NCT #: NCT04110054

Study Protocol: 1812VA323

Study Title:	A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-selection study of S-600918 in patients with refractory chronic cough
Study Number:	1812VA323
EudraCT No:	2019-002283-27
IND No.:	144078
Study Phase:	2b
Product Code Number:	S-600918
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Protocol Version	**Issue Date:**
Version 1 (Original):	04 Sep 2019
Version 2:	07 Nov 2019
Version 3:	10 Sep 2020

* The study sponsor may be one or more of the above companies. Throughout the protocol, the term “sponsor” represents the various legal entities identified as “Sponsor” in the Study Administrative Structure in the protocol. The above companies are referred to as Shionogi.

Confidentiality Statement

SYNOPSIS

Study Title:

A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-selection study of S-600918 in patients with refractory chronic cough

Study Number: 1812VA323

Study Phase: 2b

Primary Objective: To determine the optimal dose of S-600918 in patients with refractory chronic cough by evaluating the change from baseline in 24-hour cough frequency (coughs per hour) with S-600918 compared with placebo

Secondary Objectives:

- To compare the efficacy of S-600918 to that of placebo in patients with refractory chronic cough based on the following measurements:
  - Number of coughs per hour while awake
  - Number of coughs per hour while asleep
  - Severity of cough as assessed on the Visual Analog Scale (VAS)
  - Leicester Cough Questionnaire (LCQ)
  - International Consultation on Incontinence Modular Questionnaire-Short Form (ICIQ-SF)
  - Short-Form (36) Health Survey (SF-36), version 2
  - Patient Global Impression of Change (PGIC)
- To evaluate the safety of S-600918 in patients with refractory chronic cough.
- To assess the pharmacokinetics (PK) of S-600918 and its metabolite (S-600918 acyl glucuronide) in patients with refractory chronic cough.

Study Design:

This study will be conducted as a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. A total of approximately 372 patients with refractory chronic cough are planned to be treated in Japan, Europe, and the United States.

This study will include 3 periods: a screening period, a treatment period, and a follow-up period. After obtaining informed consent, patients who meet screening criteria at Visit 1 will be enrolled in the study, and a cough monitor will be applied to each patient. Patients will be instructed to remove the cough monitor after 24 hours and to return the cough monitor to the study site within 2 days after completing the cough monitor recording. At least 17 days after Visit 1, patients will return for Visit 2, at which time screening will continue and a cough monitor again will be applied to each patient for 24 hours. Patients will return 1 day later for Visit 3. Patients who continue to meet screening criteria at Visit 3 will be randomized in a 1:1:1:1 ratio (93 patients per treatment group) to study treatment with S-600918 50 mg, S-600918 150 mg, S-600918 300 mg, or placebo. Randomization will be stratified by region (Japan, Europe, or the United States) and hourly cough count based on the 24-hour cough

count recording at Visit 1 (≥30 coughs/hour or <30 coughs/hour) and will be performed by Interactive Response Technology (IRT). Following randomization, patients will take the first dose of study drug while at the study site. Study drug will be taken orally once daily for 28 days. Patients will be followed for 14 days after the last dose of study drug.

Study Population:

Patients with refractory chronic cough

Criteria for Inclusion and Exclusion:

Inclusion Criteria

Patients who meet the following criteria at the specified visit(s) will be included in the study provided no exclusion criterion is met:

Inclusion Criteria	Visit 1	Visit 2	Visit 3
1. Willing to comply with all study procedures.	√	√	
2. Capable of giving signed informed consent. (Informed consent will be obtained in accordance with local requirements.)	√		
3. Male or female outpatient ≥18 to ≤80 years of age at the time of signing the informed consent form.	√		
4. Has refractory chronic cough lasting for at least 1 year prior to Visit 1, defined as: • insufficient improvement in cough after treatment for the underlying condition(s) causing the cough *OR* • unexplained cough for which an underlying condition has not been determined.	√		
5. With severity of cough assessed as ≥40 mm on the Visual Analog Scale (VAS) at both Visit 1 and Visit 2.	√	√	
6. With cough count ≥10 times per hour based on the 24-hour cough count recording at Visit 1. (Results will be available by Visit 2; no calculation is necessary.)		√	
7. If female, agreement to use one of the following contraceptive methods from screening until 14 days after the last dose of study drug UNLESS the patient is surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation with appropriate documentation of such surgery or postmenopausal (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age):	√		

• Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action), male or female condom with or without spermicide, cap, diaphragm, or sponge with spermicide. The contraceptive methods listed above are the minimum required per protocol. Other accepted methods include combination estrogen- and progesterone-containing contraceptives, implanted devices (such as intrauterine devices [IUDs]), and injectable contraceptives.			

Exclusion Criteria

Patients who meet any of the following criteria at the specified visit(s) will be excluded from the study:

Exclusion Criteria	Visit 1	Visit 2	Visit 3
1. Missing an entry in patient electronic diary (eDiary) for the number of coughs on more than 30% of the days from day of Visit 1 up to day of Visit 2. (Entries will be assessed at Visit 2.)		√	
2. Failure to obtain the cough count recording on the cough monitor at Visit 1 or Visit 2 for any reason, including device malfunction, based on initial assessment at study site. • Assessment for Visit 1 will be completed prior to Visit 2. If recording at Visit 1 is assessed as failed, the recording may be repeated (see Section 8.1 for details). • Assessment for Visit 2 will be completed at Visit 3. If recording at Visit 2 is assessed as failed, the recording may be repeated (see Section 8.3 for details).	√		√
3. Currently smokes (including, but not limited to e-cigarettes, smokeless cigarettes, and vaping) or uses any inhalational agents (including, but not limited to marijuana) that are potential irritants or has smoked or used any inhalational agents that are potential irritants in the 1 year prior to Visit 1 or has a smoking history of ≥20 pack-years (Pack years = [Number of cigarettes per day/20] × (Number of years of smoking]).	√		

4. Produces a significant amount of sputum suggestive of infection, bronchiectasis, chronic bronchitis, etc.	√	√	√
5. In the 4 weeks prior to Visit 1 or during screening, history of infection in the upper or lower respiratory tract or a significant change in lung function or a pulmonary condition based on the judgment of the investigator.	√	√	√
6. Has chronic obstructive pulmonary disease (COPD) or, as defined in the Global Initiative for Asthma (GINA) 2019, has uncontrolled asthma symptoms (excluding cough) [a].	√		
7. Has a clinically unstable medical condition, including cardiac disease (eg, atrial fibrillation, symptomatic bradycardia, and active myocardial ischemia), hypertension, respiratory disease, biliary tract disease, hypothyroidism, renal disease, adrenocortical insufficiency, or any other medical condition that, in the opinion of the investigator, will interfere with study participation or assessment of efficacy and safety.	√	√	
8. Has history of malignancy ≤5 years prior to Visit 1 (unless nonmelanoma skin cancer).	√		
9. Has history of or current bipolar disorder, schizoaffective disorder, schizophrenia, or major depressive disorder [b], or, based on the judgment of the investigator, has other psychiatric symptoms that may interfere with study procedures.	√		
10. Has history of severe drug allergy (shock, anaphylaxis, or angioedema).	√		
11. Has history of alcohol or drug abuse in the 1 year prior to Visit 1 or uses any form of marijuana or illicit drugs.	√		
12. With alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 times the upper limit of the normal reference range (× ULN) or total bilirubin >1.5 × ULN. (ULN is as determined by the central laboratory. Results will be available by Visit 2.)		√	
13. With serum creatinine >1.5 × ULN. (ULN is as determined by the central laboratory. Results will be available by Visit 2.)		√	

14. With positive serological test for human immunodeficiency virus (HIV) antigen or antibody. (Results will be available by Visit 2.)		√	
15. With positive serological test for hepatitis B virus surface antigen. (Results will be available by Visit 2.)		√	
16. With positive serological test for hepatitis C virus RNA. (This test is required only if patient has positive serological test for hepatitis C virus antibody. Results will be available by Visit 2.)		√	
17. With systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg.	√	√	√
18. With clinically significant abnormal electrocardiogram (ECG) based on the judgment of the investigator.	√	√	
19. With a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than 60% at Visit 1. **COVID-19–related Measure:** With a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than 60% based on spirometry conducted anytime in the prior calendar year [c].	√		
20. With any finding on a chest x-ray or chest computed tomography (CT) scan (performed not more than 1 year [12 months] prior to Visit 1 after onset of chronic cough at Visit 1) that could be considered the cause of chronic cough or indicative of lung disease. (If a chest x-ray or chest CT scan needs to be performed, results will be available by Visit 2.) (Note: Patients with abnormal chest image findings not considered to be the cause of chronic cough are eligible to participate.)	√	√	
21. Previously received S-600918.	√		
22. Treated with a biological drug for asthma in the 3 months prior to Visit 1 or previously received bronchial thermoplasty.	√		

23. Treated with an angiotensin-converting-enzyme (ACE) inhibitor in the 3 months prior to Visit 1, being treated with an ACE inhibitor at Visit 1, or planned to be treated with an ACE inhibitor at any time from Visit 1 to the end-of-study (EOS) assessments at Visit 7.	√	√	√
24. Received an investigational drug in the 3 months prior to Visit 1 or planned to receive another investigational drug at any time from Visit 1 to the EOS assessments at Visit 7.	√	√	√
25. Being treated with the following therapy at Visit 1 or planned to be treated with the following therapy at any time from Visit 1 to the EOS assessments at Visit 7: • Pregabalin, gabapentin, and tricyclic antidepressants • Biological products for asthma treatment (eg, omalizumab) • Baclofen • Sitagliptin • P-glycoprotein (P-gp) inhibitors (specifically, cyclosporine, erythromycin, itraconazole, and ketoconazole [This criterion does not apply to topical formulations of these drugs, if any.]) • Breast cancer resistance protein (BCRP) inhibitors (specifically, cyclosporine [This criterion does not apply to topical formulations of this drug, if any.]) • Organic anion transporting polypeptide (OATP)1B1/1B3 inhibitors (specifically, cyclosporine and gemfibrozil [This criterion does not apply to topical formulations of these drugs, if any.]) • Digoxin or methyldigoxin	√	√	√
26. Refusal to discontinue the following therapy at Visit 1 to the EOS assessments at Visit 7: • Drugs with an antitussive action alone or in combination with other drugs • Herbal medicines with an antitussive action • First-generation (sedating) antihistamines (other than topical products)	√	√	√

• Non-drug therapies for cough relief, including cough suppressant speech therapy
• UNLESS used as specified under "Restricted Therapy" (Section 6.2.2):
  • Sleep-inducing drugs
  • Drugs with an expectorant action
  • Steroids (other than nasally administered steroids and other topically administered steroids)
  • Drugs having an effect on gastrointestinal (GI) motility or GI acid reflux, including proton pump inhibitors, prokinetic drugs, and histamine H_2 receptor antagonists
  • Anti-allergics (other than first-generation antihistamines and topical products) (histamine H_1 receptor antagonists, leukotriene receptor antagonists, thromboxane A2 synthase inhibitors, thromboxane receptor antagonists, Th_2 cytokine blockers, mediator release inhibitors)
  • Long-acting beta agonists, long-acting muscarinic antagonists, short-acting muscarinic antagonists, and bronchodilators other than short-acting beta-2 agonists (eg, methylxanthines and phosphodiesterase [PDE] inhibitors, etc.)
  • Macrolide antibiotics (other than erythromycin)
  • Oral anticholinergics
  • Immunotherapy for allergic disease			

27. If female, pregnant or trying to become pregnant or lactating.	√	√	√
28. Considered ineligible to participate in the study for any other reason, based on the investigator's judgment.	√	√	√

[a] As guidance regarding uncontrolled asthma symptoms, in the 2 to 3 months prior to Visit 1, an increase or decrease in the dose of an asthma controller drug AND, in the 4 weeks prior to Visit 1, at least 3 of the following: daytime symptoms of asthma more than twice per week, any night waking due to asthma, any activity limitation due to asthma, or use of asthma reliever more than twice per week.

[b] History of major depressive disorder is exclusionary only if there was a formal psychiatric diagnosis of major depressive disorder and the patient received antidepressant treatment. A vague history of having been depressed in the past is not exclusionary.

[c] If there are no spirometry data in the prior calendar year, spirometry is required at Visit 1. Assess whether the possible benefit from participating in the study will outweigh the risk of conducting spirometry. If the benefit-risk assessment is positive, perform spirometry in accordance with local guideline(s). If the benefit-risk assessment is negative, stop screening that patient.

Study Drug, Dose, and Mode of Administration:

Test Drug - S-600918 50-mg tablets administered orally once daily at a dose of 50 mg, 150 mg, or 300 mg.

Control Drug - Placebo matching S-600918 50-mg tablets administered orally once daily.

Timing of Study Drug Administration and Cough Monitoring:

Patients will take study drug orally once daily (preferably in the morning) with or without food on all treatment days except on the day of Visit 4.

For the day of Visit 4, patients will be instructed to come to the study site in the morning without taking the study drug that day. After patient completion of specified questionnaires and instruments on the electronic tablet, a blood sample will be collected for PK analysis and then the patient will take that day's dose of study drug.

The 24-hour cough monitor recording at Visit 4, Visit 5, and Visit 6 will be started within ± 3 hours from the start time of the cough monitor recording at baseline (Visit 2).

Duration of Treatment:

28 days

Concomitant Therapy:

Enrollment of patients being treated with or planned to be treated with specific therapy at any time at Visit 1 to the EOS assessments at Visit 7, as detailed in Exclusion Criteria #23, 24, and 25 is not permitted. Enrollment of patients who refuse to discontinue specific therapy at Visit 1 to the EOS assessments at Visit 7, as detailed in Exclusion Criterion #26, is not permitted.

The on-demand use of short-acting beta-2 agonists (SABAs) is discouraged during each of the 24-hour periods while patients are wearing a cough monitor. All patients must be specifically asked about the use of SABAs at Visit 1 and while wearing the cough monitor when reviewing prior and concomitant therapies (as applicable) at Visit 2, Visit 3, Visit 5, Visit 6, Visit 7, and/or, if applicable, the Early Discontinuation Visit.

Efficacy Assessments:

Efficacy will be assessed based on cough monitor recordings of cough counts and questionnaires or instruments used in studies in this patient population, including the

VAS to assess severity of cough, LCQ, ICIQ-SF, SF-36, and PGIC. The patient will complete the questionnaires and instruments using an electronic tablet and an eDiary.

Pharmacokinetic Assessments:

Plasma concentrations of S-600918 and its metabolite (S-600918 acyl glucuronide) will be determined.

Safety Assessments:

- Adverse events
- Physical examinations
- Clinical laboratory tests
- Blood pressure and pulse rate
- ECGs

Statistical Methods:

Efficacy Analyses

The primary endpoint is the ratio of the number of coughs per hour in 24 hours (based on cough counts recorded by the cough monitor) after administration of study drug for 4 weeks to that at baseline (Visit 2). A mixed effect model will be applied to the common logarithm of the ratio of the number of coughs per hour in 24 hours at Visit 4, Visit 5, and Visit 6 to that at baseline as response. This model will contain treatment group, week, and the interaction between treatment group and week as fixed effect; patient as random effect; and region and the common logarithm of the frequency of coughs per hour in 24 hours at baseline as covariates. The covariance structure will be determined to be unstructured. The dose-response relationship will be evaluated by a comparison of each dose level of S-600918 to placebo.

Secondary endpoints include a reduction from baseline in the number of coughs per hour in 24 hours by ≥30%, ≥50%, and ≥70%; the ratio of the number of coughs per hour while awake after administration of study drug for 4 weeks to that at baseline and a reduction by ≥30%, ≥50%, and ≥70%; the ratio of the number of coughs per hour while asleep after administration of study drug for 4 weeks to that at baseline; the change from baseline in weekly cough severity as assessed on the VAS (electronic tablet); the change from baseline in daily cough severity as assessed on the VAS through Day 7 (eDiary); the change in LCQ and achievement of an increase (ie, improvement) of ≥1.3 points; the change in ICIQ-SF; the change in SF-36; and the PGIC.

The proportion of patients who achieved a reduction from baseline in the number of coughs per hour in 24 hours by ≥30%, ≥50%, and ≥70% after administration of study drug for 4 weeks will be compared between each dose level of S-600918 and placebo by applying the Cochran-Mantel-Haenszel test with strata by region (Japan, Europe, or the United States) and cough count at baseline (≥30 coughs/hour or <30 coughs/hour).

An analysis method similar to that used to determine the ratio of the number of coughs per hour in 24 hours will be applied to the ratio of the number of coughs per hour while awake to that at baseline; change in weekly cough severity as assessed on the VAS (electronic tablet); change in daily cough severity as assessed on the VAS through

Day 7 (eDiary); change in LCQ; change in ICIQ-SF; and change in SF-36. Also, for the number of coughs per hour while awake, the cough severity as assessed on the VAS, and the LCQ, the proportion of patients who achieved a certain level of reduction will be analyzed using the same analysis method applied to the number of coughs per hour in 24 hours. The van Elteren test with strata by region (Japan, Europe, or the United States) and cough count at baseline (≥30 coughs/hour or <30 coughs/hour) will be applied to compare the assessments of PGIC at each dose level of S-600918 to placebo.

Safety Analyses

The number and percentage of patients with treatment-emergent adverse events (TEAEs) will be summarized overall and by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for all TEAEs and those considered to be related to treatment for each treatment group. Summary statistics for laboratory tests, blood pressure, and pulse rate at each planned observation point and the change from baseline at each planned observation point will be calculated by treatment group. A categorical analysis of qualitative laboratory test values (urinalysis) and qualitative ECG values at each planned observation point will be performed by treatment group.

Study Duration:

The study duration for each patient is approximately 8 to 10 weeks (screening, 18 to 28 days; treatment, 28 days; and follow-up, 14 days).

Date of Original: 04 Sep 2019

Date of Latest Amendment: 10 Sep 2020

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LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	angiotensin-converting-enzyme
AF-219	the $P2X_3$ receptor antagonist gefapixant; also referred to as MK-7264
AF-353	a selective $P2X_3$ receptor antagonist
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BMI	body mass index
C_{max}	maximum plasma drug concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CT	computed tomography (scan)
C_{trough}	trough plasma concentration; the plasma concentration of an analyte measured just prior to administration of the next dose
CV%	coefficient of variation
eCCG	electronic CRF Completion Guidelines (manual)
EDC	electronic data capture (system)
ECG	electrocardiogram, electrocardiograph
eCRF	electronic case report form
eDiary	patient electronic diary
eg	for example
ERT	eResearchTechnology, Inc.
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
GINA	Global Initiative for Asthma
GGT	gamma glutamyl transferase
GMP	Good Manufacturing Practice
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICIQ-SF	International Consultation on Incontinence Modular Questionnaire-Short Form
ID	identification (number)
ie	that is
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
LCQ	Leicester Cough Questionnaire
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MK-7264	the $P2X_3$ receptor antagonist gefapixant; also referred to as AF-219
NASH	nonalcoholic steatohepatitis
OATP	organic anion transporting polypeptide
OTC	over-the-counter
P2X	a subclass of purinoceptor
$P2X_2$, $P2X_3$	subtypes of the P2X purinoceptor
PDE	phosphodiesterase (inhibitor)
PGIC	Patient Global Impression of Change
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PPS	per protocol set
PT	prothrombin time
QOL	quality of life
S-600918	a selective $P2X_3$ receptor antagonist
SABA(s)	short-acting beta-2 agonist(s)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36	Short Form (36) Health Survey
SMQ	Standardized MedDRA Query
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNP-ATP	a P2X receptor antagonist

VAS	Visual Analog Scale
vs	versus
WHO	World Health Organization
× ULN	times the upper limit of the normal reference range

COVID-19 PANDEMIC

The first patient was screened in Study 1812VA323 on 26 Jan 2020, and the first patient was randomized in the study on 13 Feb 2020 prior to the declaration of the COVID-19 pandemic. Since then, various COVID-19–related restrictions have been imposed at some study sites by site administration, Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and/or local or national health authorities. In addition, the investigator and staff at some study sites have faced challenges in managing randomized patients who had not yet completed the study when COVID-19–related issues emerged.

