for all visits.

[3] The physical exam at the Clinically Symptomatic Respiratory Illness Visit (Unscheduled) for respiratory illness symptoms will be targeted to what is clinically indicated based on the subject's symptoms.

[4] The ECG for study eligibility determination at Screening and Baseline should be done prior to collection of blood samples for other required study assessments.

[5] Chest x-ray (CXR) does not need to be obtained at Screening if the subject had a CXR performed within the 3 months prior to Screening and the results and the x-ray film or digital copy are available.

[6] All subjects will be screened for Hepatitis B surface antigen (HBsAg), Hepatitis C and HIV. Screening for Hepatitis C will be based on HCV antibodies and if positive, HCV RNA levels should be determined. Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory study site (e.g., Western blot) should be performed.

[7] Clinical Frailty Scale score should be entered into IXRS prior to assignment of randomization code.

[8] Subjects who prematurely discontinue study treatment due to an AE should return to the study site as soon as possible for an unscheduled visit to return all study drug for reconciliation and accountability, and to perform the following assessments: Vital signs, Complete Physical Exam, Hematology, Chemistry and Urinalysis. Subjects who discontinue due to a clinically symptomatic respiratory illness AE should also undergo respiratory illness assessments such as nasopharyngeal swab collection if not already done. Subjects who discontinue treatment for reasons other than an AE should return at the next scheduled visit at which time they will return all study drug for reconciliation and accountability at the next scheduled study visit.

[9] Study drug is dispensed at Day 0, Week 4, Week 8, and Week 12 (however, in the case of lost or damaged study drug, study drug can be dispensed at any study site visit). At Weeks 4, 8 and 12, subjects will return study drug and will be dispensed new bottles.

[10a] Subjects will not return or be dispensed new study drug at these visits. Subjects will just bring their supply of study drug to the study site for pill count for compliance and then will return home with the same supply of study drug.

[10b] At visit Week 16 or premature study discontinuation (PSD), all study drug will be returned, and the final study drug accountability will be performed. All subjects will self-administer study drug at home on the morning of their Week 16 visit.

[11] All subjects will be administered their first dose of study drug at the site at the Baseline Visit. Approximately 400 subjects (per IXRS randomization) will be required to undergo PK assessment in the study (~ 200 from each treatment arm). For subjects participating in the PK analysis for the study, at the Week 4 (or Week 6 if applicable) and Week 12 study visits, study drug should not be taken at home and instead study drug will be administered together with a light meal at the study site following the pre-dose PK draw. If PK sampling cannot be performed at the Week 4 visit for logistical reasons, it should be collected at the Week 6 visit instead, but according to the schedule described above for Week 4. This applies to timing of biomarker samples originally scheduled for Week 4 as well.

[12a] Subject will be given a personal tablet device containing the eDiary and instructions on use at this visit.

[12b] The personal tablet device containing the eDiary will be collected from the subject at this visit.

[13] Health Related Quality of Life (EQ-5D-5L) to be completed by all subjects at Baseline and Week 16, and each day that they report experiencing one or more respiratory illness symptoms through Week 20.

[14] Nasopharyngeal swabs for respiratory pathogen PCR is to be done during a scheduled or an unscheduled visit for all subjects who report at least one unique respiratory symptom (runny nose, sneezing, stuffy nose, sore throat, hoarseness, or cough) on 2 consecutive entries in their eDiary. The swabs should be obtained if they are able to within 48 hours of 2 consecutive eDiary entries of one or more unique respiratory symptoms. Subjects who record at least 1 respiratory symptom and at least 1 general (headache, feverishness/chills or loss of appetite) symptom , both of which are moderate or severe on two consecutive days in their eDiary, should be brought in within 24 hours of the second day of eDiary symptom entry. Subjects who are unable to come to the study site may also have the nasopharyngeal swab (and, if indicated, a sputum specimen and RIDT) obtained during a home visit by trained personnel. Only one nasopharyngeal swab should be obtained during each episode of respiratory illness. Nasopharyngeal swabs will be collected through Week 20, see the SOM for more details.

[15] Subjects who develop influenza-like illness symptoms should have a rapid influenza diagnostic test (RIDT) done. Subjects with a positive RIDT should receive anti-influenza treatment per local standard of care, unless contraindicated, and/or other appropriate medical care.

[16] Subjects who develop a productive cough that is new or a change from their normal baseline should have a sputum gram stain and culture sent for analysis.

[17] At the Week 4 (or Week 6 if applicable) visit, only subjects participating in the PK analysis will get blood samples drawn for biomarkers. In these subjects, biomarker samples should be obtained 4 hours post-dose (see SOM and Lab Manual for instructions). If PK sampling cannot be performed at the Week 4 visit for logistical reasons, it should be collected at the Week 6 visit instead, but according to the schedule described above for Week 4, and this applies to timing of biomarker samples originally scheduled for Week 4 as well.

[18a] At Weeks 4 (or Week 6 if applicable) and 12, subjects participating in the PK analysis will not take their study drug at home and instead will take their study drug at the study site.

[18b] Subjects participating in the PK analysis should have their Week 8 visit scheduled approximately 7 hours after they take their study medication at home.

[19] If clinically indicated, samples for Hematology, Chemistry and/or Urinalysis may be obtained at the Clinically Symptomatic Respiratory Illness Visit (Unscheduled).

[20] At Week 48, a long-term follow-up questionnaire will be administered by telephone to collect information regarding any hospitalizations, skilled nursing facility admissions and/or death since the Week 20 Visit.

[21] If serum cotinine testing is unavailable, urine cotinine may be assessed in lieu of serum cotinine.

6.1. Informed Consent Procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

resTORbio or designee will provide to Investigators a proposed informed consent form (ICF) that complies with the ICHE6 (R2) GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to this consent form suggested by the Investigator must be agreed to by resTORbio before submission to the IRB/IEC.