Protocol Version 3:

- describes measures that may be implemented in the event of the emergence of COVID-19–related issues at a study site at which patients are currently being screened, or at which patients are currently randomized, but have not yet completed treatment. All such information appears in the protocol as boxed text and is identified as a "**COVID-19–related Measure.**"
- maintains the content of protocol Version 2 so that the investigator and study-site staff have 1 integrated protocol to refer to in the conduct of this study both during and after the COVID-19 pandemic.
- addresses minor revisions to protocol Version 2.

All changes in protocol Version 3 are identified in the tabular summary of changes.

Sponsor's Policy Regarding the COVID-19 Pandemic

The sponsor is committed to maintaining the safety and well-being of patients enrolled, investigators, and study-site staff, and contract research organizations and other vendors and their employees during the COVID-19 pandemic.

The sponsor has specifically considered whether the protection of the patient's safety, welfare, and rights is best served by continuing screening and randomization in this study. Accordingly, if based on the sponsor's or investigator's assessment of the local situation, patient safety and continuity of study visits cannot be ensured due to COVID-19–related issues, the investigator:

- is not permitted to initiate screening of any patients at a study site.
- is not permitted to randomize patients who are currently in screening.

As information regarding the COVID-19 pandemic may change rapidly, frequent assessment of the local situation by the investigator is necessary.

Purpose of Protocol Version 3

Protocol Version 3 describes COVID-19–related measures that may be implemented to ensure that the investigator and study-site staff can appropriately manage the patient through study completion if COVID-19–related issues arise during patient screening or

following randomization. Among the COVID-19–related measures, the following key measures are addressed:

- Modification of the requirement for spirometry at Visit 1 (see Section 4.3 [Exclusion Criteria]).
- Reconsenting the patient or obtaining additional consent if a patient requires home nursing service or drug delivery service (see Section 7.1 [Informed Consent]).
- Dispensing the remaining 3 weeks of treatment to the patient at Visit 4 (see Section 7.2 [Patient Registration and Randomization and Dispensing of Study Drug]).
- Use of a courier service if locally available and if approved for use to deliver study drug from the study site for all remaining weeks of treatment to the patient at home at Visit 4 or Visit 5 (see Section 7.2 [Patient Registration and Randomization and Dispensing of Study Drug]).
- Use of a visiting nurse service if locally available and if approved for use at Visit 4, Visit 5, Visit 6, and Visit 7 and/or the Early Discontinuation Visit (see Section 8 [Study Activities], Section 8.4 [Visit 4], Section 8.5 [Visit 5], Section 8.6 [Visit 6], Section 8.7 [Visit 7], and Section 8.8 [Early Discontinuation Visit]).

Note that the investigator may need to take measures beyond those detailed in this protocol to ensure proper patient management and care during the COVID-19 pandemic. The investigator is advised to frequently reassess the benefit and the risk of continued participation of patients in this study and to contact the Medical Monitor to discuss emerging concerns or issues.

1. INTRODUCTION

1.1 Disease Concept and Treatments

Cough is a biological defense mechanism that eliminates sputum and foreign bodies from the airways. Chronic cough is defined as cough that persists for ≥8 weeks [1,2,3], and may result in reduced quality of life (QOL). Refractory chronic cough is defined as chronic cough after the patient is treated for an identified underlying medical condition, as well as chronic cough for which an underlying medical condition has not been identified despite appropriate patient evaluation [4,5,6]. The prevalence of chronic cough is estimated to be between 11% and 13% of the worldwide population [7,8]. Nearly 40% of patients with chronic cough do not experience definitive improvement of cough despite identification of the underlying cause [9,10]. Among patients with chronic cough, the percentage of patients with refractory chronic cough ranges from 20% to 40% in Europe and the United States and is not significantly different among patients in Europe, the United States, or Japan [3,6,9,10,11].

Currently no drugs are approved for the treatment of patients with refractory chronic cough. In the absence of identifying and successfully treating the patient for underlying medical condition(s), nonspecific antitussive drugs (eg, codeine, dextromethorphan) often are used to provide symptomatic relief and improve QOL. Centrally acting antitussive drugs are associated with adverse drug reactions, such as constipation and somnolence. Overall, effective and safe pharmacologic therapies that can be administered on a long-term basis for the treatment of patients with refractory chronic cough are needed.

1.2 S-600918

1.2.1 Rationale

Adenosine triphosphate (ATP) functions as a transcellular signaling substance and induces the cough reflex when inhaled in humans [12,13,14]. Among the purinergic receptors, the P2X receptor is a subtype of an ion channel gated by ATP as a ligand. Seven subtypes of this receptor ($P2X_1$ to $P2X_7$) have been identified [15]. Among the subtypes, the $P2X_3$ receptor is mainly expressed in small-diameter primary afferents (Aδ or C-fibers), which are associated with sensory reception and transmission. Significant involvement of this receptor in the cough reflex has been suggested. In particular, stimulation of the cough reflex via activation of the $P2X_3$ receptor occurs when the sensory nerve endings (Aδ or C-fibers) in the superficial layer of the airway wall are stimulated mechanically or chemically, releasing such mediators as ATP. ATP activates the $P2X_3$ receptor, resulting in signal transmission to the cough center in the medulla oblongata via neural firing of the vagus nerve, and cough ensues.

Expression of the $P2X_3$ receptor has been reported in bronchopulmonary C-fibers/ganglion nodosum in humans, rats, and mice [16,17,18,19]. Based on electrophysiological assay of guinea pig lung tissue, treatment of lung tissue with ATP or α, β-methylene ATP (a selective $P2X_3$ receptor agonist) resulted in action potential discharge in nodose fibers, which are mainly projected from the lower airway (eg, lung/bronchial tubes) [20]. This action potential discharge was completely suppressed by

the P2X receptor antagonist TNP-ATP and the $P2X_3$ receptor-selective antagonist AF-353 [21]. Thus, it appears that ATP-$P2X_3$ receptor signals are involved in the cough reflex in animal models.

In humans, inhalation of ATP has been demonstrated to induce the cough reflex [12,13,14]. In addition, high ATP concentrations have been reported in bronchoalveolar lavage fluid of patients with diseases associated with cough (idiopathic pulmonary fibrosis and acute eosinophilic pneumonia) compared with that of healthy adults [22,23]. Furthermore, as an increased cough reflex induced by ATP inhalation has been observed in patients with chronic cough, asthma, and chronic obstructive pulmonary disease (COPD) compared with healthy adults [12,13,14], sensitivity to ATP may be increased in diseases associated with cough. Overall, ATP appears to be an important mediator of cough in humans, and the $P2X_3$ receptor consequently is being targeted in the development of pharmacologic therapies for refractory chronic cough.

In the clinical setting, single-dose administration of the $P2X_3$ receptor antagonist gefapixant (AF-219, MK-7264) significantly suppressed cough reflex compared with placebo in healthy adults and patients with chronic cough in an ATP inhalation study [14]. Moreover, twice daily administration of gefapixant 600 mg significantly decreased the number of coughs compared with placebo in a Phase 2 study in patients with refractory chronic cough [24].

S-600918 is a $P2X_3$ receptor antagonist developed by Shionogi & Co., Ltd that shows high selectivity for the $P2X_3$ receptor [25]. It is formulated as a tablet for oral administration once daily. The drug is in Phase 2 of development for refractory chronic cough.

1.2.2 Clinical Summary

Four clinical studies of S-600918 have been completed, including a Phase 1 single ascending-dose and food-effect study (Study 1616VA311 [VA311]), a Phase 1 multiple ascending-dose study (Study 1623VA312 [VA312]), a Phase 1 drug-drug interaction study of co-administration with a P-glycoprotein (P-gp) substrate and a breast cancer resistance protein (BCRP) substrate (Study 1806VA313 [VA313]), and a Phase 2 multicenter, randomized, double-blind, placebo-controlled, crossover study of S-600918 in patients with refractory or unexplained chronic cough (Study 1727VA322 [VA322]).

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

Efficacy

Study VA322 had a multicenter, randomized, double-blind, placebo-controlled, crossover design. The primary objective was to determine the rate of change in the number of coughs per hour during the daytime (defined as 7:00 am to 7:59 pm) after 14 days (2 weeks) of once-daily treatment with S-600918 150 mg or placebo. The planned sample size was 30 patients.

Among the entry criteria, patients enrolled were to have refractory or unexplained chronic cough lasting for at least 6 months and to have a self-reported cough frequency of ≥10 times per hour while awake during a 14-day screening period.

Patients were randomized to treatment sequence groups, after which study drug (S-600918 150 mg or placebo) was taken orally in the morning once daily for 2 weeks. A washout period of 2 to 3 weeks followed, after which patients crossed over to the alternate treatment and took study drug (S-600918 150 mg or placebo) orally in the morning once daily for 2 weeks. Follow-up observation was performed 7 days after the final dose of study drug.

Thirty-one (31) Japanese patients were randomized to treatment-sequence groups. The median (range) duration of chronic cough was 60.0 (9 – 421) months. A total of 25 (80.6%) of the 31 patients had refractory chronic cough with identified underlying medical conditions, which commonly included asthma (14 [45.2%] patients), cough variant asthma (10 [32.3%] patients), rhinitis (6 [19.4%] patients), and gastroesophageal reflux disease (5 [16.1%] patients). The remaining 6 (19.4%) of the 31 patients had unexplained chronic cough. The median (range) number of coughs recorded on the cough monitor during the daytime before initiation of study drug was 42.2 (1 – 261) per hour for the 31 patients.

The 31 randomized patients were included in the full analysis set (FAS). A greater reduction in daytime cough frequency was observed with S-600918 than with placebo after 2 weeks of treatment. In particular, daytime cough frequency decreased by 54.1% during S-600918 treatment compared with 33.0% during placebo treatment ($p = 0.0546$), and 24-hour cough frequency decreased by 52.6% during S-600918 treatment compared with 31.4% during placebo treatment ($p = 0.0386$). Total scores for the Leicester Cough Questionnaire (LCQ) increased (ie, improved) to 2.46 with S-600918 and 1.06 with

placebo; the difference (S-600918 minus placebo) was 1.40 (95% confidence interval [0.06, 2.75], p = 0.0415 [mixed effect model]).

Overall, the therapeutic effect of S-600918 was apparent after 2 weeks of administration in this placebo-controlled, crossover study in patients with refractory or unexplained cough. Results support further study of S-600918 in this patient population.

Pharmacokinetics

[redacted]

Safety and Tolerability

[redacted]

[redacted]

[redacted]

1.3 Rationale for the Study

Results of the Phase 2 proof-of-concept study (Study VA322) in patients with refractory or unexplained cough support the therapeutic effect of S-600918 in this target population. Thus, this current study is being conducted to determine the optimal dose of S-600918 for the treatment of adult patients with refractory chronic cough.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to determine the optimal dose of S-600918 in patients with refractory chronic cough by evaluating the change from baseline in 24-hour cough frequency (coughs per hour) with S-600918 compared with placebo.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the efficacy of S-600918 to that of placebo in patients with refractory chronic cough based on the following measurements:
  - Number of coughs per hour while awake
  - Number of coughs per hour while asleep
  - Severity of cough as assessed on the Visual Analog Scale (VAS)
  - Leicester Cough Questionnaire (LCQ)
  - International Consultation on Incontinence Modular Questionnaire-Short Form (ICIQ-SF)
  - Short Form (36) Health Survey (SF-36), version 2
  - Patient Global Impression of Change (PGIC)
- To evaluate the safety of S-600918 in patients with refractory chronic cough.
- To assess the PK of S-600918 and its metabolite (S-600918 acyl glucuronide) in patients with refractory chronic cough.

3. INVESTIGATIONAL PLAN

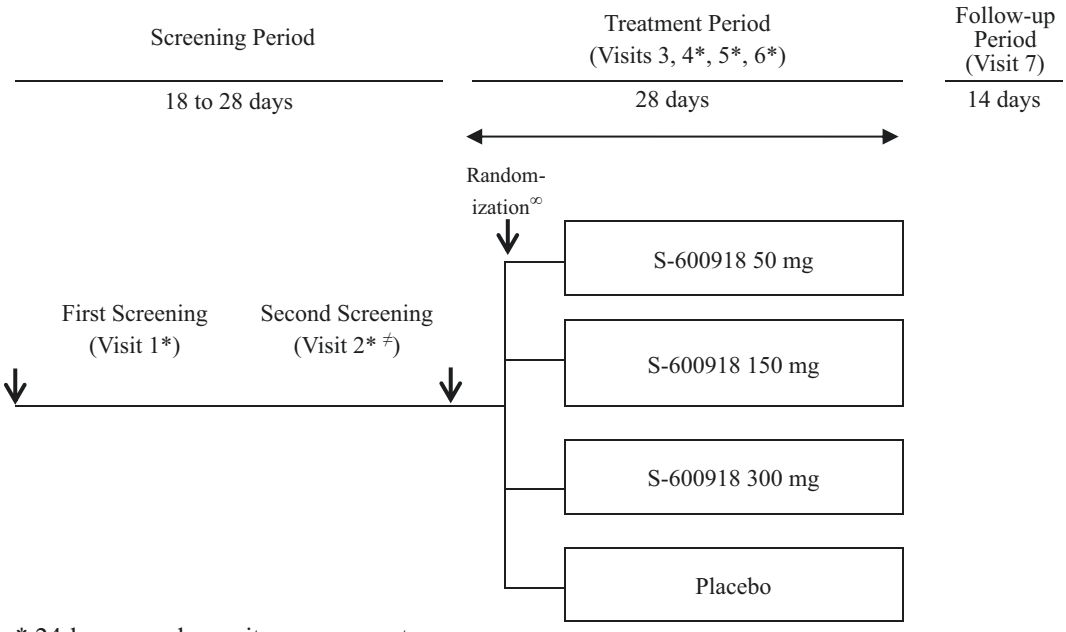
3.1 Overall Study Design and Plan

This study will be conducted as a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. A total of approximately 372 patients with refractory chronic cough are planned to be treated in Japan, Europe, and the United States.

This study will include 3 periods: a screening period, a treatment period, and a follow-up period. After obtaining informed consent, patients who meet screening criteria at Visit 1 will be enrolled in the study, and a cough monitor will be applied to each patient. Patients will be instructed to remove the cough monitor after 24 hours and to return the cough monitor to the study site within 2 days after completing the cough monitor recording. At least 17 days after Visit 1, patients will return for Visit 2, at which time screening will continue and a cough monitor again will be applied to each patient for 24 hours. Patients will return 1 day later for Visit 3. Patients who continue to meet screening criteria at Visit 3 will be randomized in a 1:1:1:1 ratio (93 patients per treatment group) to study treatment with S-600918 50 mg, S-600918 150 mg, S-600918 300 mg, or placebo. Randomization will be stratified by region (Japan, Europe, or the United States) and hourly cough count based on the 24-hour cough count recording at Visit 1 (≥30 coughs/hour or <30 coughs/hour) and will be performed by Interactive Response Technology (IRT). Following randomization, patients will take the first dose of study drug while at the study site. Study drug will be taken orally once daily for 28 days. Patients will be followed for 14 days after the last dose of study drug.

An overview of the study is shown in Figure 3-1. The Time and Events Schedule is provided in Appendix 1.

Figure 3-1 Study Schematic



* 24-hour cough monitor assessment

≠ At least 17 days after Visit 1

∞ At Visit 3 (1 day after Visit 2)

3.2 Rationale for Study Design and Control Group

A randomized, double-blind design was selected to minimize possible bias. Randomization will be stratified by region and the cough count at Visit 1. These stratification factors were selected in light of potential differences between Japan, Europe, and the United States in which this study is to be conducted and in light of the results of the S-600918 proof-of-concept study (Study VA322), which showed an association between cough count at screening and patient response to study drug.

Currently no drugs are approved for the treatment of patients with refractory chronic cough. Thus, placebo was selected as the control.

Evidence of the effect of S-600918 was observed 2 weeks after initiation of administration in the proof-of-concept study (Study VA322). [redacted] Thus, 4 weeks was selected as the duration of study treatment.

3.3 Study Duration

3.3.1 Study Duration in Individual Patients

The study duration for each patient is approximately 8 to 10 weeks (screening, 18 to 28 days; treatment, 28 days; and follow-up, 14 days).

3.3.2 Planned Study Duration for the Study

The planned study duration is addressed in a separate document.

3.3.3 Study End

The end of the study is defined as the last visit of the last patient.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 Study Population

Patients with refractory chronic cough who fulfill the eligibility criteria will be randomized to study treatment.

4.2 Inclusion Criteria

Patients who meet the following criteria at the specified visit(s) will be included in the study provided no exclusion criterion is met:

Inclusion Criteria	Visit 1	Visit 2	Visit 3
1. Willing to comply with all study procedures.	√	√	
2. Capable of giving signed informed consent. (Informed consent will be obtained in accordance with local requirements.)	√		
3. Male or female outpatient ≥18 to ≤80 years of age at the time of signing the informed consent form.	√		
4. Has refractory chronic cough lasting for at least 1 year prior to Visit 1, defined as: • insufficient improvement in cough after treatment for the underlying condition(s) causing the cough *OR* • unexplained cough for which an underlying condition has not been determined.	√		
5. With severity of cough assessed as ≥40 mm on the Visual Analog Scale (VAS) at both Visit 1 and Visit 2.	√	√	
6. With cough count ≥10 times per hour based on the 24-hour cough count recording at Visit 1. (Results will be available by Visit 2; no calculation is necessary.)		√	
7. If female, agreement to use one of the following contraceptive methods from screening until 14 days after the last dose of study drug UNLESS the patient is surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation with appropriate documentation of such surgery or postmenopausal (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age): • Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action), male or female condom with or without spermicide, cap, diaphragm, or sponge with spermicide.	√		

The contraceptive methods listed above are the minimum required per protocol. Other accepted methods include combination estrogen- and progesterone-containing contraceptives, implanted devices (such as intrauterine devices [IUDs]), and injectable contraceptives.			