Information about known side effects can be found in the RTB101 IB. This information will be included in the informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated to Investigators as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent from and approval from an IRB/EC before being discussed with the subject and having the subject consent to the revised informed consent form.

Consent for Optional Blood Storage for Future use and Consent for Optional Pharmacogenetic Analysis will also be obtained at the Baseline Visit.

6.2. Subject Screening

It is permissible to re-screen a subject once if s/he fails the initial screening assessment(s).

Please reference IXRS guide for more information on screening and re-screening instructions.

6.2.1. Information to be Collected on Screen Failures

All subjects who have signed the ICF but who have screen failed must have the reason for the screen failure (notated by inclusion or exclusion criteria number(s) documented in the IXRS system).

6.3. Dietary, Fluid and Other Restrictions

During Screening/informed consent review, Baseline visit and subsequent study visits, the subjects will be informed and reminded of the following restrictions:

- No grapefruit or Seville oranges or their juices, should be consumed for 14 days prior to dosing until 7 days following the last dose. Any consumption of grapefruit or Seville orange or their juices during this period should be documented as a protocol deviation.
- Subjects must be instructed to take the daily dose of study drug with breakfast and should try to eat similar types of food at breakfast while taking study drug. Subjects who are participating in the PK assessments will be given their study drug together with a light meal provided at the site at the Week 4 Visit and at the Week 12 Visit. If PK sampling cannot be performed at the Week 4 visit for logistical reasons, it should be collected at the Week 6 visit instead, with the same timing of dose relative to a light meal provided at site.

6.4. **Subject Demographics/Other Baseline Characteristics**

Demographic and Baseline characteristics data to be collected on all subjects include: date of birth, age, sex, race, ethnicity, and relevant medical (including smoking) history/current medical (including cardiac) conditions present. Where possible, diagnoses and not symptoms must be recorded.

It is at the discretion of the Investigator if clinically significant test findings that occurred prior to subject randomization are recorded in the medical history CRF.

6.4.1. **Hepatitis and HIV Screening**

All subjects will be screened for HIV, Hepatitis B and C. See the SOM for details.

6.5. **Treatment Exposure and Compliance**

Compliance will be assessed by a dosing eDiary completed by the subjects daily at home (with the exception of the Baseline visit, when it will be completed at the site). In addition, compliance will be assessed at each visit by study personnel doing a pill count of remaining study drug brought by subjects to the site. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6. **Concurrent Medication**

For all medications (other than the study drug) initiated after the start of study, the reason for prescribing the medication, the start and, where applicable, end dates and change in medication dose should be recorded in the eCRF.

6.7. **Efficacy**

6.7.1. Clinically Symptomatic Respiratory Illnesses

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 whether a predefined set of respiratory illness symptoms have occurred during the past 24 hours that are new or reflect a change from normal baseline symptoms. 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).

A clinically symptomatic respiratory illness will be defined programmatically as the occurrence of 2 respiratory symptoms (runny nose/sneezing (programmatically considered one symptom), stuffy nose, sore throat, hoarseness, or cough) or 1 respiratory and 1 of the following general symptoms (headache, feverishness/chills or loss of appetite), with at least 1 unique respiratory symptom (runny nose, sneezing, stuffy nose, sore throat, hoarseness or cough) being reported on 2 or more consecutive entries in an eDiary, and at least 2 symptoms being at least moderate in severity. Subjects who have clinically symptomatic respiratory illness may include subjects with a common cold, bronchitis, influenza-like illness, or pneumonia.

Further details will be provided in the Statistical Analysis Plan (SAP).

6.7.2. Laboratory-Confirmed Clinically Symptomatic Respiratory Illness

When a subject reports symptoms of a respiratory illness in which at least one unique respiratory symptom (runny nose, sneezing, stuffy nose, sore throat, hoarseness, or cough) is reported on 2 consecutive entries in their eDiary, the sites will contact the subject and instruct the subject to come to the study site if they are able to within 48 hours for evaluation and to obtain a nasopharyngeal swab. Subjects should only have one nasopharyngeal swab obtained during each episode of a respiratory illness. Please refer to the SOM for more details. Laboratory confirmation of clinically symptomatic respiratory illness will be obtained using three methods:

- The FILMARRAY Respiratory panel polymerase chain reaction (PCR) Assay of nasopharyngeal swabs in all subjects
- Sputum gram stain and culture obtained in subjects with a productive cough that is new or a change from their normal baseline
- RIDT obtained in subjects with influenza-like illness symptoms (such as 1 or more respiratory symptom (cough, sore throat or nasal symptoms) and 1 or more constitutional symptom (such as body aches or feverishness/chills)).

Subjects who are unwilling or unable to come to the study site for an unscheduled visit should have the nasopharyngeal swab (and sputum specimen or RIDT , if indicated) obtained at a home visit by trained personnel. All subjects with influenza-like illness who have influenza detected by RIDT or nasopharyngeal swab PCR should receive anti-influenza treatment per local standard of care, unless contraindicated, and/or other appropriate medical care.

Study drug treatment can be continued in subjects who require antibiotics or anti-influenza treatment for treatment of an RTI.

Laboratory-confirmed clinically symptomatic respiratory illness will be defined programmatically as a symptomatic respiratory illness that meets the prespecified clinical diagnostic criteria outlined in Section 6.7.1 and is associated with a laboratory-confirmed pathogen detected by one or more of the 3 methods described above. Further details will be provided in the SAP.

6.7.3. Assessment of Severity and Duration of Clinically Symptomatic Respiratory Illness Symptoms

Subject will self-assess and report daily in their eDiary the occurrence and severity (absent, mild, moderate or severe) of the respiratory illness symptoms.