4.3 Exclusion Criteria

Patients who meet any of the following criteria at the specified visit(s) will be excluded from the study:

Exclusion Criteria	Visit 1	Visit 2	Visit 3
1. Missing an entry in patient electronic diary (eDiary) for the number of coughs on more than 30% of the days from day of Visit 1 up to day of Visit 2. (Entries will be assessed at Visit 2.)		√	
2. Failure to obtain the cough count recording on the cough monitor at Visit 1 or Visit 2 for any reason, including device malfunction, based on initial assessment at study site. • Assessment for Visit 1 will be completed prior to Visit 2. If recording at Visit 1 is assessed as failed, the recording may be repeated (see Section 8.1 for details). • Assessment for Visit 2 will be completed at Visit 3. If recording at Visit 2 is assessed as failed, the recording may be repeated (see Section 8.3 for details).	√		√
3. Currently smokes (including, but not limited to e-cigarettes, smokeless cigarettes, and vaping) or uses any inhalational agents (including, but not limited to marijuana) that are potential irritants or has smoked or used any inhalational agents that are potential irritants in the 1 year prior to Visit 1 or has a smoking history of ≥20 pack-years (Pack years = [Number of cigarettes per day/20] × (Number of years of smoking]).	√		
4. Produces a significant amount of sputum suggestive of infection, bronchiectasis, chronic bronchitis, etc.	√	√	√

Exclusion Criteria	Visit 1	Visit 2	Visit 3
5. In the 4 weeks prior to Visit 1 or during screening, history of infection in the upper or lower respiratory tract or a significant change in lung function or a pulmonary condition based on the judgment of the investigator.	√	√	√
6. Has chronic obstructive pulmonary disease (COPD) or, as defined in the Global Initiative for Asthma (GINA) 2019, has uncontrolled asthma symptoms (excluding cough) [a].	√		
7. Has a clinically unstable medical condition, including cardiac disease (eg, atrial fibrillation, symptomatic bradycardia, and active myocardial ischemia), hypertension, respiratory disease, biliary tract disease, hypothyroidism, renal disease, adrenocortical insufficiency, or any other medical condition that, in the opinion of the investigator, will interfere with study participation or assessment of efficacy and safety.	√	√	
8. Has history of malignancy ≤5 years prior to Visit 1 (unless nonmelanoma skin cancer).	√		
9. Has history of or current bipolar disorder, schizoaffective disorder, schizophrenia, or major depressive disorder [b], or, based on the judgment of the investigator, has other psychiatric symptoms that may interfere with study procedures.	√		
10. Has history of severe drug allergy (shock, anaphylaxis, or angioedema).	√		
11. Has history of alcohol or drug abuse in the 1 year prior to Visit 1 or uses any form of marijuana or illicit drugs.	√		
12. With ALT or AST >2.0 times the upper limit of the normal reference range (× ULN) or total bilirubin >1.5 × ULN. (ULN is as determined by the central laboratory. Results will be available by Visit 2.)		√	
13. With serum creatinine >1.5 × ULN. (ULN is as determined by the central laboratory. Results will be available by Visit 2.)		√	
14. With positive serological test for human immunodeficiency virus (HIV) antigen or antibody. (Results will be available by Visit 2.)		√	

Exclusion Criteria	Visit 1	Visit 2	Visit 3
15. With positive serological test for hepatitis B virus surface antigen. (Results will be available by Visit 2.)		√	
16. With positive serological test for hepatitis C virus RNA. (This test is required only if patient has positive serological test for hepatitis C virus antibody. Results will be available by Visit 2.)		√	
17. With systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg.	√	√	√
18. With clinically significant abnormal ECG based on the judgment of the investigator.	√	√	
19. With a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than 60% at Visit 1. **COVID-19–related Measure:** With a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than 60% based on spirometry conducted anytime in the prior calendar year [c].	√		
20. With any finding on a chest x-ray or chest computed tomography (CT) scan (performed not more than 1 year [12 months] prior to Visit 1 after onset of chronic cough at Visit 1) that could be considered the cause of chronic cough or indicative of lung disease. (If a chest x-ray or chest CT scan needs to be performed, results will be available by Visit 2.) (Note: Patients with abnormal chest image findings not considered to be the cause of chronic cough are eligible to participate.)	√	√	
21. Previously received S-600918.	√		
22. Treated with a biological drug for asthma in the 3 months prior to Visit 1 or previously received bronchial thermoplasty.	√		

Exclusion Criteria	Visit 1	Visit 2	Visit 3
23. Treated with an angiotensin-converting-enzyme (ACE) inhibitor in the 3 months prior to Visit 1, being treated with an ACE inhibitor at Visit 1, or planned to be treated with an ACE inhibitor at any time from Visit 1 to the end-of-study (EOS) assessments at Visit 7.	√	√	√
24. Received an investigational drug in the 3 months prior to Visit 1 or planned to receive another investigational drug at any time from Visit 1 to the EOS assessments at Visit 7.	√	√	√
25. Being treated with the following therapy at Visit 1 or planned to be treated with the following therapy at any time from Visit 1 to the EOS assessments at Visit 7: • Pregabalin, gabapentin, and tricyclic antidepressants • Biological products for asthma treatment (eg, omalizumab) • Baclofen • Sitagliptin • P-gp inhibitors (specifically, cyclosporine, erythromycin, itraconazole, and ketoconazole [This criterion does not apply to topical formulations of these drugs, if any.]) • BCRP inhibitors (specifically, cyclosporine [This criterion does not apply to topical formulations of this drug, if any.]) • Organic anion transporting polypeptide (OATP)1B1/1B3 inhibitors (specifically, cyclosporine and gemfibrozil [This criterion does not apply to topical formulations of these drugs, if any.]) • Digoxin or methyldigoxin	√	√	√
26. Refusal to discontinue the following therapy at Visit 1 to the EOS assessments at Visit 7: • Drugs with an antitussive action alone or in combination with other drugs • Herbal medicines with an antitussive action • First-generation (sedating) antihistamines (other than topical products)	√	√	√

Exclusion Criteria	Visit 1	Visit 2	Visit 3

• Non-drug therapies for cough relief, including cough suppressant speech therapy
• UNLESS used as specified under "Restricted Therapy" (Section 6.2.2):
  • Sleep-inducing drugs
  • Drugs with an expectorant action
  • Steroids (other than nasally administered steroids and other topically administered steroids)
  • Drugs having an effect on gastrointestinal (GI) motility or GI acid reflux, including proton pump inhibitors, prokinetic drugs, and histamine H_2 receptor antagonists
  • Anti-allergics (other than first-generation antihistamines and topical products) (histamine H_1 receptor antagonists, leukotriene receptor antagonists, thromboxane A2 synthase inhibitors, thromboxane receptor antagonists, Th_2 cytokine blockers, mediator release inhibitors)
  • Long-acting beta agonists, long-acting muscarinic antagonists, short-acting muscarinic antagonists, and bronchodilators other than short-acting beta-2 agonists (eg, methylxanthines and phosphodiesterase [PDE] inhibitors, etc.)
  • Macrolide antibiotics (other than erythromycin)
  • Oral anticholinergics
  • Immunotherapy for allergic disease			

27. If female, pregnant or trying to become pregnant or lactating.	√	√	√
28. Considered ineligible to participate in the study for any other reason, based on the investigator's judgment.	√	√	√

Exclusion Criteria	Visit 1	Visit 2	Visit 3

[a] As guidance regarding uncontrolled asthma symptoms, in the 2 to 3 months prior to Visit 1, an increase or decrease in the dose of an asthma controller drug AND, in the 4 weeks prior to Visit 1, at least 3 of the following: daytime symptoms of asthma more than twice per week, any night waking due to asthma, any activity limitation due to asthma, or use of asthma reliever more than twice per week.

[b] History of major depressive disorder is exclusionary only if there was a formal psychiatric diagnosis of major depressive disorder and the patient received antidepressant treatment. A vague history of having been depressed in the past is not exclusionary.

[c] If there are no spirometry data in the prior calendar year, spirometry is required at Visit 1. Assess whether the possible benefit from participating in the study will outweigh the risk of conducting spirometry. If the benefit-risk assessment is positive, perform spirometry in accordance with local guideline(s). If the benefit-risk assessment is negative, stop screening that patient.

4.4 Screen Failures

Screen failures are defined as patients who consent to participate in the study, but who are not randomized to study treatment. At a minimum, the following information (if applicable) must be recorded in the electronic case report form (eCRF) for all screen failures: date of informed consent, baseline patient characteristics, all eligibility criteria not met, reason(s) for screen failure, adverse events that led to screen failure, and any SAEs.

As the cause for screen failure will vary, rescreening of screen failures will be determined on a case-by-case basis by the Medical Monitor in consultation with the sponsor. A patient may be rescreened only once during the study. Provided the initial screening tests were completed not more than 28 days prior to rescreening and there were no abnormal test results based on the initial screening, previously completed screening tests do not need to be repeated. Any patient permitted to be rescreened will be assigned a patient identification number different from that assigned at the initial screening; cough monitor recordings and questionnaires or instruments completed on the electronic tablet and eDiary during the initial screening must be repeated.

4.5 Withdrawal of Patients from the Study and Discontinuation of Study Drug

The investigator or qualified designee will make every reasonable attempt to ensure a patient completes the study.

4.5.1 Withdrawal of Patients from the Study

A patient may withdraw consent to participate in the study for any reason at any time. If a patient withdraws consent, the investigator or qualified designee will access the IRT to record this withdrawal of consent, the reason for withdrawal of consent, and the date of completion or discontinuation of study drug (as applicable). The investigator or qualified

designee also will record the date of and reason for withdrawal of consent on the appropriate eCRF page.

COVID-19–related Measure:

If a patient misses more than 5 consecutive days of study drug administration due to a COVID-19–related issue, the patient should be withdrawn from the study by the investigator.

All study assessments specified for Visit 7 (ie, the End-of-study Visit) should be completed provided consent has not yet been withdrawn.

4.5.2 Discontinuation of Study Drug

Discontinuation of study drug is required if the patient becomes pregnant (Section 7.6.5.10) or meets any of the discontinuation criteria for abnormal liver chemistry tests (Appendix 2). In addition, the investigator may discontinue administration of study drug to a patient for any of the following reasons:

- A serious or intolerable adverse event occurs and the investigator considers it in the best interest of the patient to withdraw the patient from the study.
- The target disease worsens and the investigator considers it in the best interest of the patient to withdraw the patient from the study.
- The patient is proved to be ineligible to participate in the study after the initiation of study drug.
- The patient requests to stop study drug.
- The patient is lost to follow-up.
- The investigator determines that the patient should stop study drug for any other reason.

COVID-19–related Measure:

Study drug must be discontinued if protocol-specified safety assessments (as described by visit in Section 8.3 [Visit 3], Section 8.4 [Visit 4], Section 8.5 [Visit 5], and Section 8.6 [Visit 6]) are unable to be conducted for more than 18 days (ie, the longest duration between study visits previously allowed by protocol) between study visits.

In addition, after randomization, if a patient develops COVID-19 infection or is highly suspected to have COVID-19 infection, discontinuation of study drug should be considered. The site staff should report the infection as an adverse event and make every effort to complete the study assessments at the time of discontinuation of study drug (ie, the Early Discontinuation Visit) and all study assessments specified for Visit 7 (ie, the End-of-study Visit) remotely. If continuation of study drug is considered by the investigator to be in the best interest of the patient, the investigator must contact the Medical Monitor to discuss the continuation of study drug and obtain approval.

If a patient discontinues study drug, the investigator or qualified designee will access the IRT to record this discontinuation and also will record the date of discontinuation of study drug and the reason for discontinuation on the appropriate eCRF page.

Provided the patient has not withdrawn consent, a patient who discontinues study drug will still be considered to be in the study. The investigator or qualified designee will make every effort to complete the study assessments at the time of discontinuation of study drug (ie, the Early Discontinuation Visit) and all study assessments specified for Visit 7 (ie, the End-of-study Visit).

For patients who discontinue study drug due to adverse events, any adverse event considered to be related to study drug that is ongoing 14 days after the last dose of study drug and any SAE regardless of relationship to study drug that is ongoing 14 days after the last dose of study drug will be followed until resolution, until it is judged by the investigator or qualified designee to have stabilized or become chronic, or until the patient is lost to follow-up.

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Test Drug

The S-600918 50-mg tablet is a light orange to deep orange, round-shaped film-coated tablet containing 50 mg of S-600918. It is manufactured by Shionogi Pharma Co., Ltd.

5.1.2 Control

The placebo tablet matches the S-600918 50-mg tablet in appearance, but does not contain the active drug substance. It is manufactured by Shionogi Pharma Co., Ltd.

5.2 Treatments to be Administered

Patients will receive study treatment with S-600918 50 mg, S-600918 150 mg, S-600918 300 mg, or matching placebo for 4 weeks (28 days), as follows:

- S-600918 50-mg group: 1 × 50-mg tablet and 5 placebo tablets
- S-600918 150-mg group: 3 × 50-mg tablets and 3 placebo tablets
- S-600918 300-mg group: 6 × 50-mg tablets
- Placebo group: 6 × placebo tablets

5.3 Selection and Timing of Dose for Each Patient

Patients will be randomly assigned to study treatment.

The investigator or qualified designee will instruct patients to take study drug orally once daily (preferably in the morning) with or without food on all treatment days except on the day of Visit 4.

For the day of Visit 4, patients will be instructed to come to the study site in the morning without taking the study drug that day. After patient completion of specified questionnaires and instruments on the electronic tablet, a blood sample will be collected for PK analysis and then the patient will take that day's dose of study drug.

5.4 Method of Assigning Patients to Treatment Groups

Eligible patients will be randomized in a ratio of 1:1:1:1 by IRT to one of the following treatment groups: S-600918 50-mg group, S-600918 150-mg group, S-600918 300-mg group, or placebo. Randomization will be stratified by region (Japan, Europe, or the United States) and the cough count at Visit 1 (≥30 coughs/hour or <30 coughs/hour).

Randomization numbers will be assigned centrally by IRT according to the randomization schedule, which contains the patient identification numbers and the corresponding treatment assignments.

5.5 Blinding

The study will be conducted in a double-blind manner. Placebo tablets will match in appearance the S-600918 50-mg tablet, and the labeling and packaging of S-600918 and placebo will be identical.

The randomization schedule will be maintained by IRT until data lock, as specified in the IRT User Manual. Except for unblinded sponsor staff (eg, the Investigational Medicinal Product Manager) or designees, the sponsor and the sponsor's designees, the investigator, and all study-site personnel will be blinded to treatment assignment until data lock. As plasma drug concentration data may reveal the study treatment to which a patient was randomized, only the sponsor's bioanalytical expert will be provided these data prior to data lock to determine whether the bioanalysis is conducted appropriately.

After data lock of all eCRF data, the sponsor will obtain the randomization schedule and all data from the IRT. This procedure is specified in the Data Transfer Specifications. Plasma drug concentration data will also be provided; this procedure is specified in a separate document.

Unblinding at the request of an investigator should occur only in the event of an emergency, pregnancy of a patient, or an adverse event for which it is necessary to know the study drug to determine an appropriate course of therapy. Prior to unblinding and if the situation allows it, the investigator should contact the Medical Monitor. If the investigator judges it necessary to know the randomization code for a specific patient, the investigator will obtain the randomization code through the IRT, which will capture (at a minimum) the date and time of unblinding and the reason for unblinding. If the investigator is unable to speak with the Medical Monitor prior to unblinding, the investigator must notify the site monitor or the Medical Monitor as soon as possible after unblinding, WITHOUT revealing the treatment assignment for that patient. Procedures for emergency unblinding are specified in the IRT User Manual. The patient should remain in the study and complete all study events and activities (as shown in Appendix 1) after unblinding.

5.6 Packaging and Labeling

Study drug will be packaged in blister cards containing a supply of study drug adequate for 7 days of treatment plus 3 days of extra study drug in the event the patient cannot return for the next visit as scheduled. Each blister card will be packaged in a study drug wallet. One study drug wallet will be dispensed at Visit 3 and Visit 5, and 2 study drug wallets will be dispensed at Visit 4. Each wallet will be labelled with a unique identification number (ie, a study drug code), protocol number, contents (without treatment assignment), directions for use, storage conditions, and any other required information in accordance with local regulations. The expiry date will be stored in the IRT or printed on the label in accordance with local regulations.

Study drug must not be used after the expiry date. All packaged and labelled supplies will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines and applicable regional regulatory requirements.

5.7 Storage and Accountability

The sponsor will supply study drug to the person responsible for study drug handling in accordance with the contract between the sponsor and the study site. The person responsible for study drug handling will manage study drug in accordance with procedures specified in the Pharmacy Manual.

The investigator or person responsible for study drug handling will ensure that all study drug is stored and dispensed in accordance with local regulations concerning investigational drugs. All study drug must be kept in a secure, locked area with access limited to those authorized by the investigator and stored at room temperature (15°C to 30°C [59°F to 86°F]).

The investigator, pharmacist, or qualified designee will maintain accurate records of the date of receipt of all study drug and its condition when received, the date of dispensing of study drug and the quantity dispensed to each patient, the quantity of study drug used by each patient, and any deviation from the protocol-specified dispensing instructions, including a reason for that deviation. Drug accountability records will be available for verification by the sponsor or designee at each monitoring visit. At the completion of the study, a final reconciliation of all study drug will be performed. Further details on study drug procedures and accountability are specified in the Pharmacy Manual.

Study drug must not be used for any purpose other than this study.

5.8 Investigational Product Retention at Study Site

Once the study has been completed at the study site, all unused and used study drug wallets must be returned to the sponsor or designee following final reconciliation of study drug. Procedures for study drug return are specified in the Pharmacy Manual.

Unused and used study drug at the study site after study completion, as well as supply that expires during the study, are not required to be stored at room temperature.

5.9 Treatment Compliance

The investigator, pharmacist, or qualified designee will instruct patients to bring the study drug wallet (including any unused study drug) to each study visit.

At each visit (as applicable), the investigator or qualified designee will collect the study drug wallet, check to ensure that the study drug code listed on the wallet is identical to the number issued by the IRT, assess the wallet contents to verify that the correct number of doses and tablets has been taken based on the number of days elapsed between study visits, and record the number of tablets taken daily and the date taken and the number of tablets returned and the date returned on the appropriate eCRF page. For specified days

(see next paragraph), the investigator or qualified designee will record the time that study drug was taken on the appropriate eCRF page. If the inspection of the study drug wallet reveals that the study drug was not taken in accordance with the instructions, the importance of treatment compliance will be reemphasized with the patient, and, if applicable, the investigator or qualified designee will report Special Situations (Section 7.6.5.9) on the appropriate eCRF page.

Additionally, the investigator or qualified designee will confirm that the patient has entered the date and time of study drug administration, as specified for Visit 3 (ie, the first dose of study drug in the study), Visit 4 (the day before and the day of the visit), Visit 6 (the day before and the day of the visit), and the day after Visit 6 (ie, the last dose of study drug in the study) in the study drug wallet, and record this information on the appropriate eCRF page.

COVID-19–related Measure:

In the event a visiting nurse service is used at Visit 4, Visit 5, Visit 6, Visit 7, and/or the Early Discontinuation Visit (if applicable) as described in Section 8, the visiting nurse will assume responsibility for the assessment of treatment compliance as described above in Section 5.9.

In addition, if a supply of study drug adequate for the remaining 3 weeks of treatment is dispensed to the patient at Visit 4 or is delivered via courier to the patient's home (as described in Section 7.2) and that patient was not compliant with study drug administration in the week between Visit 3 and Visit 4 (ie, either took more or less study drug than specified in the protocol), the investigator or qualified designee will contact the patient 7 ± 2 days after delivery of study drug at Visit 4 to assess treatment compliance.

5.10 Post-study Access to the Study Drug

Study drug will not be provided once a patient completes (or withdraws from) the study.

6. RESTRICTIONS

6.1 Prior Therapy

Prior therapy is defined as any therapy taken prior to the first dose of study drug. Restrictions with regard to prior therapy are defined in the exclusion criteria.

All prior therapies (including prescription drugs, OTC drugs, vitamins and herbal or other supplements, natural treatments, and non-medication therapies or procedures) taken within 3 months prior to Visit 1 and during the screening period will be recorded by the investigator or qualified designee on the appropriate eCRF page, including (as applicable) the name of the therapy or procedure, route of administration, start date and end date of use, and reason for use.

6.2 Concomitant Therapy

Concomitant therapy is defined as any therapy taken on the day of the first dose of study drug or thereafter.

All concomitant therapies (including prescription drugs, OTC drugs, vitamins and herbal or other supplements, natural treatments, and non-medication therapies or procedures) at or after the start of study drug until the end of follow-up will be recorded by the investigator or qualified designee on the appropriate eCRF page, including (as applicable) the name of the therapy or procedure, route of administration, start date and end date of use, and reason for use.

The on-demand use of short-acting beta-2 agonists (SABAs) is discouraged during each of the 24-hour periods while patients are wearing a cough monitor. All patients must be specifically asked about the use of SABAs at Visit 1 and while wearing the cough monitor when reviewing prior and concomitant therapies (as applicable) at Visit 2, Visit 3, Visit 5, Visit 6, Visit 7, and/or, if applicable, the Early Discontinuation Visit.

For SABAs and for Restricted Therapy (as described in Section 6.2.2), the dosage will be recorded by the investigator or qualified designee on the appropriate eCRF page. In addition, if a SABA is used during the 24-hour period while patients are wearing a cough monitor, the time(s) of administration will be recorded on the appropriate eCRF page.

6.2.1 Prohibited Therapy

Enrollment of patients being treated with specific therapy, as detailed in Exclusion Criteria #23, 24, and 25 is not permitted. Enrollment of patients who refuse to discontinue specific therapy at Visit 1 to the EOS assessments at Visit 7, as detailed in Exclusion Criterion #26, is not permitted. Consistent with these exclusion criteria, the following therapies (including OTC drugs that have similar effects) are prohibited from Visit 1 to the EOS assessments at Visit 7:

- ACE inhibitors
- Investigational drug other than that administered in this study

- Pregabalin, gabapentin, and tricyclic antidepressants
- Biological products for asthma treatment (eg, omalizumab)
- Baclofen
- Sitagliptin
- P-gp inhibitors (specifically, cyclosporine, erythromycin, itraconazole, and ketoconazole [This criterion does not apply to topical formulations of these drugs, if any.])
- BCRP inhibitors (specifically, cyclosporine [This criterion does not apply to topical formulations of this drug, if any.])
- OATP1B1/1B3 inhibitors (specifically, cyclosporine and gemfibrozil [This criterion does not apply to topical formulations of these drugs, if any.])
- Digoxin or methyldigoxin

The following therapies (including OTC drugs that have similar effects) are prohibited from Visit 1 to the EOS assessments at Visit 7:

- Drugs with an antitussive action (eg, codeine, codeine phosphate, hydrocodone, morphine, dextromethorphan) alone or in combination with other drugs
- Herbal medicines with an antitussive action
- First-generation (sedating) antihistamines (eg, chlorpheniramine, diphenhydramine, hydroxyzine) (other than topical products)
- Non-drug therapies for cough relief, including cough suppressant speech therapy speech therapy
- Sleep-inducing drugs unless used as specified under “Restricted Therapy” (Section 6.2.2)
- Drugs with an expectorant action unless used as specified under “Restricted Therapy” (Section 6.2.2)
- Steroids (other than nasally administered steroids and other topically administered steroids), unless used as specified under “Restricted Therapy” (Section 6.2.2)
- Drugs having an effect on GI motility or GI acid reflux, including proton pump inhibitors, prokinetic drugs, and histamine H_2 receptor antagonists unless used as specified under “Restricted Therapy” (Section 6.2.2)
- Anti-allergics (other than first-generation antihistamines and topical products) (histamine H_1 receptor antagonists, leukotriene receptor antagonists, thromboxane receptor antagonists, thromboxane A2 synthase inhibitors [eg, ozagrel], Th_2 cytokine blockers, mediator release inhibitors) unless used as specified under “Restricted Therapy” (Section 6.2.2)
- Long-acting beta agonists, long-acting muscarinic antagonists, short-acting muscarinic antagonists, and bronchodilators other than short-acting beta-2 agonists (eg, methylxanthines and PDE inhibitors, etc.) unless used as specified under “Restricted Therapy” (Section 6.2.2)

- Macrolide antibiotics (other than erythromycin) unless used as specified under "Restricted Therapy" (Section 6.2.2)
- Oral anticholinergics
- Immunotherapy for allergic disease

6.2.2 Restricted Therapy

Restricted therapy is defined as any concomitant therapy for which use is permitted only with restrictions.

The following therapies (including OTC drugs that have similar effects) are prohibited from the start of the screening period at Visit 1 to the EOS assessments at Visit 7 UNLESS use is continuous and at a stable dosage (ie, administered at the same dose and frequency) for at least 2 weeks before Visit 1 AND use will continue at that dosage unchanged from Visit 1 through Visit 7, in which case these therapies will be considered restricted therapies and will be permitted:

- Sleep-inducing drugs
- Drugs with an expectorant action
- Steroids (other than nasally administered steroids and other topically administered steroids)
- Drugs having an effect on GI motility or GI acid reflux, including prokinetic drugs and histamine H_2 receptor antagonists
- Anti-allergics (other than first-generation antihistamines and topical products) (histamine H_1 receptor antagonists, leukotriene receptor antagonists, thromboxane receptor antagonists, thromboxane A2 synthase inhibitors [eg, ozagrel], Th_2 cytokine blockers, mediator release inhibitors)
- Long-acting beta agonists, long-acting muscarinic antagonists, short-acting muscarinic antagonists, and bronchodilators other than short-acting beta-2 agonists (eg, methylxanthines and PDE inhibitors, etc.)
- Oral anticholinergics
- Immunotherapy for allergic disease

Use of proton pump inhibitors, vonoprazan, and macrolide antibiotics (other than erythromycin) is prohibited from the start of the screening period at Visit 1 to the EOS assessments at Visit 7 UNLESS use is continuous and at a stable dosage (ie, administered at the same dose and frequency) for at least 3 months prior to Visit 1 AND use will continue at that dosage unchanged from Visit 1 through Visit 7, in which case these therapies will be considered restricted therapies and will be permitted.

7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS

The approach to specific study procedures and methods of assessment are discussed in Section 7. Activities at each visit are listed in Section 8. The Time and Events Schedule is provided in Appendix 1.

7.1 Informed Consent

Informed consent will be obtained in accordance with local requirements from all patients who are screened for this study. The investigator or qualified designee will fully explain the nature of the study to a patient using the informed consent form approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC). If a patient agrees to participate, the patient must voluntarily sign the informed consent form prior to initiation of any study procedures. A copy of the signed and dated informed consent form will be given to the patient. The original signed and dated informed consent form will be retained by the investigator or qualified designee. A patient cannot be entered into the study until he/she has signed and dated the informed consent form.

COVID-19–related Measure:

The COVID-19 pandemic may expose patients to additional risks while they are participating in the study; thus, changes to study conduct may be required.

If it becomes necessary for an investigator to implement home nursing service or drug delivery service, re-consenting or additional consent of all patients at that site who require one or more of these services and who have not yet completed the study (including those in screening and those randomized) is required at the time of the investigator's decision, if such consent has not previously been obtained.

Re-consent or additional consent of the patient must be documented through the use of a written consent form that has been approved by the IRB/IEC.

In the event that the patient is not able to come to the study site, any validated and secure electronic system that complies with local regulations and is already used by a study site for obtaining informed consent can be used to re-consent or obtain additional consent as per the usual practice. The original of the newly signed and dated informed consent form is to be given to the investigator or qualified designee at the next study visit (whether conducted at the study site or by a visiting nurse service) and retained at the study site. A copy of the newly signed and dated informed consent form will be given to the patient.

The investigator or qualified designee is responsible for ensuring that the patient understands the risks and benefits (if any) of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his/her participation in the study.

7.2 Patient Registration and Randomization and Dispensing of Study Drug

After the patient is determined to be eligible at the start of the screening period at Visit 1, the investigator or qualified designee will access the IRT to enroll the patient. Upon registration, the patient will be assigned a unique patient identification number.

At study sites with limited or no weekend hours, patients should be randomized on a Tuesday, Wednesday, Thursday, or Friday. It is recommended that study visits be scheduled in the morning, as multiple blood samples are required to be obtained over a period of several hours at Visit 4.

After final confirmation of eligibility at Visit 3, the investigator or qualified designee will access the IRT to randomize the patient and will obtain the patient identification number, as well as the code for the study drug wallet to be dispensed. At each subsequent visit during the treatment period when study drug is dispensed, the investigator or qualified designee will access the IRT to obtain the code for the study drug wallet to be dispensed. The investigator or qualified designee will record the code for the study drug wallet on the appropriate eCRF page at each visit during the treatment period.

A supply of study drug adequate for 1 week of treatment will be dispensed at Visit 3 and Visit 5, and a supply of study drug adequate for 2 weeks of treatment will be dispensed at Visit 4 (Section 5.6).

COVID-19–related Measure:

If it is anticipated that the patient will not be able to return to the study site after Visit 4, a supply of study drug adequate for the remaining 3 weeks of treatment may be dispensed to the patient at Visit 4.

Alternatively, if a patient is unable to return to the study site at Visit 4 or Visit 5, a supply of study drug adequate for all remaining weeks of treatment may be dispensed by the investigator or qualified designee and delivered via a site-to-patient delivery vendor (using a courier service) if locally available and if approved for use. Details, including contact information for the site-to-patient delivery vendor in each country, are specified in the Pharmacy Manual.

7.3 Eligibility Assessments

The screening period during which patient eligibility is determined may range in duration from 18 to 28 days. A screening period of a longer duration than 18 days (eg, 28 days) allows for repeating the cough count recording at Visit 1 if the Visit 1 recording initially fails and for repeating the cough count recording at Visit 2 if the Visit 2 recording initially fails (see Section 7.4.1).

Enrolled patients will be assessed versus the inclusion and exclusion criteria in the protocol (Section 4.2 and Section 4.3, respectively). As part of this assessment, patients will be given an eDiary at the start of the screening period at Visit 1 and instructed on its use and to record daily the average number of coughs per hour on the preceding day (ie, prior 24 hours) in the eDiary, starting from the day of Visit 1 and continuing up to the day of Visit 2.

Data entered by the patient in the eDiary will be automatically uploaded from the device to the database maintained by the device vendor. Procedures regarding the eDiary are specified in a separate document.

7.4 Efficacy Assessments

Efficacy assessment methods are described in Section 7.4, as well as presented in the Time and Events Schedule (Appendix 1).

Efficacy will be assessed based on cough monitor recordings of cough counts and questionnaires or instruments routinely used in studies in this patient population. The patient will complete these questionnaires and instruments in an electronic tablet and in an eDiary. At those visits at which questionnaires or instruments are required to be completed, completion by the patient is required prior to study site personnel conducting any other study procedures. Procedures regarding completion of these questionnaires and instruments, including the order of their administration at each visit, are specified in a separate document.

Data entered by the patient in the electronic tablet and eDiary will be automatically uploaded from the devices to the database maintained by the device vendor. Procedures regarding the electronic tablet and eDiary are specified in a separate document.

7.4.1 Number of Coughs (VitaloJAK™ Cough Monitor)

The number of coughs over a 24-hour period will be recorded at Visit 1, Visit 2, Visit 4, Visit 5, and Visit 6 with the VitaloJAK™ cough monitor [27]. This cough monitor has CE marking in the European Union and 510(k) approval from the United States Food and Drug Administration (FDA).

The cough monitor will be applied to the patient at each of these visits, and the patient will be instructed to remove the monitor after 24 hours. Instructions for the application of the cough monitor to the patient are specified in a separate document.

If, based on initial assessment at the study site, the cough count recording at Visit 1 or Visit 2 is considered to have failed for any reason, the recording may be repeated (see details for Visit 1 in Section 8.1 and for Visit 2 in Section 8.3). Repeat recording of the cough count is not permitted at any other visits in the study.

Data collected with the cough monitor will be sent from the study site to the cough monitor analysis institution via the web portal of that institution. The number of coughs will be measured (including classification of awake and asleep hours) by cough analysis technicians for each of the following periods:

- 24 hours
- Waking hours
- Sleeping hours

The number of coughs will be reported by the cough monitor analysis institution to the sponsor, with counts provided for each 24-hour period and for the waking hours and the sleeping hours within each 24-hour period. Procedures regarding the cough monitor analysis are specified in a separate document.

7.4.2 Cough Severity as Assessed on the Visual Analog Scale (VAS)

7.4.2.1 Weekly Severity of Cough (Electronic Tablet)

The patient will be asked to provide his/her assessment of the severity of cough during the past week at Visit 1, Visit 2, Visit 4, Visit 5, and Visit 6 and/or, if applicable, at the time of discontinuation of study drug on the VAS using the electronic tablet.

Data collected with the electronic tablet will be automatically uploaded from the device to the database maintained by the device vendor. Procedures regarding the electronic tablet are specified in a separate document.

7.4.2.2 Daily Severity of Cough (eDiary)

The patient will be instructed to record daily the severity of cough on the preceding day (ie, prior 24 hours) on the VAS in the eDiary, starting at Visit 1 and continuing up to Visit 4 (ie, through Day 7) and/or, if applicable, at the time of discontinuation of study drug.

Data collected with the eDiary will be automatically uploaded from the device to the database maintained by the device vendor. Procedures regarding the eDiary are specified in a separate document.

7.4.3 Leicester Cough Questionnaire (LCQ) (Electronic Tablet)

The LCQ is a patient-reported QOL measure of chronic cough [28]. The questionnaire consists of 19 items to which the patient responds on a 7-point Likert response scale. Each item assesses symptoms during cough and the effect of cough on 3 main domains: physical, psychological and social. The LCQ generally takes about 5 minutes to complete.

The patient will be asked to complete the LCQ at Visit 1, Visit 2, Visit 4, Visit 5, and Visit 6 and/or, if applicable, at the time of discontinuation of study drug using the electronic tablet [28].

Data collected with the electronic tablet will be automatically uploaded from the device to the database maintained by the device vendor. Procedures regarding the electronic tablet are specified in a separate document.

7.4.4 International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) (Electronic Tablet)

The ICIQ-SF is a patient-reported measure of the severity of urinary incontinence and QOL for those with urinary incontinence [29]. The questionnaire consists of 4 items that evaluate the frequency, severity, and impact of urinary incontinence on QOL. The ICIQ-SF takes a few minutes to complete.

The patient will be asked to complete the ICIQ-SF at Visit 2 and Visit 6 and/or, if applicable, at the time of discontinuation of study drug using the electronic tablet.

Data collected with the electronic tablet will be automatically uploaded from the device to the database maintained by the device vendor. Procedures regarding the electronic tablet are specified in a separate document.

7.4.5 Short Form (36) Health Survey (SF-36) (Electronic Tablet)

The SF-36 is a patient-reported measure of overall health status. The questionnaire consists of 8 scaled scores (health concepts) and evaluates vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Scores for each scale range from 0 to 100; the lower the score, the greater the disability [30]. The SF-36 takes approximately 5 to 10 minutes to complete [31].

The patient will be asked to complete the SF-36 at Visit 2 and Visit 6 and/or, if applicable, the Early Discontinuation Visit using the electronic tablet.

Data collected with the electronic tablet will be automatically uploaded from the device to the database maintained by the device vendor. Procedures regarding the electronic tablet are specified in a separate document.

7.4.6 Patient Global Impression of Change (PGIC) (Electronic Tablet)

The PGIC is a patient-reported measure of overall health status and consists of one item adapted from the Clinical Global Impressions scale [32].

The patient will be asked to complete the PGIC at Visit 6 or, if applicable, the Early Discontinuation Visit using the electronic tablet.

Data collected with the electronic tablet will be automatically uploaded from the device to the database maintained by the device vendor. Procedures regarding the electronic tablet are specified in a separate document.

7.5 Pharmacokinetics Assessments

All patients will have blood samples collected for measurement of plasma concentrations of S-600918 and its metabolite (S-600918 acyl glucuronide) at Visit 4 and Visit 6, and/or, if applicable, at the time of discontinuation of study drug.

At Visit 4, the patient is not to take study drug until after arrival at the study site; at Visit 6, the patient is permitted to take study drug before arrival at the study site (Section 5.3).

At Visit 4, three blood samples will be collected. The first blood sample will be collected after patient completion of specified questionnaires and instruments prior to the patient taking the dose of study drug that day. The dose of study drug will then be taken, and then the second and third blood samples will be collected 1 hour and 2 hours after the dose of study drug. If the patient inadvertently takes the dose of study drug before coming to the study site on the day of Visit 4, a blood sample will be collected after patient completion of specified questionnaires and instruments and then again 1 hour and 2 hours after collection of the first blood sample.

At Visit 6, a blood sample will be collected after patient completion of specified questionnaires and instruments.

The blood will be collected in a tube containing an anticoagulant (heparin sodium) and immediately centrifuged. Centrifuged plasma will be separately dispensed into polypropylene tubes and frozen and stored below −20°C. Samples will be shipped under freezing conditions with dry ice to the laboratory. Instructions for sample collection, handling, and shipment are provided separately.

COVID-19–related Measure:

In the event a visiting nurse service is used at Visit 4, Visit 6, and/or the Early Discontinuation Visit (if applicable) as described in Section 8, refer to the separate document for directions regarding handling and shipping of blood samples for PK analysis.

The investigator or qualified designee will record the date and time the blood samples were obtained on the appropriate eCRF page.

7.6 Safety Assessments

Safety assessment methods are described in Section 7.6, as well as presented in the Time and Events Schedule (Appendix 1).

7.6.1 Physical Examinations

A complete physical examination (including measurement of height [in centimeters] and body weight [in kilograms]) will be performed by the investigator or qualified designee at Visit 1. An abbreviated physical examination (limited to the respiratory system) will be performed at Visit 2, Visit 3, Visit 4, Visit 6, and Visit 7, and/or, if applicable, the Early Discontinuation Visit.

The investigator or qualified designee will record the date of the complete and abbreviated physical examinations and whether the physical examination is normal, abnormal but not clinically significant, or abnormal and clinically significant on the appropriate eCRF page. At Visit 1 only, the measurements of height and weight will also be recorded on the appropriate eCRF page. The investigator or qualified designee also will record clinically significant changes as adverse events on the appropriate eCRF page.

7.6.2 Clinical Laboratory Tests

7.6.2.1 Routine Laboratory Tests

The investigator or qualified designee will collect blood and urine samples for the routine laboratory tests shown in Table 7-1 at Visit 1, Visit 2, Visit 4, Visit 6, and Visit 7, and/or, if applicable, the Early Discontinuation Visit.

Blood samples for the routine laboratory tests will be collected in the fasting state at Visit 1 only; patients will be required to fast for 12 hours prior to blood sample collection. For sample collection subsequent to Visit 1, fasting is not required. Patients will be in a seated position during blood collection.

Table 7-1 Routine Laboratory Tests

Test	Analyte
Hematology	Hematocrit, hemoglobin, platelet count, erythrocytes (red blood cells), and leukocytes (white blood cells) with differential (eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count)
Blood chemistry	ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase
Urinalysis	Glucose, occult blood, protein, and urobilinogen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase.

The investigator will determine whether abnormal changes are clinically significant (Section 7.6.5.6), and record any clinically significant changes as adverse events on the appropriate eCRF page.