These data will be used to determine the time to alleviation of moderate and/or severe clinically symptomatic respiratory illness symptoms, and the percentage of subjects who experience severe symptoms due to clinically symptomatic respiratory illness. Further details are provided in the SAP.

6.7.4. Appropriateness of Efficacy Assessments

The primary and secondary efficacy assessments selected for this protocol are appropriate to measure the incidence, severity and duration of clinically symptomatic respiratory illness. Daily reporting of respiratory illness symptoms via an eDiary will help assure that clinically symptomatic respiratory illness events are rapidly captured during the trial. Obtaining laboratory confirmation if you are able to within 48 hours of symptom confirmation when viral detection is likely to be highest using a Food and Drug Administration (FDA)-approved PCR panel assay (FilmArray Respiratory Panel, 510(k) NO: K152579 [Dual track]) that detects 17 viral and 3 bacterial respiratory pathogens will also help increase rates of laboratory-confirmation of clinically symptomatic respiratory illness.

6.8. **Safety**

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Table of Assessments (Table 6-1) detailing when each assessment is to be performed.

6.8.1. **Medical History and Physical Examination**

A complete physical examination will be done at Screening and at Week 16 and Week 20. A targeted physical exam of at least lungs, heart, oral cavity, and skin will be done at all other scheduled visits. Subjects who come in to the study site for an unscheduled visit due to clinically symptomatic respiratory illness will also receive a targeted physical exam based on their presenting symptoms.

A complete medical history should be performed at the Screening visit. The medical history at the Baseline visit should include dates of the most recent administration of the pneumococcal and current seasonal influenza vaccinations. At all subsequent visits, a review of any new interval medical history (including, but not limited to review of any new cardiac symptoms) should be performed. See the SOM for details.

6.8.2. **Vital Signs**

The following vital signs will be collected with the subject in a seated position and recorded in the source notes and eCRF:

- Body temperature (oral or tympanic)
- Blood pressure (BP)
  - Orthostatic BP will be measured at the Baseline visit.
- Heart Rate
- Respiratory Rate

6.8.3. **Height and Weight**

- Height (cm)
- Body weight (kg)
- Body mass index (BMI) will be calculated by the electronic data capture (EDC) system as (Body weight (kg) / [Height (m)]^2).

6.8.4. **Electrocardiogram (ECG)**

ECGs will be collected in accordance with the schedule outlined in the Table of Assessments (Table 6-1). ECGs may be obtained at additional times when deemed clinically necessary.

ECGs must be reviewed by a qualified physician (the Investigator or qualified designee) at the study site. Subjects with acute ischemic changes and/or with a QTcF >480 msec on ECG at Screening or Baseline are excluded from study participation (see Section 4.2). In all cases, the Investigator must document in the source documents the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to be enrolled in the study.

Clinically significant ECG changes from Baseline occurring during the study must be evaluated for criteria defining an AE and reported as such if the criteria are met. Any QTcF >500 msec or >60 msec QTcF change from a subject's Baseline ECG, or any other clinically significant abnormal ECG change from Baseline should be reported as an AE. Appropriate follow-up medical care should be provided to all subjects who develop clinically significant ECG changes during the study.

6.8.5. **Laboratory Evaluations**

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at Screening, the assessment may be repeated once prior to randomization for the purpose of inclusion and to rule out laboratory error. If the repeat value remains outside of protocol-specified ranges at the Baseline visit, the subject is excluded from the study.

In the case where a laboratory range is not specified by the protocol but is outside the reference range for the laboratory at Screening, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization for the purpose of inclusion and to rule out laboratory error.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to be enrolled in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no

longer clinically relevant. In case of doubt, the Sponsor Medical Monitor or designee should be contacted.

6.8.5.1. Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.

6.8.5.2. Clinical Chemistry

Alkaline phosphatase, total bilirubin, bicarbonate/CO_2, cholesterol, chloride, glucose, potassium, AST, ALT, sodium, triglycerides, urea/blood urea nitrogen (BUN) and creatinine will be measured.

At Screening, any single parameter of ALT, AST, alkaline phosphatase, or serum bilirubin must not exceed 1.5 x ULN in subjects who do not have Gilbert's syndrome. If the subject has a history of Gilbert's syndrome, direct and indirect reacting bilirubin should be differentiated, and the direct bilirubin must be less than 1.5 x ULN.

At Screening, any elevation above ULN of more than one parameter of ALT, AST, alkaline phosphatase, or serum bilirubin will exclude a subject from participation in the study.

Any elevation of ALT, AST or total bilirubin >3 x ULN from the time of first dose of study drug should be reported as a severe (CTCAE Grade 3) AE.

6.8.6. Appropriateness of Safety Measurements

The safety assessments are appropriate for the subject population as well as for monitoring the known safety profile of mTOR inhibitors.

6.9. Pharmacokinetic (PK) Assessments (only for those subjects identified per IXRS randomization)

PK samples will be collected at the time-points defined in the Table of Assessments (Table 6-1). Follow instructions outlined in the SOM regarding sample collection, numbering, processing, and shipment.

Approximately 400 (as identified by the IXRS) subjects (200 in each treatment group) will undergo PK sampling at the timepoints described below:

Week 4 Visit or Week 6 (if applicable) (Subjects will be instructed not to take their morning dose at home that day.)

1. Pre-dose

   Study drug will be administered at the study site together with a light meal after the pre-dose blood sample is obtained.
2. 30 minutes post-dose (window: ± 10minutes)
3. 1.0 hours post-dose (window: ± 15 minutes)
4. 2.0 hours post-dose (window: ± 30 minutes)
5. 4.0 hours post-dose (window: ± 30 minutes)

   If PK sampling cannot be performed at the Week 4 visit for logistical reasons, it should be collected at the Week 6 visit instead, with the same timing of dose relative to a light meal provided at site.

Week 8 Visit (Subjects will be instructed to take their morning dose at home with breakfast, approximately 7 hours prior to their scheduled visit.)

1. 8.0 hours post-dose (window: ± 1 hour)

Week 12 Visit (Subjects will be instructed not to take their morning dose at home that day.)

1. Pre-dose

   Study drug will be administered at the study site together with a light meal after the pre-dose blood sample is obtained
2. 30 minutes post-dose (window: ± 10minutes)
3. 1.0 hours post-dose (window: ± 15 minutes)
4. 2.0 hours post-dose (window: ± 30 minutes)

6.9.1. **PK Analytical Methods**

RTB101 plasma concentrations will be determined by a LC-MS/MS method following protein precipitation. Plasma concentrations of RTB101 metabolites such as M29 and M41 may also be measured.

The analysis may be conducted with mixed-effects (population) methods. A dataset suitable for the analysis may be constructed using R (r-project.org, version 3.3.2 or later). The analysis may be conducted using the NONMEM system (Icon Development Solutions, Hanover, MD, version 7.3 or later) and PLT Tools (pltsoft.com; version 5.3.0 or later). One- and two-compartment

linear models with first-order absorption and first-order elimination may be evaluated initially. If diagnostic graphics suggest that these models are not appropriate, other models will be considered. A systemic search will then be applied to determine the impact of covariates such as age, body size, gender, race, organ function, clinical frailty score, diarrhea, and drug-drug interactions (including concomitant treatment with drugs that alter gastric pH such as proton pump inhibitors or gastroprokinetics such as domperidone) on the pharmacokinetic parameters, focusing on apparent clearance and absorption rate. Once a final model is determined, model validation will include some combination of visual predictive check (with and without prediction-correct), likelihood profiles, and bootstrap analyses.

6.10. Other Assessments

6.10.1. Subject-Reported Outcomes Assessments

Subject-Reported Study Drug Administration

Subjects will report the time of their daily study drug administration each day in an eDiary. This information will be used to assess treatment compliance together with pill count (per section 5.4). Further details are provided in the SAP.

Subject-Reported Health Outcomes/Quality of Life

The EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) will be administered at the Baseline Visit and the Week 16 Visit. In addition, subjects will be prompted in their eDiary to complete the EQ-5D-5L each day that they report experiencing one or more respiratory illness symptoms in their eDiary through Week 16.

EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (see Section 13.3 [Appendix 3]). The EQ-5D-5L questionnaire consists of 2 pages: the EQ-5D-5L descriptive system and the EQ visual analogue scale (VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which is divided into 5 levels. The EQ VAS records the patient's self-rated health on a 20-cm vertical visual analogue with "the best health you can imagine" as 100 and "the worst health you can imagine" as 0.

Further information is provided in the SOM and the SAP.

6.10.2. Health-Care Resource Utilization

Information about healthcare resource utilization will be obtained from subjects and from SAE reports. The following events occurring between the Baseline and Week 20 visits will be recorded in the eCRF:

- Hospitalizations
- ER visits
- Urgent care clinic visits
- Admissions to a skilled nursing facility

The following events occurring between the Week 20 and Week 48 visits will be recorded in the eCRF at the Long Term Follow Up visit:

- Hospitalizations
- Admissions to a skilled nursing facility
- Death

6.10.3. **Exploratory Biomarkers**

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 visits, and at the Week 4 (or Week 6 if applicable) visit (4 hours after study drug administration) only for subjects participating in the PK analysis (as identified by the IXRS). If biomarker and PK sampling cannot be performed at the Week 4 visit for logistical reasons, it should be performed at the Week 6 visit instead. Biomarkers studied may include, but are not limited to, ribonucleic acid (RNA) expression analysis in whole blood samples using RNA analytical technologies, such as expression microarrays, immunoassays or others, and serum protein expression analysis. 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.

A single blood sample will also be obtained from all subjects who provide consent at the Baseline Visit for the purposes of future pharmacogenomic analysis.

Follow instructions for sample collection, numbering, processing, and shipment provided in the SOM.

6.11. **Use of Residual Biological Samples**

Any samples remaining after protocol-defined analyses have been performed may be used for additional exploratory analyses, to be defined, if a subject signs the Consent for Optional Blood Storage for Future Use. This may include, but is not limited to, using samples for exploratory biomarker analyses or other bioanalytical purposes that have yet to be defined (e.g. cross check between different study sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

7. Safety Monitoring

7.1. Adverse Events (AEs)

An AE is defined as any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a study subject from the Baseline Visit until the end of study visit (Week 20 Visit). Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Pre-existing medical conditions/diseases are considered AEs if they worsen after the Baseline Visit.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are non-typical in subjects with underlying disease. Investigators, along with other study staff, have the responsibility for managing the safety of individual subjects and identifying AEs.

All AEs (except RTI AEs) must be recorded on the AE eCRF accompanied by the following information:

- The severity grade using the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute's CTCAE v5.0, available at https://evs.nci.nih.gov/ftp1/CTCAE/About.html. For terms not included, the severity of the AE should be based on the following general guidelines:
    - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2 Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
    - Grade 3 Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (i.e., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
    - Grade 4 Life-threatening consequences; urgent intervention indicated.
    - Grade 5 Death related to AE.

  NOTE:
    - Any elevation of ALT, AST or total bilirubin > 3x ULN from the time of first dose of study drug should be reported as a Grade 3 (severe) AE.
- Its relationship to the study treatment:
    - Related
    - Not related
- Its duration (start and end dates)
    - If the event is ongoing, an outcome of either not recovered/ not resolved or recovering/ resolving must be reported.
- Whether it constitutes an SAE (see Section 7.2 for definition of SAE) and which seriousness criteria have been met to define it as an SAE.
- Action taken regarding investigational treatment.