The investigator or qualified designee will record the date of sample collection for routine laboratory tests on the appropriate eCRF page.

7.6.2.2 Additional Tests

A blood sample will be obtained at Visit 1 for testing for HIV antigen, HIV antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody. For patients with a positive result for hepatitis C virus antibody, the blood sample also will be tested for hepatitis C virus RNA.

For female patients who have not been identified to be postmenopausal (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age) or surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation with appropriate documentation of such surgery, a urine pregnancy test will be performed at Visit 1, Visit 2, Visit 6, and Visit 7 and/or, if applicable, the Early Discontinuation Visit.

The investigator or qualified designee will record the date of sample collection at the specified visit(s) (as applicable) on the appropriate eCRF page.

7.6.2.3 Sample Collection, Storage, and Shipping

Blood and urine samples will be collected at specified observation points by the investigator or qualified designee. All samples except urine samples for pregnancy testing will be sent to the central laboratory for processing. Urine samples for pregnancy testing should be tested at the study site or sent to the local laboratory for testing. Procedures for sample collection, handling, labeling, storage, and shipping are specified in the Laboratory Manual.

COVID-19–related Measure:

In the event a visiting nurse service is used at Visit 4, Visit 5, Visit 6, Visit 7, and/or the Early Discontinuation Visit (if applicable) as described in Section 8, refer to the separate document for directions regarding handling and shipping of blood and urine samples for analysis.

7.6.3 Blood Pressure and Pulse Rate

The investigator or qualified designee will measure systolic and diastolic blood pressure and pulse rate at Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 and/or, if applicable, the Early Discontinuation Visit. Blood pressure and pulse rate will be measured after the patient has been in a sitting position for approximately 3 minutes.

The investigator or qualified designee will record the date of these measurements and the blood pressure and pulse rate measurements at each of these visits on the appropriate eCRF page. The investigator or qualified designee also will record clinically significant changes as adverse events on the appropriate eCRF page (Section 7.6.5.6).

7.6.4 Electrocardiograms

The investigator or qualified designee will perform a standard 12-lead ECG at Visit 1, Visit 2, Visit 6, and Visit 7, and/or, if applicable, the Early Discontinuation Visit. The

ECG will be performed after the patient has been in a recumbent or semi-recumbent position for approximately 3 minutes.

The investigator or qualified designee will assess whether the ECG is normal or abnormal and, if considered abnormal, whether the ECG finding(s) is(are) clinically significant and, if clinically significant, whether related to medical history. Abnormal ECG findings considered to demonstrate a clinically significant change will be recorded as adverse events on the appropriate eCRF page (Section 7.6.5.6).

The investigator or qualified designee will record the date of the ECG at each of these visits, along with the assessment of whether the ECG was normal, abnormal but not clinically significant, or abnormal and clinically significant and, if applicable, relevant medical history on the appropriate eCRF page.

7.6.5 Adverse Events Assessment

7.6.5.1 Definition and Assessment of Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient administered a pharmaceutical product (including investigational drug) during the course of a clinical investigation. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. An elective procedure not reflecting a worsening of a known underlying medical condition is not considered an adverse event, and therefore will not be considered an SAE despite requiring hospitalization. However, complications of a procedure will be considered an adverse event and may be considered an SAE if hospitalization is prolonged (or any other SAE criterion is met). A hospitalization or prolongation of a hospitalization for reasons other than an adverse event would not be considered an SAE.

Adverse events include events that are new in onset, as well as events that are present at Visit 1 and increase in severity or frequency during the study and medical conditions that are present at Visit 1 and worsen during the study. In addition, adverse events include abnormal results of study procedures (eg, physical examinations, laboratory tests, measurements of blood pressure and pulse rate, and ECGs) that are considered by the investigator or qualified designee to be clinically significant.

The investigator or qualified designee is responsible for identifying adverse events. Adverse events may be identified based on the patient’s spontaneous report or based on non-leading questions by the investigator or qualified designee, physical examinations, laboratory tests, blood pressure and pulse rate measurements, and ECGs.

The investigator or qualified designee is responsible for fully investigating and recording the following information about adverse events on the appropriate eCRF page: period of onset (screening period, treatment period, or follow-up period), start date, end date (if an outcome is reported as recovered/resolved or fatal), severity, seriousness with the reason

for considering the adverse event to be serious, relationship to the study drug, action taken to manage the adverse event, and outcome of the adverse event.

7.6.5.2 Assessment Period

Adverse events will be collected from the date of signing the informed consent form through Visit 7 (or 14 days after the date of the last dose of study drug if study drug was discontinued). If a patient withdraws from the study, the investigator or qualified designee will make every effort to collect adverse events for 14 days after the last dose of study drug.

Any adverse event considered to be related to study drug that is ongoing 14 days after the last dose of study drug and any SAE regardless of relationship to study drug that is ongoing 14 days after the last dose of study drug will be followed until resolution, until it is judged by the investigator or qualified designee to have stabilized or become chronic, or until the patient is lost to follow-up.

7.6.5.3 Severity

The investigator or qualified designee will grade the severity of an adverse event according to the following 3 definitions:

- Mild: The event is minor and does not interfere with usual daily activities.
- Moderate: The event causes discomfort and interferes with usual daily activities or affects clinical status.
- Severe: The event interrupts patient's usual daily activities or has a clinically significant effect.

7.6.5.4 Relationship to the Study Drug

The investigator or qualified designee will determine the relationship of an adverse event to the study drug according to the following criteria:

- Related: The adverse event can be reasonably explained as having been caused by the study drug. For example, the occurrence of the adverse event can be explained by a pharmacological effect of the study drug (eg, a similar event has been reported previously); an increase or decrease of the dose affects the occurrence or seriousness of the adverse event; or all other causative factors (eg, medical history, concomitant medication, etc.) have been ruled out after careful analysis of sufficient information.
- Not related: An adverse event that cannot be reasonably explained as having been caused by the study drug.

7.6.5.5 Expectedness

An adverse event considered by the investigator or qualified designee to be related to study drug is considered expected if it is identified in the Investigator's Brochure for

S-600918 in the "Summary of Data and Guidance for Investigators, Reference Safety Information" section.

7.6.5.6 Adverse Event Assessment of Clinical Laboratory Test Results and Other Safety Parameters

For any new abnormal results for routine laboratory tests (defined as values outside the reference range) or for other safety assessments (ie, physical examinations, blood pressure and pulse rate measurements, and ECGs) after Visit 1, the investigator or qualified designee will assess whether those results are clinically significant. For test results that are abnormal at Visit 1 and worsen during the study, the investigator or qualified designee will assess whether those results are clinically significant. Any test result considered to be clinically significant by the investigator or qualified designee is to be recorded as an adverse event. If an abnormal laboratory finding is associated with disease or organ toxicity, the investigator or qualified designee should record only the disease or organ toxicity as an adverse event.

In the following circumstances, the investigator or qualified designee must consider test results to be clinically significant:

- Test results lead to any of the outcomes included in the definition of an SAE (Section 7.6.5.7).
- Test results lead to a change in study drug dosing or discontinuation from the study.
- Test results lead to pharmacologic or other therapy.
- Test results lead to additional diagnostic testing (other than a repeat of the initial test to confirm the result) or other medical intervention.
- Test results meet the management and discontinuation criteria for abnormal liver chemistry tests shown in Appendix 2. In this case, the results of further assessments of liver chemistry criteria and required follow-up must be recorded when completing the appropriate eCRF page.

In all other circumstances, assessment of the clinical significance of test results will be based on the clinical judgment of the investigator or qualified designee.

7.6.5.7 Serious Adverse Events

7.6.5.7.1 Definition

An SAE is defined by regulation as any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening condition
- Hospitalization or prolongation of existing hospitalization for treatment
- Persistent or significant disability/incapacity

- Congenital anomaly/birth defect
- Other medically important condition

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Test results that meet any of the following criteria are considered to be an SAE:

- AST or ALT >3 × ULN and total bilirubin >2 × ULN
- AST or ALT >3 × ULN and prothrombin time or international normalized ratio (PT or INR) >1.5 (Note: The specified INR threshold does not apply to patients receiving anticoagulant therapy.)

The investigator or qualified designee will assess the seriousness of each adverse event.

7.6.5.7.2 Reporting Serious Adverse Events

The investigator or qualified designee must report all SAEs (regardless of the causal relationship to study drug) to the sponsor within 24 hours of becoming aware of the SAE by completing the appropriate eCRF page.

If the electronic data capture (EDC) system is unavailable or technical difficulties are encountered, the SAE must be reported by completing the paper SAE Form and sending it by fax or e-mail to the sponsor. A sample of the paper SAE Form and further instructions are included in the site regulatory binder.

All SAEs, whether or not attributable to study drug, must be reported to the sponsor by completing the eCRF within 24 hours of awareness of the SAE. If the EDC system is unavailable or technical difficulties are encountered, complete the paper SAE Form and fax or e-mail it to:

Country/Region	Phone No.	Fax No.	e-mail
Japan	[redacted]		
Europe			
United States			

If there are any questions, please contact the sponsor at the phone number shown in the table above.

When reporting SAEs, the investigator or qualified designee should record the diagnosis whenever possible. If no diagnosis is available at the time of reporting, individual signs and symptoms can be reported.

The same SAE occurring at a different time interval or considered completely unrelated to a previously reported occurrence of that SAE must be reported as a new SAE. Recurrent episodes, complications, or progression of an initial SAE must be reported as follow-up reports to the original report of that SAE within 24 hours of becoming aware of that new information by completing the appropriate eCRF page or, if the EDC system is not available or technical difficulties are encountered, by completing the paper SAE Form and sending it by fax or e-mail to the sponsor. In addition, follow-up information on an SAE may be requested by the sponsor or designee. The investigator or qualified designee should provide the requested information as soon as it becomes available by completing the appropriate eCRF page. Discharge summaries, consultant reports (from other departments or other hospitals), autopsy reports, and other relevant documents must be evaluated by the investigator, and all relevant information must be reported. Copies of these reports may be requested by the sponsor.

Appropriate measures should be taken by the investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded.

Investigator causality must be provided for all SAEs reported to the sponsor. SAEs with missing investigator causality will be followed up urgently by the sponsor or designee until provided. Clinical, laboratory, and diagnostic tests should be employed by the investigator as needed to adequately determine the etiology of the SAE.

The investigator is not obligated to actively seek adverse events or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE (including a death) at any time after a patient has been discharged from the study and the investigator considers the event to be reasonably related to study drug or study participation, the investigator must promptly notify the sponsor.

The investigator will be responsible for reporting all SAEs to the sponsor and to the IRB or IEC in accordance with local regulatory requirement. The sponsor or designee will be responsible for reporting SAEs to the local regulatory authorities in accordance with applicable regulatory requirements; reporting responsibility is specified in the contract.

7.6.5.8 Adverse Events of Special Interest

No adverse events are considered to be of special interest.

7.6.5.9 Special Situations: Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, and medication errors regarding administration of study drug (as defined below) must be reported to the sponsor or designee as soon as possible by completing the appropriate eCRF page. If there is an associated SAE, the investigator or qualified designee must report the SAE as described in Section 7.6.5.7.2; at the time of reporting the SAE, the special situation also must be reported by completing the appropriate eCRF page.

- Abuse – persistent or sporadic, intentional excessive use of an investigational product, which is accompanied by harmful physical or psychological effects.
- Misuse – Intentional and inappropriate use of an investigational product other than use as directed or indicated at any dose.
- Overdose – Intentional or unintentional intake of investigational product in excess of the assigned dose in the protocol.
- Medication error – any unintended error in the prescribing, dispensing or administration of an investigational product. **Note:** A missed dose or doses of an investigational product are not to be reported as a medication error.

7.6.5.10 Pregnancy

As part of the informed consent process, female patients will be instructed to report pregnancy that occurs after the first dose of the study drug through the follow-up visit as soon as possible to the investigator or qualified designee. If a female patient becomes pregnant during the treatment period, the investigator must instruct the patient to discontinue study drug.

All pregnancies that occur after the first dose of the study drug through the follow-up visit must be reported within 24 hours of becoming aware of the pregnancy. The Pregnancy Form should be completed and sent by fax or e-mail to the sponsor. The investigator or qualified designee must attempt to collect pregnancy information on any patient who becomes pregnant. Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event or SAE, as appropriate. Spontaneous abortions must be reported as an SAE. The outcome of the pregnancy must be followed by the investigator and reported to the sponsor.

All pregnancies must be reported to the sponsor within 24 hours of becoming aware of the pregnancy. Complete the Pregnancy Form and fax or e-mail it to:

Country/Region	Phone No.	Fax No.	e-mail
Japan	[redacted]		
Europe			
United States			

If there are any questions, please contact the sponsor at the phone number shown in the table above.

7.7 Appropriateness of Measurements

In assessing patients with chronic cough, the use of both subjective and objective measures is recommended [33]. This recommendation is particularly important when one considers that cough frequency (an objective measure) is not informative with respect to the severity of cough or the impact of cough on a patient's life. Accordingly, a combination of subjective and objective tools was selected for use in this study. In particular, patient-reported outcomes to assess efficacy will be collected using validated

questionnaires or other instruments, including the VAS to assess cough severity and the LCQ, SF-36, and PGIC to assess QOL or health status. In addition, cough frequency will be determined using a cough monitor widely used in global studies (the VitaloJak™). Overall, the efficacy measures selected for this study are well accepted and commonly used in clinical trials of patients with chronic cough [24,26].

Cough frequency is increasingly used as the primary endpoint in clinical studies in light of the availability of cough monitors to provide objective measurements. Thus, in this study, the primary endpoint was based on the change from baseline (Visit 2) in cough frequency over a 24-hour period after 4 weeks of treatment.

As urinary incontinence is not uncommon in patients with chronic cough, as an exploratory measure, the ICIQ-SF, which is a validated instrument, was selected for use in this study to evaluate the effect of study drug on urinary incontinence [29].

Based on the currently known safety profile of S-600918 and other $P2X_3$ receptor antagonists in development, standard safety assessments were selected for this study, including assessment of adverse events, physical examinations, routine laboratory testing, measurement of blood pressure and pulse rate, and ECGs. These are typical of those used in this patient population and are widely accepted in the conduct of clinical studies.

As taste change was reported with an investigational $P2X_3$ receptor antagonist (gefapixant) [26] and in 2 of 31 (6.5%) of patients in the S-600918 proof-of-concept study (Study VA322), a questionnaire was created to capture descriptive information from any patient who has an adverse event that reflects a taste change after initiation of study drug (Section 9.12.1).

7.8 Allowable Time Windows

Efficacy and safety assessments will be performed according to the schedule in Appendix 1. The time windows shown in Table 7-2 will be allowed for efficacy and safety assessments if the timing of the assessment departs from the schedule specified in Appendix 1.

Table 7-2 Allowable Time Windows for Efficacy and Safety Assessments

Period	Visit	Day	Day of Study Visit	Allowable Time Window (No. of Days)
Screening	1	Day −28 to −18	Day −28 to −18	—[a]
	2	Day −1	Day −1	0 [b]
Treatment	3	Day 1	Day 1 (the day after Day −1)	0
	4	Day 8	1 week after Visit 3	± 2
	5	Day 22	3 weeks after Visit 3	± 2
	6	Day 27	4 weeks after Visit 3	− 2
	Early Discontinuation [c, d]	-	-	+ 3
Follow-up	7 (End-of-study)	Day 42	2 weeks after the last dose of study drug	+ 7

[a] If the cough count recording at Visit 1 is assessed as failed based on initial assessment at the study site, the recording for Visit 1 may be repeated provided it is initiated not later than 8 days after Visit 1 of a 28-day screening period (ie, not later than Day −20).

[b] If the cough count recording at Visit 2 is assessed as failed based on initial assessment at the study site, the recording for Visit 2 may be repeated provided it is initiated not later than 1 day before the end of a 28-day screening period (ie, not later than Day −1).

[c] The last dose of study drug is taken 1 day after Visit 6. Discontinuation of study drug prior to this is considered early discontinuation of study drug.

[d] If the patient discontinues from the study early on the day of a scheduled visit while at the study site, a separate Early Discontinuation Visit is not required. Rather, assessments required at that scheduled visit, as well as those required at the Early Discontinuation Visit, should be performed at that scheduled visit. In addition, the patient should return for follow-up at the End-of-study Visit. Alternatively, if the patient discontinues from the study early on a day between scheduled visits while not at the study site (eg, notifies study site personnel by phone), a separate Early Discontinuation Visit is required. In addition, the patient should return for follow-up at the End-of-study Visit.

Blood sampling for PK assessments will be performed according to the schedule in Appendix 1. The time windows shown in Table 7-3 will be allowed for blood samples for the measurement of plasma drug and metabolite concentrations. Plasma drug and metabolite concentrations determined in blood samples obtained outside of these time windows will be included in PK analyses and will not be handled as missing data.

Table 7-3 Allowable Time Windows for Blood Sample Collection for Measurement of Plasma Drug and Metabolite Concentrations

Period	Visit	Sample Collection	Allowable Time Window
Treatment	4 [a]	1st sample: After patient completion of specified questionnaires and instruments [b]	Pre-dose
		2nd sample: 1 hour after dose [b]	± 15 minutes
		3rd sample: 2 hours after dose [b]	± 15 minutes
	6	After patient completion of specified questionnaires and instruments	Pre-dose or post-dose [c]

[a] On the day of Visit 4, study drug is not to be taken until the first (of 3) blood samples has been collected.

[b] If the patient inadvertently takes the dose of study drug prior to arriving at the study site for Visit 4, the first blood sample will be collected after patient completion of specified questionnaires and instruments. The second and third blood samples will be collected 1 hour and 2 hours after collection of the first blood sample.

[c] There is no restriction regarding the timing of administration of study drug on the day of Visit 6.

8. STUDY ACTIVITIES

Study activities at Visit 1 through Visit 7 and the Early Discontinuation Visit are listed in Section 8. The Time and Events Schedule is provided in Appendix 1.

COVID-19–related Measure:

All patients are required to be evaluated at the study site at Visit 1, Visit 2, and Visit 3 (ie, from screening through randomization).

If, after randomization at Visit 3, a COVID-19–related issue prevents the patient from returning to the study site for Visit 4, Visit 5, Visit 6, Visit 7, and/or the Early Discontinuation Visit, a visiting nurse service may be utilized if locally available and if approved for use. Through this service and under the oversight of the investigator, appropriately trained nurses may complete all protocol-specified activities at Visit 4, Visit 5, Visit 6, Visit 7, and the Early Discontinuation Visit EXCEPT for accessing the IRT for study drug dispensation.

At each visit, the patient must complete all questionnaires or instruments (as described in Section 7) on the electronic tablet before study site personnel perform any other procedures, except at Visit 1 when informed consent must first be obtained.

The investigator and qualified designees are expected to treat patients in accordance with the standard of care and thus may need to take measures beyond those detailed in this protocol to ensure proper patient management and care.

8.1 Visit 1

Every effort should be made to conduct the Visit 1 activities on the same day. However, sometimes this may not possible. For example, the patient may need to go to a different location to complete some of the screening tests or the patient may be reluctant to allow application of the cough monitor at Visit 1 due to personal plans in the next 24 hours. Accordingly, some flexibility is allowed.