- Outcome (recovered/resolved, recovered/resolved with sequelae, not recovered/resolved, recovering/resolving, unknown, fatal).

Any beneficial therapeutic effects reported by subjects should also be recorded in the adverse events CRF.

All AEs (including diagnosed influenza) must be treated per local standard of care. Treatment/action taken may include one or more of the following:

- No action taken (e.g. further observation only)
- Investigational treatment interrupted/withdrawn
- Concomitant medication or non-drug therapy given
- Hospitalization/prolonged hospitalization (see Section 7.2 for definition of SAE)
- Study participation withdrawn

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

Any RTI that meets the definition of an SAE should be reported to resTORbio or designee as per Section 7.2.2 and documented on the AE eCRF.

Any deterioration of asthma symptoms that requires treatment with systemic steroids should be recorded as an asthma exacerbation on the AE eCRF.

7.2. Serious Adverse Event (SAE) Reporting

7.2.1. Definition of SAE

An SAE is defined as any AE (appearance of [or worsening of any pre-existing] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- Elective or pre-planned treatment for a pre-existing condition that has not worsened since the start of study drug treatment.
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
- Social reasons and respite care in the absence of any deterioration in the subject's general condition.

- Is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an ER or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (Annex IV, ICH-E2D Guideline).

Any suspected transmission of an infectious agent via a medicinal product is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF.

SAEs also require individual reporting to resTORbio or designee as per Section 7.2.2.

7.2.2. SAE Reporting

To ensure subject safety, every SAE, regardless of causality, occurring from the Baseline Visit to the Week 20 Visit (i.e., completion of the Short-term Follow-up Period) must be reported to resTORbio or designee within 24 hours of learning of its occurrence as described below. Any SAEs experienced after completion of the Short-term Follow-up Period of the study should only be reported to resTORbio or designee if the Investigator suspects a causal relationship to study treatment.

Information about all SAEs is collected and recorded on the SAE report form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess the relationship of each SAE to each specific component of study treatment, complete the SAE report form in English, and submit the completed form within 24-hours to resTORbio or designee. Detailed instructions regarding the submission process and requirements for signature are to be found in the SOM.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

An SAE considered completely unrelated to a previously reported SAE must be reported separately as a new event.

SAEs experienced by subjects must be followed until resolution or until judged to be permanent by the Investigator.

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs to resTORbio or designee.

7.3. **Pregnancy Reporting**

Should a female partner of a male subject become pregnant while the male subject is receiving study drug or within 7 days after the last dose of study drug, the pregnancy must be reported (see the SOM for further information).

If the female partner of the male subject consents, the Pregnancy Reporting Form/Exposure *in Utero* Form must be completed with all known information regarding the pregnancy at the time of reporting. Investigative site personnel will update the form with additional information regarding the pregnancy and the outcome of the pregnancy as it becomes available until the outcome of the pregnancy is reported. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death within 1 month of birth, or congenital anomaly [including that in an aborted fetus]), the Investigator will

follow the procedures for reporting a SAE within 24 hours of awareness, as described in Section 7.2.2 of the protocol. A pregnancy in and of itself is not considered an AE; however, unexpected complications are considered AEs. After delivery of the child, follow-up information on the health of the child will be collected for one year if an additional informed consent form is signed by a parent or legal guardian of the child.

8. Data Review and Database Management

8.1. Study Site Monitoring

During the study resTORbio or their representatives employ several methods of ensuring protocol and GCP compliance and the quality/integrity of the study sites' data. The study monitor will periodically visit the study site to check the completeness of subject records, the accuracy of entries on the CRFs (for, at minimum, critical variables related to primary and secondary endpoints and safety), the adherence to the protocol and to ICH GCP E6 (R2), the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits. Continuous remote monitoring of each study site's data may be performed by the Sponsor and/or representative to ensure that data in entered in a timely manner, prior to all on-study site visits and to address discrepancies that can be identified through remote monitoring.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or study site medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file unless the CRF is considered source. The Investigator must also keep the original informed consent form signed by the subject, document the process for obtaining informed consent and provide a signed copy to the subject.

The Investigator must give the study monitor access to all relevant source documents to confirm their consistency with the CRF entries. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

Study Record Retention

Essential documents should be retained for the period of time required by applicable local law. The essential documents include the signed and dated final protocol, signed and dated amendments(s), if applicable, signed and dated Curriculum Vitae (CVs) of the Investigators, copies of the completed CRFs, signed ICFs, IEC/IRB approval and all related correspondence, financial agreements, regulatory approval, drug accountability, study correspondence, and subject identification codes. Records will not be destroyed without informing resTORbio in writing and giving resTORbio the opportunity to store the records for a longer period of time at resTORbio's expense.

Documents not for submission to resTORbio (e.g. signed ICFs) should be maintained by the Investigator in strict confidence.

ICH GCP requires that study records be retained for at least 15 years after the completion or discontinuation of the study.

8.2. **Data Collection**

Designated Investigator staff will enter the data required by the protocol (as documented on the Delegation of Authority Log) into the CRFs using fully validated software that conforms to 21 CFR Part 11 requirements.

- Designated Investigator study site staff will not be given access to the EDC system until they have been trained.
- Automatic validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the contract research organization (CRO) working on behalf of resTORbio.
- The Investigator must certify that the data entered into the CRFs are complete and accurate.

The subjects will also be recording data directly into an eDiary and these data will serve as the source data. Data from the eDiary will be transferred electronically to the clinical database.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification and respects the confidentiality of study participants.

8.3. **Database Management and Quality Control**

A CRO working on behalf of resTORbio will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the study site personnel to make any required corrections or additions. Queries are sent to the investigational study site using an electronic data query. Designated Investigator study site staff are required to respond to the query and confirm or correct the data.

- Coding of medications, medical history and AEs:
    - Prior and/or concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

- Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples will be processed by a central certified laboratory, and the results will be sent to the Investigator, study site staff, and Sponsor or a designated CRO. In exceptional circumstances, when central laboratory testing is unavailable, testing of safety labs for hematology, chemistry and urinalysis may occur at a local laboratory with the Sponsors prior approval.

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an IXRS.

- The system will be supplied by a vendor, who will also manage the database.
- The database will be sent electronically to a designated CRO.
- Each occurrence of a code break via IXRS will be reported to the clinical team, study monitor and Sponsor Medical Monitor. The code break functionality will remain available until unblinding or upon request of the Sponsor.

The occurrence of any protocol deviations will be determined. Protocol deviations will be captured via observations by the CRO study monitor or site.

After these actions have been completed and the database has been declared to be complete and accurate, the database will be locked and final study data made available for analysis.

8.4. **Data Monitoring Committee**

A DMC has been established for the study with the primary goal to perform an ongoing review of safety data. The DMC is an external board comprised of physicians with specific knowledge of infectious diseases, geriatrics and issues related to conducting clinical studies.

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 related SAEs, and a monthly unblinded analysis 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.

Further details are provided in the DMC charter.

9. Data Analysis

9.1. Analysis sets

The analysis populations are specified in the table below. The final decision to exclude subjects from any analysis population will be made during a blinded data review meeting prior to database unblinding.

Analysis Set	Description
Screening (SCR)	All subjects, who provided informed consent, regardless of the subject's randomization and study treatment status in the study.
Randomized set (RS)	All randomised subjects treated or not.
Full Analysis Set (FAS)	All subjects in RS who received at least 1 dose of trial medication.
Per-Protocol (PP)	All FAS subjects who complete the 16-week treatment period, missed < 20% of doses, and had no major protocol deviations impacting efficacy data. Clinically important protocol deviations that would lead to a subject being excluded from the PP Analysis Set will be defined in the SAP. Subjects will be analyzed per the treatment group to which they were randomized.
Safety (SAF)	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 4 weeks after the end of the treatment period.

9.2. Subject Demographics and Other Baseline Characteristics

Demographic and background information will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Relevant medical history, current medical conditions, results of laboratory tests, and any other relevant information will be listed by treatment group and subject.

9.3. Treatments

There are two treatments arms: Arm 1: RTB101 10mg, Arm 2: Placebo.

9.4. Analysis of the Primary Variable

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

Analysis of the primary efficacy endpoint will be based on the intention-to-treat principle, comprising all subjects who are randomized and have received at least one dose of assigned treatment during the trial. Subjects who discontinue study prematurely due to a respiratory tract infection (RTI) adverse event (AE) or an RTI serious adverse event (SAE) and did not meet the definition of a CSRI will be imputed as having experienced a CSRI; 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 will be imputed as not having a CSRI; subjects who completed the study and did not meet the definition of a CSRI, but have intermittent missing eDiary data will be imputed as not having a CSRI. Details of handling missing data will be further discussed in the SAP. For efficacy, subjects will be analyzed in the treatment group for which they were randomized, whereas for safety, subjects will be analyzed based on the treatment they received.

9.4.1. Statistical Model, Hypothesis, and Method Analysis

This is a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of RTB101 10 mg to prevent clinically symptomatic respiratory illness in the elderly. All eligible subjects will be randomized in a 1:1 ratio at Baseline to receive either RTB101 10 mg or placebo.

The statistical model for the binary endpoint is logistic regression model.

Null hypothesis: The true underlying percentage of subjects with at least 1 clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen) by Week 16 is equal between RTB101 10 mg and placebo.

Alternate hypothesis: The true underlying percentage of subjects with at least 1 clinically symptomatic respiratory illness (with or without an associated laboratory-confirmed pathogen) is not equal between RTB101 10 mg and placebo.

The primary efficacy endpoint will be analyzed through a logistic regression model to obtain an estimate of the population odds ratio and associated CIs between RTB101 and placebo. This primary efficacy model will be adjusted for factors that may influence response to treatment for

clinically symptomatic respiratory illness, such as age, frailty score, receipt of current season influenza vaccination and medical history of asthma, CHF, or Type 2 diabetes mellitus.

In testing multiple hypotheses, control of the study-wise error rate will be implemented. As the number of statistical tests within a trial increases (multiplicity), the chance of making a false conclusion (false positive) about a drug's effect with respect to at least one of the endpoints increases, if multiplicity is not addressed. In this study, 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 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.

9.4.2. Handling of Missing Value/Censoring/Discontinuations

All efforts will be made to obtain the reason for missing data or discontinuation.

Of all randomized and treated subjects in the Phase 2b trial, the missing data rate in the assessment of the primary endpoint was 0.56% (1/179) and 6.8% (32/473) in the Southern and Northern Hemispheres, respectively. The combined missing data rate was 5.1%. It is expected that only a minimal amount of missing data will be present in the Phase 3 trial.

Further steps to reduce and address the occurrence and impact of missing data are planned. Subjects who discontinue treatment will be followed and assessed for the evaluation of the primary endpoint. To further explore the potential effect of missing data on the reliability of the primary efficacy results, and to investigate the response profile of dropout patterns, several sensitivity analyses including a tipping point analysis will be conducted (see Section 9.4.4). Further details to address missing data are described in Section 9.4.4 and will be provided in the SAP.