- Obtain informed consent.
- Access the IRT to enroll the patient. Record the unique patient identification number assigned to the enrolled patient on the appropriate eCRF page.
- Before conducting any other study procedures, instruct the patient on use of the electronic tablet and have the patient complete on the electronic tablet:
  - the assessment of weekly cough severity on the VAS.
  - the LCQ.
- Assess patient eligibility based on inclusion and exclusion criteria (Section 4.2 and Section 4.3, respectively).
- Obtain the following information and record on the appropriate eCRF page:
  - Administrative: the date the informed consent form was signed and the version of the protocol under which the patient is enrolled.

  - Demographics: year of birth; age; sex; ethnicity; race; for female patients, presence or absence of pregnancy and breastfeeding; drinking (alcohol); smoking (including the number of pack-years if the patient has a prior history of smoking); marijuana use (including all forms of marijuana); and illicit drug use.
  - Medical history includes prior and current conditions (including ocular issues) and their duration, surgeries, and cough-related history (duration of chronic cough and, if previously identified, underlying medical condition[s]).
  - Prior therapies in the 3 months before Visit 1, as well as current therapies. **Note:** "Therapy" includes medications and therapies. Specifically inquire about use of SABAs. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.

- Perform a complete physical examination (including measurement of height and body weight [Section 7.6.1]). Record on the appropriate eCRF page, as specified in Section 7.6.1.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Obtain blood and urine samples for testing (Section 7.6.2), including:
  - Hematology (hematocrit, hemoglobin, platelet count, erythrocytes [red blood cells], and leukocytes [white blood cells] with differential [eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count]).
    - Blood chemistry (ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase).
  - Urinalysis (glucose, occult blood, protein, and urobilinogen).
  - HIV antigen and HIV antibody tests.
  - Hepatitis B virus surface antigen test.
  - Hepatitis C virus antibody test; if test is positive, hepatitis C virus RNA test.
  - Urine pregnancy test for women not identified to be postmenopausal. (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age) or surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation (Section 7.6.2.2).

  Note: Record on the appropriate eCRF page, as specified in Section 7.6.2.1 and Section 7.6.2.2.
- Obtain a chest x-ray or chest CT scan if the patient has not had a chest x-ray or chest CT scan within the past year after the onset of chronic cough. Record the date of the chest imaging and the results as normal, abnormal but not clinically significant, or abnormal and clinically significant on the appropriate eCRF page.

- Obtain an ECG after the patient has been in a recumbent or semi-recumbent position for approximately 3 minutes. Record on the appropriate eCRF page, as specified in Section 7.6.4.
- Measure FEV_1 and FVC and record the date of this testing and these measurements on the appropriate eCRF page. **Note:** The ratio of FEV_1 to FVC will be automatically calculated in the EDC system.

COVID-19–related Measure:

Record FEV_1, FVC, and the date of spirometry testing in the prior calendar year on the appropriate eCRF page. If multiple spirometry data exist, enter the most recent data that reflect the patient's baseline condition. Also, reconfirm that Exclusion Criterion #6 (no known COPD and no uncontrolled asthma symptoms) is not met at the time of screening. **Note:** The ratio of FEV_1 to FVC will be automatically calculated in the EDC system.

- Record adverse events (Section 7.6.5).
- Provide the patient with an eDiary and instruct the patient:
  - on its use and to bring the eDiary to Visit 2, Visit 3, and Visit 4.
  - to think about the waking hours in the preceding day (ie, prior 24 hours) and to record in the eDiary the average number of coughs per hour in the waking hours in that preceding day (ie, prior 24 hours) from the day of Visit 1 up to the day of Visit 2.
  - to record in the eDiary the daily cough severity on the VAS through Day 7 (up to Visit 4).
- Instruct the patient on use of the cough monitor and to wear the monitor for the next 24 hours and then to remove the monitor and return it to the study site within 2 days after completing the cough monitor recording. Apply the cough monitor to the patient, and record the date it was applied on the appropriate eCRF page.
- If the cough monitor has not been returned within 4 days after Visit 1 (ie, 3 days after the patient completes the recording), contact the patient by telephone to follow up on the return of the cough monitor.
- Upon receipt of the cough monitor, assess whether the cough count recording was obtained. If recording is assessed as failed based on initial assessment at the study site, the cough count recording for Visit 1 may be repeated provided it is initiated not later than 8 days after Visit 1 of a 28-day screening period (ie, not later than Day –20).

8.2 Visit 2

- Before conducting any other study procedures, instruct the patient on use of the electronic tablet and have the patient complete on the electronic tablet:
  - the assessment of weekly cough severity on the VAS.
  - the LCQ.
  - the ICIQ-SF.

  - the SF-36.

  Note: The order of administration of these questionnaires/instruments is specified in a separate document.

- Assess patient eligibility based on inclusion and exclusion criteria (Section 4.2 and Section 4.3, respectively).
- Review cough count data from the eDiary to assess compliance with the required 70% completion rate.
- Obtain an updated medical history and the patient's therapies since the last visit. Specifically inquire about use of SABAs while the patient was wearing the cough monitor. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.
- Perform an abbreviated physical examination (respiratory system only) (Section 7.6.1). Record on the appropriate eCRF page, as specified in Section 7.6.1.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Obtain blood and urine samples for testing (Section 7.6.2), including:
  - Hematology (hematocrit, hemoglobin, platelet count, erythrocytes [red blood cells], and leukocytes [white blood cells] with differential [eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count]).
  - Blood chemistry (ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase).
  - Urinalysis (glucose, occult blood, protein, and urobilinogen).
  - Urine pregnancy test for women not identified to be postmenopausal. (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age) or surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation (Section 7.6.2.2).

  Note: Record on the appropriate eCRF page, as specified in Section 7.6.2.1 and Section 7.6.2.2.
- Obtain an ECG after the patient has been in a recumbent or semi-recumbent position for approximately 3 minutes. Record on the appropriate eCRF page, as specified in Section 7.6.4.
- Record adverse events (Section 7.6.5).
- Instruct the patient on use of the eDiary (if indicated) and to continue to record daily cough severity on the VAS through Day 7 (ie, up to Visit 4) in the eDiary when not at the study site.
- Apply the cough monitor to the patient, and record the date it was applied on the appropriate eCRF page. Instruct the patient to wear the cough monitor for the next

24 hours and then to remove the monitor and return it to the study site at the next scheduled visit. **Note:** As Visit 3 takes place 1 day after Visit 2, ensure that the time of Visit 3 is scheduled such that a recording of cough count for the full 24 hours can be obtained.

- Access the IRT to record whether the patient remains eligible to participate in the study and will continue screening at Visit 3.

8.3 Visit 3

- Assess patient eligibility based on inclusion and exclusion criteria (Section 4.2 and Section 4.3, respectively).
- Collect the cough monitor from the patient and assess whether the cough count recording was obtained. If recording is assessed as failed at the study site, the cough count recording for Visit 2 may be repeated provided it is initiated not later than 1 day before the end of a 28-day screening period (ie, not later than Day –1).
- Obtain an updated medical history and the patient's therapies since the last visit. Specifically inquire about use of SABAs while the patient was wearing the cough monitor. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.
- Perform an abbreviated physical examination (respiratory system only) (Section 7.6.1). Record on the appropriate eCRF page, as specified in Section 7.6.1.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Record adverse events (Section 7.6.5).
- After the patient is confirmed to be eligible, access the IRT to randomize the patient. Once the assigned code for the study drug wallet is received, record the code and the randomization date on the appropriate eCRF pages. Then dispense a supply of study drug adequate for 1 week of treatment, and instruct the patient on study drug administration (Section 5.6). Have the patient take that day's dose of study drug while at the study site and enter the date and time study drug is taken in the study drug wallet. Record the date and time of the first dose of study drug on the appropriate eCRF page.
- Instruct the patient on use of the eDiary (if indicated) and to continue to record daily cough severity on the VAS through Day 7 (ie, up to Visit 4) in the eDiary when not at the study site.
- With respect to the next visit (Visit 4), instruct the patient:
  - Not to take study drug before coming to the study site for Visit 4. Explain that study drug will be taken after the patient is at the study site for Visit 4 and when the patient is directed by study site personnel to take study drug that day.

  - To record in the study drug wallet the date and time study drug is taken on the day before Visit 4.
- Upload the cough monitor recording to the specified site within 1 business day after receipt of the cough monitor.

8.4 Visit 4

- Before conducting any other study procedures, instruct the patient on use of the electronic tablet and have the patient complete on the electronic tablet:
  - the assessment of weekly cough severity on the VAS.
  - the LCQ.

  Note: The order of administration of these questionnaires/instruments is specified in a separate document.
- Then obtain the first blood sample for PK analysis (Section 7.5).
- Obtain blood and urine samples for testing (Section 7.6.2), including:
  - Hematology (hematocrit, hemoglobin, platelet count, erythrocytes [red blood cells], and leukocytes [white blood cells] with differential [eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count]).
  - Blood chemistry (ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase).
  - Urinalysis (glucose, occult blood, protein, and urobilinogen).

  Note: Record on the appropriate eCRF page, as specified in Section 7.6.2.1.
- Access the IRT for Study Drug Dispensation. Once the assigned code for the study drug wallet is received, record the code on the appropriate eCRF page. Then dispense a supply of study drug adequate for 2 weeks of treatment and, if indicated, instruct the patient on study drug administration (Section 5.6).
- Have the patient take that day's dose of study drug from the supply of study drug just dispensed after the first blood sample has been obtained for PK analysis, and have the patient record the date and time of this administration in the study drug wallet.
- Obtain the second and third blood samples for PK analysis 1 hour and 2 hours after the patient has taken study drug while at the study site. If the patient inadvertently takes the dose of study drug prior to arriving at the study site, collect the second and third blood samples for PK analysis 1 hour and 2 hours after the collection of the first blood sample.
- Obtain an updated medical history and the patient's therapies since the last visit. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.

- Perform an abbreviated physical examination (respiratory system only) (Section 7.6.1). Record on the appropriate eCRF page, as specified in Section 7.6.1.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Record adverse events (Section 7.6.5).
- Apply the cough monitor to the patient, and record the date it was applied on the appropriate eCRF page. Instruct the patient to wear the cough monitor for the next 24 hours and then to remove the monitor and return it to the study site at the next scheduled visit. **Note:** The cough count recording is to be started within ± 3 hours from the start time of the cough monitor recording at Visit 2.
- Collect the study drug wallet and assess patient compliance with study drug administration (Section 5.9). Record the number of tablets of study drug taken daily and the date taken on the appropriate eCRF page, as well as the number of tablets returned and the date of return.
- Confirm that the patient has entered in the study drug wallet the date and time of study drug administration for the day before Visit 4 and for the day of Visit 4. Record the date and time of study drug administration for the day before Visit 4 and for the day of Visit 4 on the appropriate eCRF page.
- Collect the eDiary from the patient and record the date of collection on the appropriate eCRF page.

8.5 Visit 5

- Before conducting any other study procedures, instruct the patient on use of the electronic tablet and have the patient complete on the electronic tablet:
  - the assessment of weekly cough severity on the VAS.
  - the LCQ.

  Note: The order of administration of these questionnaires/instruments is specified in a separate document.
- Collect the cough monitor from the patient and assess whether the device operated without malfunction and whether the patient used it properly.
- Obtain an updated medical history and the patient's therapies since the last visit. Specifically inquire about use of SABAs while the patient was wearing the cough monitor. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Record adverse events (Section 7.6.5).

- Apply the cough monitor to the patient, and record the date it was applied on the appropriate eCRF page. Instruct the patient to wear the cough monitor for the next 24 hours and then to remove the monitor and return it to the study site at the next scheduled visit. **Note:** The cough count recording is to be started within ± 3 hours from the start time of the cough monitor recording at Visit 2.
- Collect the study drug wallet and assess patient compliance with study drug administration (Section 5.9). Record the number of tablets of study drug taken daily and the date taken on the appropriate eCRF page, as well as the number of tablets returned and the date of return.
- Access the IRT for Study Drug Dispensation. Once the assigned code for the study drug wallet is received, record the code on the appropriate eCRF page. Then dispense a supply of study drug adequate for 1 week of treatment and, if indicated, instruct the patient on study drug administration (Section 5.6).
- With respect to the next visit (Visit 6), instruct the patient that:
  - Study drug may be taken prior to coming to the study site on the day of Visit 6.
  - To record in the study drug wallet the date and time study drug is taken on the day before Visit 6 and on the day of Visit 6.
- Upload the cough monitor recording to the specified site within 1 business day after receipt of the cough monitor.

8.6 Visit 6

- Before conducting any other study procedures, instruct the patient on use of the electronic tablet and have the patient complete on the electronic tablet:
  - the assessment of weekly cough severity on the VAS.
  - the LCQ.
  - the ICIQ-SF.
  - the SF-36.
  - the PGIC.

  Note: The order of administration of these questionnaires/instruments is specified in a separate document.
- Then obtain a blood sample for PK analysis (Section 7.5).
- Obtain blood and urine samples for testing (Section 7.6.2), including:
  - Hematology (hematocrit, hemoglobin, platelet count, erythrocytes [red blood cells], and leukocytes [white blood cells] with differential [eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count]).
  - Blood chemistry (ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase).

  - Urinalysis (glucose, occult blood, protein, and urobilinogen).
  - Urine pregnancy test for women not identified to be postmenopausal. (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age) or surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation (Section 7.6.2.2).

  Note: Record on the appropriate eCRF page, as specified in Section 7.6.2.1 and Section 7.6.2.2.

- Collect the cough monitor from the patient and assess whether the device operated without malfunction and whether the patient used it properly.
- Obtain an updated medical history and the patient's therapies since the last visit. Specifically inquire about use of SABAs while the patient was wearing the cough monitor. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.
- Perform an abbreviated physical examination (respiratory system only) (Section 7.6.1). Record on the appropriate eCRF page, as specified in Section 7.6.1.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Obtain an ECG after the patient has been in a recumbent or semi-recumbent position for approximately 3 minutes. Record on the appropriate eCRF page, as specified in Section 7.6.4.
- Record adverse events (Section 7.6.5).
- If, at any time during the study, the patient had a taste-related adverse event after initiation of study treatment, have the patient complete on the electronic tablet the taste questionnaire.
- Apply the cough monitor to the patient, and record the date it was applied on the appropriate eCRF page. Instruct the patient to wear the cough monitor for the next 24 hours and then to remove the monitor and return it to the study site at the next scheduled visit. **Note:** The cough count recording is to be started within ± 3 hours from the start time of the cough monitor recording at Visit 2.
- Collect the study drug wallet and assess patient compliance with study drug administration (Section 5.9). Record the number of tablets of study drug taken daily and the date taken on the appropriate eCRF page. Ensure that the patient has adequate study drug for the final day of study treatment (Section 5.9).
- Confirm that the patient has entered in the study drug wallet the date and time of study drug administration for the day before Visit 6 and for the day of Visit 6. Record the date and time of study drug administration for the day before Visit 6 and for the day of Visit 6 on the appropriate eCRF page.
- Remind the patient that the last dose of study drug must be taken the day after Visit 6, and instruct the patient to record in the study drug wallet the date and time study drug is taken on the day after Visit 6.

- Upload the cough monitor recording to the specified site within 1 business day after receipt of the cough monitor.

8.7 Visit 7 (End-of-study Visit)

- Collect the cough monitor from the patient and assess whether the device operated without malfunction and whether the patient used it properly.
- Obtain an updated medical history and the patient's therapies since the last visit. Specifically inquire about use of SABAs while the patient was wearing the cough monitor. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.
- Perform an abbreviated physical examination (respiratory system only) (Section 7.6.1). Record on the appropriate eCRF page, as specified in Section 7.6.1.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Obtain blood and urine samples for testing (Section 7.6.2), including:
  - Hematology (hematocrit, hemoglobin, platelet count, erythrocytes [red blood cells], and leukocytes [white blood cells] with differential [eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count]).
  - Blood chemistry (ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase).
  - Urinalysis (glucose, occult blood, protein, and urobilinogen).
  - Urine pregnancy test for women not identified to be postmenopausal. (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age) or surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation (Section 7.6.2.2).

  Note: Record on the appropriate eCRF page, as specified in Section 7.6.2.1 and Section 7.6.2.2.
- Obtain an ECG after the patient has been in a recumbent or semi-recumbent position for approximately 3 minutes. Record on the appropriate eCRF page, as specified in Section 7.6.4.
- Record adverse events (Section 7.6.5).
- Collect the study drug wallet and assess patient compliance with study drug administration (Section 5.9). Record the number of tablets of study drug taken daily and the date taken on the appropriate eCRF page, as well as the number of tablets returned and the date of return.
- Confirm that the patient has entered in the study drug wallet the date and time of study drug administration for the day after Visit 6. Record the date and time of study drug administration on the day after Visit 6 on the appropriate eCRF page.

- Upload the cough monitor recording to the specified site within 1 business day after receipt of the cough monitor.

8.8 Early Discontinuation Visit

Note: If the patient discontinues from the study early on the day of a scheduled visit while at the study site, a separate Early Discontinuation Visit is not required. Rather, assessments required at that scheduled visit, as well as those required at the Early Discontinuation Visit, should be performed at that scheduled visit. In addition, the patient should return for follow-up at the End-of-study Visit. Alternatively, if the patient discontinues from the study early on a day between scheduled visits while not at the study site (eg, notifies study site personnel by phone), a separate Early Discontinuation Visit is required. Note, however, that assessments performed at the prior scheduled visit do not need to be repeated at the Early Discontinuation Visit if those assessments remain within the allowed window (as shown in Table 7-2, Table 7-3, and Appendix 1) for that prior visit AND the patient is not discontinuing due to an adverse event. In addition, the patient should return for follow-up at the End-of-study Visit.

- Before conducting any other study procedures, instruct the patient on use of the electronic tablet and have the patient complete on the electronic tablet:
  - the assessment of weekly cough severity on the VAS.
  - the LCQ.
  - the ICIQ-SF.
  - the SF-36.
  - the PGIC.

  Note: The order of administration of these questionnaires/instruments is specified in a separate document.
- Obtain an updated medical history and the patient's therapies since the last visit. If applicable, specifically inquire about use of SABAs while the patient was wearing the cough monitor. Record on the appropriate eCRF page the information specified for SABAs and restricted therapy in Section 6.2.
- Perform an abbreviated physical examination (respiratory system only) (Section 7.6.1). Record on the appropriate eCRF page, as specified in Section 7.6.1.
- Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes and record these measurements on the appropriate eCRF page (Section 7.6.3).
- Obtain a blood sample for PK analysis (Section 7.5).
- Obtain blood and urine samples for testing (Section 7.6.2), including:
  - Hematology (hematocrit, hemoglobin, platelet count, erythrocytes [red blood cells], and leukocytes [white blood cells] with differential [eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count]).

  - Blood chemistry (ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase).
  - Urinalysis (glucose, occult blood, protein, and urobilinogen).
  - Urine pregnancy test for women not identified to be postmenopausal (defined as at least 12 months of spontaneous amenorrhea in women >45 years of age) or surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation (Section 7.6.2.2).