9.4.3. Summary Statistics of Safety

9.4.3.1. Vital Signs

Observed values at each visit and changes from Baseline to each post-baseline visit in vital signs (BP, heart rate, respiratory rate and temperature) will be summarized by time point and treatment group using descriptive statistics. Out-of-range values of vital signs will be tabulated as appropriate. All vital signs will be provided in subject data listings.

9.4.3.2. Electrocardiograms (ECGs)

Observed values at each visit and changes from Baseline to each post-baseline visit in ECG parameters will be summarized by time point and treatment group using descriptive statistics. All ECG parameters will also be provided in subject data listings, with values defined as clinically relevant highlighted.

9.4.3.3. Clinical Laboratory Evaluations

Laboratory data will be analyzed quantitatively and qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of subjects with abnormal values or clinically relevant abnormal values. Furthermore, laboratory data will be evaluated longitudinally; changes from baseline in laboratory parameters will be compared between RTB101 10 mg and placebo.

9.4.3.4. Adverse Events

All safety data will be displayed and analyzed using descriptive statistical methods. No formal inferential analysis is planned for safety comparison.

Frequency, intensity and causal relationship of AEs will be tabulated by system organ class after coding according to MedDRA. All AEs will be summarized by treatment group. The number and percentage of subjects who experienced at least 1 AE will be summarized by SOC and preferred term. The percentage will be based on the number of subjects in each treatment group. AEs will also be summarized by relationship to intervention and by severity within each treatment group. Deaths, SAEs, AEs leading to study drug discontinuation and AEs leading to study discontinuation will be tabulated and presented in data listings. Subject level data listings of all AEs will be presented. A subject with multiple AEs within a body system is only counted once towards the total of this body system.

9.4.4. Sensitivity Analyses

9.4.4.1. Primary endpoint

To provide evidence in support of the strength of treatment effect, several sensitivity analyses will be conducted.

A tipping point analysis for the primary efficacy endpoint will be conducted to investigate the impact of the missing data assumptions on the primary endpoint results, . Missing data from the placebo arm due to early treatment discontinuation 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, will be imputed with CSRI odds from the placebo group, adjusted for the duration of missing eDiary entries through Week 16 in the placebo arm. 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, will be

imputed 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 objective is to determine the maximum odds in the RTB101 arm that continue to yield statistically significant results compared to placebo. Further details on the above tipping point analysis and other sensitivity analyses are included in the SAP.

Supplemental analyses will also be conducted to further understand the impact of missing data on the primary efficacy endpoint results, specifically, the primary efficacy analysis will be conducted in 1) the Per Protocol analysis set, 2) 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) and 3) the subset of subjects who did not discontinue from the study prematurely (Completers Analysis 2).

Summary statistics 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.

Further details on handling missing data will be provided in the SAP.

9.4.4.2. **Subpopulations**

An evaluation of the primary and certain secondary endpoints may be conducted in some subpopulations. The following subpopulations may be explored, subjects who are at least 85 years old, subjects with asthma, the frail elderly, female subjects, subjects with CHF, and also subjects who have or have not received a pneumococcal or current season influenza vaccination.

Details will be provided in the SAP as appropriate.

9.5. **Analyses of Secondary Efficacy Variables**

The key secondary endpoint of “The rate of 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 will be evaluated from an estimation framework where the treatment effect and associated CIs are estimated, rather than a framework of multiplicity adjustments and statistical significance. This endpoint is not powered to demonstrate a pre-specified treatment effect. There will be no formal statistical tests of hypotheses and no p-values. 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 compared descriptively between RTB101 versus placebo.

For secondary endpoints (other than the key secondary endpoint) of a rate outcome (e.g., the rate of clinically symptomatic respiratory illnesses (with or without an associated laboratory-confirmed pathogen) by Week 16 and the rate of clinically symptomatic respiratory illness associated with ≥1 laboratory-confirmed pathogen(s) by Week 16), a negative binomial regression model will be used to obtain an estimate of the population rate ratio and associated CIs between RTB101 and placebo. The negative binomial model will be adjusted for factors/covariates consistent with the primary endpoint.

The secondary endpoints of (1) percentage of subjects with one or more clinically symptomatic respiratory illnesses associated with ≥1 laboratory-confirmed pathogen(s) by Week 16, and (2) percentage of subjects with severe symptoms due to clinically symptomatic respiratory illnesses through Week 16, will be analyzed using the same method as the primary efficacy endpoint.

Next, we demonstrate the evaluation of the secondary endpoint of time to alleviation of moderate and/or severe clinically symptomatic respiratory illness symptoms through Week 16. The point estimate of the hazard ratios and the associated 95% CIs for RTB101 versus placebo will be obtained using the Cox proportional hazards regression model with fixed effects for treatment group and covariates consistent with the primary endpoint. An approximate Chi-square test based on Wald statistic will be used to compare treatment groups. Survival curves (Kaplan-Meier estimates) for the “time to alleviation” (i.e., proportion with no alleviation) may be presented by treatment group.

Exploratory efficacy endpoints will be evaluated in a similar fashion as the primary or secondary endpoints, the same set of covariates as for the primary analysis model will be included in each model. Specifically, exploratory endpoints with a binary outcome will be analyzed using the same methods as the primary endpoint. Time-to-event exploratory endpoints will be evaluated using the Cox proportional hazard model, continuous exploratory endpoints may be analyzed using an Analysis of Covariance (ANCOVA) model, or by a mixed model repeated measures model (MMRM).

Exploratory endpoints will be summarized descriptively, as appropriate, continuous endpoints will be summarized with the use of box plots, while proportions will be displayed by histograms. In addition, changes in biomarker levels over time will be described by treatment group. The details of these analyses will be included in the SAP.

9.6. **Sample Size Calculation**

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 of 19.7% in the RTB101 arm, a total sample size of 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. Approximately 1066 subjects will be enrolled. Power analysis was conducted using Likelihood Ratio Chi-square Test.

9.7. **Interim Analyses**

There is no planned interim analysis.

10. Ethical Considerations

10.1. Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, U.S. CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2. Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment materials (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to resTORbio or designee monitors, auditors, Quality Assurance representatives, designated agents of resTORbio, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical study site is requested by a regulatory authority, the Investigator must inform resTORbio or designee immediately that this request has been made.

10.3. Publication of Study Protocol and Results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov or wherever applicable. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results. Upon study completion and finalization of the study report the results of this trial may be submitted for publication (e.g., peer-reviewed journal).

10.4. Quality Control and Quality Assurance

resTORbio maintains a Quality Management system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during

the review of incidents, audits and inspections. Audits of Investigator study sites, vendors, and resTORbio systems may be performed independently from those involved in conducting, monitoring or performing quality control of the clinical study. Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operation procedures.

11. Protocol Adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study subjects. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators certify that they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by resTORbio and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1. Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by resTORbio, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 must be followed.

11.2. Financial Disclosure Reporting Obligations

Each Investigator (including principal and any sub-Investigators and any other study personnel) directly involved in the treatment or evaluation of study subjects is required to provide financial disclosure information according to all applicable legal requirements. In addition, Investigators

must commit to promptly updating this information if any relevant changes occur during the study and for a period of one year after the completion of the study.

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13. Appendices

13.1. Appendix 1: List of Drugs that are CYP450 Inhibitors or Inducers to be used with Care or Prohibited with RTB101 Treatment and Narrow Therapeutic Index P-gp Substrate that is Prohibited with RTB101

Table 13-1 Strong CYP4503A4 Inhibitors (prohibited)

Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole
Moderate inhibitors (use with caution)
Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, crizotinib, darunavir, diltiazem, elvitegravir, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, *Schisandra* sphenanthera, tipranavir, tofisopam, verapamil

Table 13-2 Strong CYP4503A4 Inducers (prohibited)

Avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort, troglitazone
Moderate Inducers (use with caution)
Bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir, talviraline, tipranavir, pioglitazone

Table 13-3 Strong CYP4501A2 Inhibitors (prohibited)

Ciprofloxacin, enoxacin, fluvoxamine(a), zafirlukast

Table 13-4 Strong CYP4501A2 Inducers (prohibited)

Rifampin

Table 13-5 Narrow Therapeutic Index P-gp Substrates (prohibited, example below)

Digoxin

13.2. Appendix 2: Algorithm for Management of Pneumonitis

To be applied only if:

1. radiological findings of newly-occurring/worsening lung infiltration
2. absence of infectious or malignant etiology (based on diagnostic procedure such as bronchoscopy &/or trial of anti-infectious treatment, as appropriate)

CTC Grade	Investigations	Additional Measures
1	CT scan w/ lung windows PFTs	Discontinue study drug
2 and 3	Lung monitoring CT scan (if only chest X-ray carried out) Involve pulmonologist (consider bronchoscopy) PFTs	Discontinue study drug bronchoscopy if indicated (to exclude infection or malignancy) short course of steroids to be considered if symptoms important or persisting beyond I month lung monitoring for 2 months then return to initial monitoring frequency if no recurrence. continue monthly lung monitoring until return to grade ≤1 or stabilization
4	Lung monitoring CT scan (if only chest X-ray carried out) Involve pulmonologist (consider bronchoscopy) Repeat PFTs, if possible	Discontinue study drug bronchoscopy with BAL, if possible steroids and other support as necessary continue monthly lung monitoring until return to grade ≤1 or stabilization

Notes:

PFT (Pulmonary function tests) to include: diffusing capacity corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation.

Guideline for significant deterioration in lung function from baseline: Decrease in Spirometry and/or DLCO of 30% and/or O_2 saturation ≤88% at rest on room air.

Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end.

If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible.

13.3. Appendix 3: EQ-5D-L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

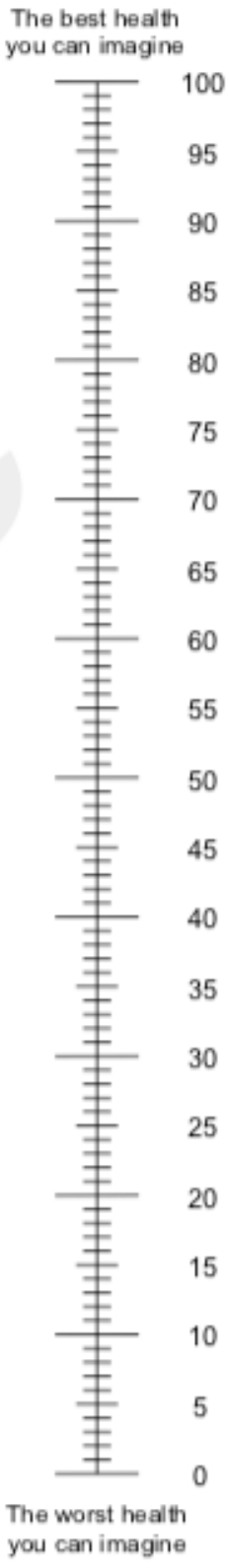
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



13.4. Appendix 4: Clinical Frailty Scale

1 *Very fit* — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age

2 *Well* — without active disease, but less fit than people in category 1

3 *Well, with treated comorbid disease* — disease symptoms are well controlled compared with those in category 4

4 *Apparently vulnerable* — although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms

5 *Mildly frail* — with limited dependence on others for instrumental activities of daily living

6 *Moderately frail* — help is needed with both instrumental and non-instrumental activities of daily living

7 *Severely frail* — completely dependent on others for the activities of daily living, or terminally ill

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