  Note: Record on the appropriate eCRF page, as specified in Section 7.6.2.1 and Section 7.6.2.2.
- Obtain an ECG after the patient has been in a recumbent or semi-recumbent position for approximately 3 minutes. Record on the appropriate eCRF page, as specified in Section 7.6.4.
- Record adverse events (Section 7.6.5).
- If, at any time during the study, the patient had a taste-related adverse event after initiation of study treatment, have the patient complete on the electronic tablet the taste questionnaire.
- If applicable, collect the cough monitor from the patient and assess whether the device operated without malfunction and whether the patient used it properly.
- Collect the study drug wallet and assess patient compliance with study drug administration (Section 5.9). Record the number of tablets of study drug taken daily and the date taken on the appropriate eCRF page, as well as the number of tablets returned and the date of return.
- Confirm that the patient has entered in the study drug wallet the date and time of study drug administration for (as applicable) the day of Visit 3, Visit 4, and Visit 6. **Note:** For Visit 4 and Visit 6, an entry of the date and time of study drug administration is required for the day before the visit and the day of the visit. Record the date and time of study drug administration for (as applicable) the day of Visit 3, Visit 4, and Visit 6 on the appropriate eCRF page.
- If applicable, collect the eDiary from the patient.
- If applicable, upload the cough monitor recording to the specified site within 1 business day after receipt of the cough monitor.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical analysis and PK analysis will be performed by the sponsor or designee. Statistical analysis and PK analysis methods are briefly summarized in Section 9. Detailed statistical and PK analysis methods will be specified in a statistical analysis plan (SAP). The SAP will be finalized before the scheduled unblinding.

Unless otherwise noted, continuous variables will be summarized based on the number of non-missing observations (N), arithmetic mean (Mean), SD, median, minimum, and maximum values. Categorical variables will be summarized based on the frequency count and the percentage of patients in each category.

All statistical tests will be performed at the 0.05 significance level using 2-sided tests, unless otherwise noted, and statistical testing will not be adjusted for multiple comparisons.

Study data will be presented in by-patient data listings. In general, all tables will be presented by treatment group. Individual patient data, PK data, and any derived data will be presented by treatment group (study drug) (S-600918 50 mg, S-600918 150 mg, S-600918 300 mg, and placebo). All analyses and tabulations will be performed by using SAS Version 9.2 or higher and WinNonlin Version 6.3 or higher.

9.2 Determination of Sample Size

In determining sample size, results of the proof-of-concept study (Study 1727VA322) were considered. In particular, the mean (± SD) of the common log-transformed ratio of cough frequencies per hour in 24 hours after 2 weeks of treatment to that at baseline was −0.327 (0.379) in the S-600918 150-mg treatment (N = 31) and −0.160 (0.363) in the placebo treatment (N = 30). The difference in the common log-transformed ratio of the cough frequencies per hour in 24 hours after 4 weeks of treatment to that at baseline between each S-600918 dose group and placebo and the standard deviation (SD) in each treatment group in the Phase 2b study were assumed to be the same as those after 2 weeks of treatment observed in the proof-of-concept study, and −0.163 and 0.371, respectively. As a result, the effect size, ie, the difference divided by the SD, was determined to be −0.44. Based on this assumption, the sample size required to assure 80% power with a 2-sided 5% level of significance was calculated to be 83 subjects per treatment group. Allowing for exclusion of 10% of subjects per treatment group, 93 subjects per treatment group will be needed. Therefore, the planned sample size at randomization was determined to be a total of 372 subjects. [redacted]

9.3 Analysis Populations

The following analysis populations will be analyzed for this study:

- **Full analysis set (FAS)**, which includes all randomized patients who receive at least 1 dose of study drug and who have cough monitor assessment at baseline and at least 1 visit after initiation of study drug administration. Patients will be analyzed as randomized and not by the actual study drug received in the event of an error in study drug administration.
- **Per-protocol set (PPS)**, which includes all randomized patients who are included in the FAS provided they:
  - Meet all inclusion criteria affecting evaluation of efficacy
  - Meet no exclusion criteria affecting evaluation of efficacy
  - Do not have any major protocol deviations (as defined in the SAP) affecting evaluation of efficacy
  - Do not use any prohibited therapy affecting evaluation of efficacy during the study

  The details will be determined and included in a separate document.
- **PK concentration population**, which includes all patients who receive at least 1 dose of S-600918 and have at least 1 evaluable concentration.
- **Safety population**, which includes all randomized patients who receive at least 1 dose of study drug.

For efficacy, patients will be analyzed by the study drug to which they were randomized. For safety, patients will be analyzed by the study drug received.

9.4 Handling of Missing Data

Missing data will not be imputed in principle.

9.5 Patient Disposition

Among patients randomized, the number and percentage of patients who complete the study and who withdraw from the study, as well as the reasons leading to withdrawal, will be summarized by treatment group. The number of patients included in each analysis population and the number and percentage of patients randomized to each treatment group will also be presented.

9.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the FAS and the Safety Population. Cough counts at both Visit 1 and Visit 2 will be summarized.

9.7 Extent of Exposure and Treatment Compliance

Summary statistics for treatment duration will be presented by treatment group for the Safety Population.

Summary statistics for compliance with study drug administration will be presented by treatment group for the FAS.

9.8 Prior Therapy

Prior drug therapies will be coded using the World Health Organization (WHO) Drug Dictionary and will be summarized by treatment group for the Safety Population.

9.9 Concomitant Therapy

Concomitant drug therapies will be coded using the WHO Drug Dictionary and will be summarized by treatment group for the Safety Population.

9.10 Efficacy Analyses

The FAS will be the primary population for efficacy analyses. The PPS will be used for supplementary analysis of the primary endpoint.

9.10.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the ratio of the number of coughs per hour in 24 hours (based on cough counts recorded by the cough monitor) after administration of study drug for 4 weeks to that at baseline.

9.10.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- A reduction from baseline in the number of coughs per hour in 24 hours by ≥30%, ≥50%, and ≥70%
- The ratio of the number of coughs per hour while awake after administration of study drug for 4 weeks to that at baseline and a reduction by ≥30%, ≥50%, and ≥70%
- The ratio of the number of coughs per hour while asleep after administration of study drug for 4 weeks to that at baseline
- The change from baseline in weekly cough severity as assessed on the VAS (electronic tablet)
- The change from baseline through Day 7 in daily cough severity as assessed on the VAS (eDiary)
- The change in LCQ and achievement of an increase (ie, improvement) of ≥1.3 points
- The change in ICIQ-SF

- The change in SF-36
- PGIC

9.10.3 Analyses of Efficacy Endpoints

For analyses of all efficacy endpoints unless otherwise noted, baseline is defined as Visit 2. All efficacy endpoints will be summarized by visit. The analysis window for the primary endpoint will be defined in the SAP and may not match the visit window in the protocol. The number of coughs (including cough counts by waking and sleeping hours [see Section 7.4.1]) will be provided by cough analysis technicians to the sponsor.

9.10.3.1 Analysis of Primary Endpoint

A mixed effect model will be applied to the common logarithm of the ratio of the number of coughs per hour in 24 hours at Visit 4, Visit 5, and Visit 6 to that at baseline as response. This model will contain treatment group, week, and the interaction between treatment group and week as fixed effect; patient as random effect; and region and the common logarithm of the frequency of coughs per hour in 24 hours at baseline as covariates. The covariance structure will be determined to be unstructured. When the mixed model with unstructured covariance fails in convergence, compound symmetry will be applied as covariance structure. Under this model, the ratio of the number of coughs per hour in 24 hours after 4 weeks of administration to that at baseline will be compared between each dose level of S-600918 and placebo. The dose-response relationship will be evaluated by a comparison of each dose level of S-600918 to placebo. This analysis will be performed for the FAS and the PPS.

Summary statistics for the number of coughs at each visit will include the geometric mean and its 95% confidence interval.

A subgroup analysis based on the combination of region and cough count at baseline will be performed and will include the following subgroups: region (Japan, Europe, and the United States) and cough count at baseline (≥30 coughs/hour and <30 coughs/hour). Another subgroup analysis based on the combination of region and cough count at screening (Visit 1) will be performed and will include the following subgroups: region (Japan, Europe, and the United States) and cough count at screening (≥30 coughs/hour or <30 coughs/hour).

9.10.3.2 Analysis of Secondary Endpoints

The proportion of patients who achieved a reduction from baseline in the number of coughs per hour in 24 hours by ≥30%, ≥50%, and ≥70% after administration of study drug for 4 weeks will be compared between each dose level of S-600918 and placebo by applying the Cochran-Mantel-Haenszel test with strata by region (Japan, Europe, or the United States) and cough count at baseline (≥30 coughs/hour or <30 coughs/hour).

An analysis method similar to that used to determine the ratio of the number of coughs per hour in 24 hours will be applied to the ratio of the number of coughs per hour while awake to that at baseline; change in weekly cough severity as assessed on the VAS

(electronic tablet); change in daily cough severity as assessed on the VAS through Day 7 (eDiary); change in LCQ; change in ICIQ-SF; and change in SF-36. Also, for the number of coughs per hour while awake, the cough severity as assessed on the VAS, and the LCQ, the proportion of patients who achieved a certain level of reduction will be analyzed using the same analysis method applied to the number of coughs per hour in 24 hours. The van Elteren test with strata by region (Japan, Europe, or the United States) and cough count at baseline (≥30 coughs/hour or <30 coughs/hour) will be applied to compare the assessments of PGIC at each dose level of S-600918 to placebo.

9.11 Pharmacokinetic Analysis

Individual plasma concentrations of S-600918 and its metabolite S-600918 acyl glucuronide will be listed with the actual time elapsed from administration of the last dose by patient and plotted against the actual time elapsed from the last dose. In addition, plasma concentrations of S-600918 and S-600918 acyl glucuronide within 20 to 28 hours after the last dose will be summarized as plasma trough concentrations (C_{trough}) by dose and scheduled visit (Visit 4 and Visit 6) with N, Mean, SD, and coefficient of variation (CV%, calculated by SD/Mean × 100); geometric mean (Geometric Mean) and coefficient of variation for geometric mean (CV% Geometric Mean); and median, minimum (Min) and maximum (Max) values. The CV% Geometric Mean will be calculated according to the following formula: CV% Geometric Mean = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd is the standard deviation for natural log (ln)-transformed data. The relationships between C_{trough} of S-600918 and dose will be presented graphically by scheduled visit (Visit 4 and Visit 6).

If C_{trough} is below the lower limit of quantitation, Mean, SD, CV%, Min, Median, and Max will be calculated as 0, and that value will not be included in the calculation of Geometric Mean and CV% Geometric Mean.

9.12 Safety Analyses

9.12.1 Adverse Events

Adverse events will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events reported after the initial dose of study drug will be considered TEAEs and will be analyzed.

The number and percentage of patients with at least 1 TEAE, fatal and nonfatal treatment-emergent SAEs, and TEAEs leading to discontinuation of study drug will be summarized by treatment group. The percentages of patients in these TEAE categories and the 95% confidence intervals will be calculated by using the Clopper-Pearson method. The number and percentage of TEAEs will also be presented. Treatment-related TEAEs will be summarized in the same manner as TEAEs.

The number and percentage of patients with TEAEs will be summarized by MedDRA system organ class and preferred term for each treatment group. The number and percentage of patients with TEAEs by severity and outcome will be presented by MedDRA system organ class and preferred term for each treatment group.

The number and percentage of patients with an adverse event that reflects taste change as defined using the Standardized MedDRA Query (SMQ) category of "Taste and smell disorders" will be summarized by preferred term for each treatment group. Responses to the taste questionnaire will be summarized descriptively.

9.12.2 Clinical Laboratory Tests

For laboratory test results measured quantitatively (ie, hematology and blood chemistry), summary statistics will be provided at each scheduled observation point and for the change from baseline at each scheduled observation point by treatment group. Baseline will be defined as the last value obtained before randomization.

For laboratory test results measured qualitatively (urinalysis), the distribution of results in each category will be summarized at each scheduled observation point by treatment group.

9.12.3 Blood Pressure and Pulse Rate

Summary statistics will be provided for blood pressure and pulse rate at each scheduled observation point and for the change from baseline at each scheduled observation point by treatment group. Baseline will be defined as the last value obtained before randomization.

9.12.4 Electrocardiograms

The distribution of ECG findings (categorized as normal; abnormal but not clinically significant; or abnormal and clinically significant) will be summarized at each observation point by treatment group. Baseline will be defined as the last ECG obtained prior to randomization.

9.13 Interim Analysis

No interim analysis is planned.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Sponsor for Japan:	Shionogi & Co., Ltd. (Head Office) 1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan
Sponsor for the US:	Shionogi Inc. 300 Campus Drive Florham Park, NJ 07932 USA
Sponsor for the countries in Europe:	Shionogi B.V. Kingsfordweg 151 1043 GR Amsterdam, Netherlands
Sponsor's contact:	[redacted] Shionogi & Co., Ltd. 12F, Hankyu Terminal Bldg., 1-4, Shibata 1-chome, Kita-ku, Osaka 530-0012, Japan TEL: [redacted] [redacted] Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA TEL: [redacted] [redacted] Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA TEL: [redacted] [redacted] Shionogi B.V. 33 Kingsway, Holborn, London, WC2B 6UF, UK TEL: [redacted]
Sponsor's chief medical officer:	[redacted] Shionogi & Co., Ltd.
Medical monitor:	[redacted] TEL: [redacted]
Investigator and study site:	Multinational study

Study monitoring:

Central laboratory for clinical laboratory tests:

Bioanalytical laboratory:

Cough monitor laboratory:

Development and operation of IRT:

Device vendor (eDiary and electronic tablet):

Site-to-patient delivery of study drug:

Visiting nurse service:

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The IRB/IEC will safeguard the rights, safety, and well-being of patients by reviewing the following study documents: the protocol, informed consent form, written information

on patient recruitment procedures (if applicable), other written information given to the patients, investigator's brochure, safety updates, annual progress reports (if applicable), and any significant revisions to these documents. The investigator or the sponsor will provide these study documents to the IRB/IEC. The IRB/IEC will be appropriately constituted in accordance with ICH GCP and local requirements, as applicable. The study will be initiated at the study site only after the IRB/IEC has given full approval and the investigator has received written notification of that approval.

Amendments to the protocol will be subject to the same requirements as the initial protocol. The investigator will submit all periodic reports and updates as required by the IRB/IEC. The investigator will inform the IRB/IEC of any reportable adverse events.

10.3 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol approved by the IRB/IEC, all applicable regulatory requirements (including patient privacy requirements), current ICH GCP, and the ethical principles that are outlined in the Declaration of Helsinki.

10.4 Informed Consent Process

The sponsor will provide the investigator with a proposed informed consent form that complies with the ICH GCP and regulatory requirements. The informed consent form will include all the elements required by ICH GCP and any additional elements required by local regulations. The investigator may modify the informed consent form, but the sponsor must approve any modifications before submission to the IRB/IEC. The informed consent form will be reviewed and approved by the appropriate IRB/IEC before use, and the IRB/IEC-approved version must be provided to the site monitor after IRB/IEC approval.

The investigator or qualified designee will explain the nature, purpose and methods, reasonable anticipated benefits (if any), and potential hazards of the study to the patient in simple terms by using the informed consent form approved by the IRB/IEC. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirements.

10.5 Patient Confidentiality

Procedures for protecting patient privacy must adhere to applicable data privacy laws and regulations. In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by the patient identification number only. The investigator will grant site monitor(s) and auditor(s) of the sponsor or designee and regulatory authority(ies) access to all source documents for verification of data collected in the eCRFs and for verification of the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations

for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Patient data collected in the eCRF during the study will be documented in an anonymous fashion, and the patient will only be identified by the patient identification code. In the emergent or rare event that it is necessary to identify a patient for safety or regulatory reasons, the sponsor and the investigator are bound to keep this information confidential in accordance with the applicable laws and regulations.

10.6 Study Monitoring

The sponsor or designee will monitor the study to ensure that the study is conducted in accordance with ICH GCP requirements and the protocol. Study monitoring will be performed by the sponsor or designee through on-site monitoring visits as frequently as necessary, frequent communications (e-mail, letter, telephone, and fax), and centralized monitoring, as appropriate. The site monitor will review data recorded in the eCRF, verify the eCRF entries with source documents, verify that amounts of unused and used study drug are accurate, and confirm the retention of source documents and essential documents.

10.7 Case Report Forms and Source Documents

10.7.1 Case Report Forms

The eCRF will be prepared by using the EDC system. An eCRF for each patient who signed the informed consent form will be provided, and historical information and study data (as specified in this protocol) will be recorded in the eCRF by the investigator or qualified designee within the timeframe specified in the contract. Required patient data as specified in the protocol must be documented in source documents and entered in the eCRF. Only the investigator or qualified designee is authorized to make entries in the eCRF.

When the sponsor or designee generates any queries to the participating study site, eCRF data will be changed or a response to the query will be recorded in accordance with the specific instructions given. The investigator must ensure that data reported in the eCRF is accurate, complete, legible, and timely, as well as sign the eCRF to verify the integrity of the data recorded. Procedures are specified in the electronic CRF Completion Guidelines (eCCG) Manual.

A list of the reference ranges for all laboratory tests to be undertaken will be provided by the central laboratory prior to the initiation of the study and are required to be re-provided if they are changed during the study.

10.7.2 Source Data and Source Documents

Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events, and patient status. The following data can be recorded directly in the eCRF as source data:

- Reason for use of prior therapy and concomitant therapy
- Severity and seriousness of an adverse event and its causal relationship to the study drug
- Any comments entered in the eCRF

The following patient characteristics are automatically calculated in the EDC system:

- Body mass index (BMI)
- FEV_1/FVC

The investigator must maintain source documents, such as laboratory test results, as well as complete and maintain required documentation (eg, medical history and physical examination results). All source documents must be accessible for verification by the site monitor, auditor, the IRB/IEC, and inspections by regulatory authorities. Direct access to these documents must be provided by the investigator or qualified designee at all times. For all sources of original data required to complete the eCRF, the nature and location of the source documents will be identified by the sponsor or designee and study-site personnel. If electronic records are used at the study site, the method of verification must be recorded.

10.7.3 External Data

The following data will be reported separately in documents other than the eCRF:

- Determination of the number of coughs based on the cough monitor
- Patient entries in the electronic tablet and eDiary
- Plasma drug concentration data for S-600918 and its metabolite (S-600918 acyl glucuronide)
- Clinical laboratory data analyzed by the central laboratory

10.8 Committees

10.8.1 Case Review Committee

No case review committee will be established for this study.

10.8.2 Independent Data Monitoring Committee

No independent data monitoring committee will be established for this study.

10.9 Termination or Suspension of the Study

10.9.1 Termination or Suspension of the Entire Study

If a similar suspected unexpected serious adverse reaction (SUSAR) (per sponsor assessment) is reported for 2 different subjects, the Shionogi Global Safety Management Committee will be urgently convened to determine the action to be taken with the study, including (but not limited to) premature termination or suspension of the study.

The sponsor may prematurely terminate or suspend the study at any time for the following reasons:

- Ensuring the safety of patients is difficult due to safety concerns
- Achieving the study objective(s) is considered impossible due to such reasons as failure to recruit an adequate number of patients

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigator. The investigator or qualified designee should promptly inform the participating patients and change the study treatment to other appropriate therapy(ies), if possible.

10.9.2 Termination or Suspension of the Study by Study Site

The investigator may prematurely terminate or suspend the study at the study site with the prior notification of the sponsor at any time when the investigator considers that ensuring the safety of the patient is difficult (eg, occurrence of many SAEs).

The sponsor may request the investigator to prematurely terminate or suspend the study at any time when there are major violations of the protocol or other procedures or lack of compliance with ICH GCP and failure to address these issues.

If the study is prematurely terminated or suspended, the investigator or qualified designee should promptly inform the IRB/IEC and participating patients.

10.10 Protocol Modifications and Deviations

The investigator will conduct the study in compliance with the protocol provided by the sponsor and approval/favorable opinion given by the IRB/IEC and the regulatory authority. Modifications to the protocol are not to be implemented without the prior agreement of the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when a modification is needed to eliminate an immediate hazard(s) to patients or for other inevitable medical reasons.

The investigator should document any deviation from the protocol and the reason. If the investigator deviates from the protocol or makes a change to the protocol to eliminate an immediate hazard(s) to patients, the record should be immediately submitted to the sponsor, the medical institution (if required by local regulation), and the IRB/IEC by the investigator; any deviations or modifications require expedited review and approval by the IRB. After the investigator obtains approval/favorable opinion from the IRB/IEC, the investigator should obtain the written agreement of the sponsor.

When deviation from the protocol is required to eliminate immediate hazard(s) to patients or for other inevitable medical reasons, the investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented.

10.11 Data Management

The sponsor or designee will be responsible for data management. Procedures are specified in separate documents, including but not limited to the Data Management Plan.

10.12 Retention of Data

Study documents must be maintained as specified in the ICH GCP guideline and as required by applicable regulatory requirements. The investigator and study-site personnel should take measures to prevent these documents from being damaged or prematurely destroyed.

If the sponsor is granted manufacturing or marketing approval for the drug, the sponsor will promptly notify the head of the study site in writing.

Records will be retained for the longest of the following periods:

- At least 2 years after approval of the last marketing application
- Three years after formal discontinuation of the clinical development of the investigational product or after discontinuation or completion of the study
- For a minimum of 15 years after the end of the clinical trial or longer if required by local regulations and EU Directive 2003/63/EC Article 5.2
- Other period in accordance with applicable local laws, regulations, and other regulatory requirements, whichever is latest

However, the duration of retention may be extended in accordance with an agreement with the sponsor. If the investigator withdraws from study responsibilities, responsibility for record retention must be transferred to an appropriate person willing to accept the responsibility.

10.13 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof; ICH GCP guidelines; and applicable regulatory requirements.

Training necessary for the study will be provided to the investigator and study-site personnel prior to study initiation at the site.

10.14 Publication and Disclosure Policy

All information regarding S-600918 supplied by the sponsor to the investigator is confidential. The investigator agrees to use this information to conduct the study and not

to use it for other purposes without the written consent of the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical trial will be used toward the development of S-600918 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

The sponsor will retain ownership of all data. All proposed publications based on this study will be subject to the sponsor's approval.

The key design elements of this protocol will be posted in a publicly accessible database.

10.15 Financial Disclosure

The information on financial disclosure for investigators is addressed in a separate agreement between the sponsor and the investigator.

11. REFERENCE LIST

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Appendix 1 Time and Events Schedule

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	—	—	—	1	3	4	—	—
Day	Day −28 to −18	Day −1	Day 1	Day 8	Day 22	Day 27 [b]	—	Day 42
Study Visit	Day −28 to −18	Day −1	Day 1 (the day after Day −1)	1 week after Visit 3	3 weeks after Visit 3	2 days prior to 4 weeks after Visit 3	Day of last dose of study drug	2 weeks after last dose of study drug
Allowable time window (days)	—	0	0	± 2	± 2	− 2	+ 3	+ 7
Administrative activities								
Obtain informed consent	X							
Assess inclusion/exclusion criteria	X	X	X					
Access IRT to enroll pt	X							
Obtain administrative and demographic data [c]	X							
Obtain medical history [d]	X	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]
Obtain prior and current therapies [f]	X	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]
Access IRT to record whether pt remains eligible to participate and will continue screening at Visit 3		X						
Access IRT to randomize pt			X					
Electronic device activities								
Instruct pt on use of electronic tablet and eDiary at Visit 1 and, if indicated, at subsequent visits	X	X		X	X	X	X	

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	—	—	—	1	3	4	—	—
Day	Day −28 to −18	Day −1	Day 1	Day 8	Day 22	Day 27 [b]	—	Day 42
Study Visit	Day −28 to −18	Day −1	Day 1 (the day after Day −1)	1 week after Visit 3	3 weeks after Visit 3	2 days prior to 4 weeks after Visit 3	Day of last dose of study drug	2 weeks after last dose of study drug
Allowable time window (days)	—	0	0	± 2	± 2	− 2	+ 3	+ 7
Remind pt to make entries in eDiary when not at study site	X	X	X					
Instruct pt to bring eDiary to Visit 2, Visit 3, and Visit 4	X							
Patient self-assessment (electronic tablet)								
• Weekly severity of cough (VAS)	X	X		X	X	X	X	
• LCQ	X	X		X	X	X	X	
• ICIQ-SF		X				X	X	
• SF-36		X				X	X	
• PGIC						X	X	
Patient self-assessment (eDiary):								
• Average daily number of coughs per hour; at Visit 2, assess pt vs Exclusion Criterion #1 [g]	←	→						
• Daily severity of cough (VAS); at Visit 1 and Visit 2, assess pt vs Inclusion Criterion #5 [h]	←		→					
Instruct pt on use of cough monitor and apply monitor	X	X [i]		X [j]	X [j]	X [j]		

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	**—**	**—**	**—**	**1**	**3**	**4**	**—**	**—**
Day	**Day −28 to −18**	**Day −1**	**Day 1**	**Day 8**	**Day 22**	**Day 27 [b]**	**—**	**Day 42**
Study Visit	**Day −28 to −18**	**Day −1**	**Day 1 (the day after Day −1)**	**1 week after Visit 3**	**3 weeks after Visit 3**	**2 days prior to 4 weeks after Visit 3**	**Day of last dose of study drug**	**2 weeks after last dose of study drug**
Allowable time window (days)	**—**	**0**	**0**	**± 2**	**± 2**	**− 2**	**+ 3**	**+ 7**
Receive cough monitor from pt and assess its use [k]	X [l]		X [m]		X	X	X [n]	X
Upload cough monitor recording within 1 business day after receipt of cough monitor	X		X		X	X	X [n]	X
Clinical assessments								
Perform physical examination	X [o]	X [p]	X [p]	X [p]		X [p]	X [p]	X [p]
Measure blood pressure and pulse rate [q]	X	X	X	X	X	X	X	X
Record adverse events	X	X	X	X	X	X	X [r]	X
Administer taste questionnaire [s]						X [s]	X [s]	
Laboratory assessments								
Obtain blood and urine samples for routine laboratory tests; if applicable, report liver chemistry abnormalities (Appendix 2) on appropriate page of eCRF [t, u]	X	X		X		X	X	X

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	—	—	—	1	3	4	—	—
Day	Day −28 to −18	Day −1	Day 1	Day 8	Day 22	Day 27 [b]	—	Day 42
Study Visit	Day −28 to −18	Day −1	Day 1 (the day after Day −1)	1 week after Visit 3	3 weeks after Visit 3	2 days prior to 4 weeks after Visit 3	Day of last dose of study drug	2 weeks after last dose of study drug
Allowable time window (days)	—	0	0	± 2	± 2	− 2	+ 3	+ 7
Obtain blood sample(s) for HIV antigen and antibody, hepatitis B virus surface antigen, hepatitis C virus antibody and, if indicated, hepatitis C virus RNA tests [v]	X							
If not identified to be postmenopausal or surgically sterile by hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy or tubal ligation [u, w], perform urine pregnancy test	X	X				X	X	X
Obtain blood sample(s) for PK analysis				X [x]		X [y]	X [z]	
Other assessments								
If no chest x-ray or chest CT scan within past year after onset of chronic cough, obtain chest x-ray or chest CT scan	X							
Perform ECG [aa]	X	X				X	X	X

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	—	—	—	1	3	4	—	—
Day	Day −28 to −18	Day −1	Day 1	Day 8	Day 22	Day 27 [b]	—	Day 42
Study Visit	Day −28 to −18	Day −1	Day 1 (the day after Day −1)	1 week after Visit 3	3 weeks after Visit 3	2 days prior to 4 weeks after Visit 3	Day of last dose of study drug	2 weeks after last dose of study drug
Allowable time window (days)	—	0	0	± 2	± 2	− 2	+ 3	+ 7
Measure FEV_1 and FVC OR, if operating under COVID-19 measures, record FEV_1, FVC, and the date of spirometry testing in the prior calendar year on the appropriate eCRF page and reconfirm pt does not meet Exclusion Criterion #6; then assess pt vs Exclusion Criterion #19 [bb].	X							
Study drug administration								
Access IRT for Study Drug Dispensation; dispense study drug and instruct pt on administration at Visit 3 and, if indicated, at Visit 4 and Visit 5 [b]			X	X	X			
Ensure pt has study drug for day after Visit 6 and instruct pt to take last dose of study drug on day after Visit 6						X		
Pt study drug administration			←	—	—	→		

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	—	—	—	1	3	4	—	—
Day	Day −28 to −18	Day −1	Day 1	Day 8	Day 22	Day 27 [b]	—	Day 42
Study Visit	Day −28 to −18	Day −1	Day 1 (the day after Day −1)	1 week after Visit 3	3 weeks after Visit 3	2 days prior to 4 weeks after Visit 3	Day of last dose of study drug	2 weeks after last dose of study drug
Allowable time window (days)	—	0	0	± 2	± 2	− 2	+ 3	+ 7
For Visit 3 and Visit 4, have pt take dose of study drug while at study site and have pt record date and time study drug is taken in study drug wallet			X	X				
For upcoming Visit 4, instruct pt: • not to take study drug before coming to study site for Visit 4 and explain that study drug will be taken when pt is at study site for Visit 4 and is directed by study site personnel to take study drug that day • to record date and time study drug is taken on day before Visit 4 in study drug wallet			X					
For upcoming Visit 6, instruct pt to record date and time study drug is taken on day before AND day of Visit 6 in study drug wallet					X			
Instruct pt to record date and time study drug is taken on day after Visit 6 in study drug wallet						X		

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	—	—	—	1	3	4	—	—
Day	Day −28 to −18	Day −1	Day 1	Day 8	Day 22	Day 27 [b]	—	Day 42
Study Visit	Day −28 to −18	Day −1	Day 1 (the day after Day −1)	1 week after Visit 3	3 weeks after Visit 3	2 days prior to 4 weeks after Visit 3	Day of last dose of study drug	2 weeks after last dose of study drug
Allowable time window (days)	—	0	0	± 2	± 2	− 2	+ 3	+ 7
Collect study drug wallet; assess pt compliance/drug accountability and record number of tablets of study drug taken daily and date taken and number of tablets returned and date returned; if applicable, report Special Situations (Section 7.6.5.9) on eCRF [cc]				X	X	X	X	X
If operating under COVID-19 measures and study drug adequate for 3 weeks of treatment is dispensed at Visit 4 or delivered (as described in Section 7.2) to a patient who was not compliant with study drug administration in the week between Visit 3 and Visit 4 (ie, either took more or less study drug than specified in the protocol), contact the patient 7 ± 2 days after delivery of study drug at Visit 4 to assess treatment compliance.				X [dd]				

Visit	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
	Visit 1 (First screening)	Visit 2 (Second screening ≥17 days after Visit 1)	Visit 3	Visit 4	Visit 5	Visit 6	Early Discontinu-ation Visit (if study drug is discontin-ued prior to 1 day after Visit 6) [a]	Visit 7 (End-of-study Visit)
Week	—	—	—	1	3	4	—	—
Day	Day −28 to −18	Day −1	Day 1	Day 8	Day 22	Day 27 [b]	—	Day 42
Study Visit	Day −28 to −18	Day −1	Day 1 (the day after Day −1)	1 week after Visit 3	3 weeks after Visit 3	2 days prior to 4 weeks after Visit 3	Day of last dose of study drug	2 weeks after last dose of study drug
Allowable time window (days)	—	0	0	± 2	± 2	− 2	+ 3	+ 7
Confirm pt has entered date and time of study drug administration in study drug wallet for Visit 3, Visit 4 (day before and day of visit), Visit 6 (day before and day of visit), and day after Visit 6			X	X [ee]		X [ee]	X	X [ff]
Record date and time of study drug administration for Visit 3, Visit 4 (day before and day of visit), Visit 6 (day before and day of visit), and day after Visit 6 on eCRF			X	X		X		X
Collect eDiary from pt				X			X	

CT = computed tomography; eCRF = electronic case report form; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; HIV = human immunodeficiency virus; ICIQ-SF = International Consultation on Incontinence Modular Questionnaire-Short Form; ID = identification; IRT = Interactive Response Technology; LCQ = Leicester Cough Questionnaire; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; pt = patient; SABAs = short-acting beta-2 agonists; SF-36 = Short Form (36) Health Survey; VAS = Visual Analog Scale; vs = versus.

[a] If the patient discontinues from the study early on the day of a scheduled visit while at the study site, a separate Early Discontinuation Visit is not required. Rather, assessments required at that scheduled visit, as well as those required at the Early Discontinuation Visit, should be performed at that scheduled visit. In addition, the patient should return for follow-up at the End-of-study Visit. Alternatively, if the patient discontinues from the study early on a day between scheduled visits while not at the study site (eg, notifies study site personnel by phone), a separate Early Discontinuation Visit is required. Note, however, that assessments performed at the prior scheduled visit do not need to be repeated at the Early Discontinuation Visit if those assessments remain within the allowed window (as shown in Table 7-2 and Table 7-3) for that prior visit AND the patient is not discontinuing due to an adverse event. In addition, the patient should return for follow-up at the End-of-study Visit.

[b] The last dose of study drug is taken 1 day after Visit 6.

[c] Administrative data includes date informed consent form was signed and version of protocol under which patient was enrolled. Demographic data includes year of birth; age; sex; ethnicity; race; for female patients, presence or absence of pregnancy and breastfeeding; drinking (alcohol); smoking (including the number of pack-years if the patient has a prior history of smoking); marijuana use (including all forms of marijuana); and illicit drug use.

[d] Medical history includes prior and current conditions (including ocular issues) and their duration, surgeries, and cough-related history (duration of chronic cough and, if previously identified, underlying medical condition[s]).

[e] Update from prior visit.

[f] "Therapy" includes medications and therapies. As applicable during the study period, review prior therapy in the 3 months before Visit 1, as well as current therapy. All patients must be asked about the use of SABAs at Visit 1 and while wearing the cough monitor when reviewing prior and concomitant therapies (as applicable) at Visit 2, Visit 3, Visit 5, Visit 6, Visit 7, and/or, if applicable, the Early Discontinuation Visit.

[g] Assess patient compliance with eDiary completion criterion of at least 70% from day of Visit 1 up to day of Visit 2; completion percentage will be automatically calculated in the eDiary.

[h] Assess the patient for severity of cough of ≥40 mm on the VAS (eDiary).

[i] As Visit 3 takes place 1 day after Visit 2, ensure that the time of Visit 3 is scheduled such that a recording of cough count for the full 24 hours can be obtained.

[j] The cough count recording is to be started within ± 3 hours from the start time of the cough monitor recording at baseline (Visit 2).

[k] Following completion of the 24-hour recording, the cough monitor applied at Visit 1 will be returned by the patient within 2 days after completing the recording, and the cough monitor applied at Visit 2, Visit 4, Visit 5, and Visit 6 will be returned by the patient at the next visit (ie, Visit 3, Visit 5, Visit 6, and Visit 7, respectively). Upon receipt of cough monitor, assess whether the recording was successfully obtained.

[l] If the cough monitor has not been returned within 4 days after Visit 1 (ie, 3 days after the patient completes the recording), contact the patient by telephone to follow up on the return of the cough monitor. If the cough monitor recording at Visit 1 is assessed as failed based on initial assessment at the study site, the recording for Visit 1 may be repeated provided it is initiated not later than 8 days after Visit 1 of a 28-day screening period (ie, not later than Day −20).

[m] If the cough monitor recording at Visit 2 is assessed as failed based on initial assessment at the study site, the recording for Visit 2 may be repeated provided it is initiated not later than 1 day before the end of a 28-day screening period (ie, not later than Day −1).

[n] If applicable.

[o] The physical examination at Visit 1 includes height and body weight.

[p] The physical examination at all visits after Visit 1 is abbreviated and limited to the respiratory system only.

[q] Measure blood pressure and pulse rate after the patient has been in a sitting position for approximately 3 minutes.

[r] Provided consent has not been withdrawn, the investigator or qualified designee will make every effort to collect adverse events for 14 days after the last dose of study drug.

[s] Administer the taste questionnaire at Visit 6 or, if applicable, the Early Discontinuation Visit to only those patients who have reported a taste-related adverse event after initiation of study drug.

[t] Routine laboratory tests are to be conducted with the patient in a fasting state at Visit 1 only; patients will be required to fast for 12 hours prior to blood sample collection. For sample collection subsequent to Visit 1, fasting is not required. Tests include: Hematology (hematocrit, hemoglobin, platelet count, erythrocytes [red blood cells], and leukocytes [white blood cells] with differential [eosinophil count, basophil count, neutrophil count, monocyte count, and lymphocyte count]; blood chemistry (ALP, ALT, AST, total bilirubin, GGT, lactate dehydrogenase, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid, total cholesterol, and creatine phosphokinase); and urinalysis (glucose, occult blood, protein, and urobilinogen).

[u] All samples except urine samples for pregnancy testing will be sent to the central laboratory for processing. Urine samples for pregnancy testing should be tested at the study site or sent to the local laboratory for testing.

[v] Testing for hepatitis C virus RNA is required only for patients with a positive hepatitis C virus antibody test.

[w] Postmenopausal is defined as at least 12 months of spontaneous amenorrhea in women >45 years of age. Once a female patient is identified to be postmenopausal, the urine pregnancy test is not to be repeated.

[x] On the day of Visit 4, the first blood sample for PK analysis is to be collected after patient completion of specified questionnaires and instruments prior to study drug administration and 1 hour and 2 hours after study drug administration at the study site. If the patient inadvertently takes study drug prior to arrival at the study site, collect the first blood sample for PK analysis after patient completion of specified questionnaires and instruments and collect the second and third blood samples for PK analysis 1 hour and 2 hours after collection of the first blood sample for PK analysis.

[y] On the day of Visit 6, study drug may be taken prior to coming to the study site. The blood sample for PK analysis is to be collected after patient completion of specified questionnaires and instruments.

[z] Collect sample for PK analysis only if the patient discontinues study drug prior to 1 day after Visit 6.

[aa] The ECG is obtained after the patient has been in a recumbent or semi-recumbent position for approximately 3 minutes.

[bb] The ratio of FEV_1 to FVC will be automatically calculated in the EDC system.

[cc] Special situations include abuse, misuse, overdose, and medication errors regarding administration of study drug (as defined in Section 7.6.5.9).

[dd] Contact 1 week after Visit 4.

[ee] For Visit 4 and Visit 6, confirm that the patient has entered in the study drug wallet the date and time study drug is taken the day before the visit AND the day of the visit.

[ff] At Visit 7, confirm that the patient has entered in the study drug wallet the date and time study drug is taken on the day after Visit 6.

Appendix 2 Management and Discontinuation Criteria for Abnormal Liver Chemistry Tests

Management and Discontinuation Criteria for Abnormal Liver Chemistry Tests have been designed to ensure patient safety and evaluate liver event etiology. (See Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, FDA: July 2009)

1. Abnormal Liver Chemistry Criteria

The investigator or qualified designee must review patient laboratory test results to identify if any levels meet the following criteria:

a. AST or ALT >5 × ULN
b. AST or ALT >3 × ULN and total bilirubin >2 × ULN or, if measured, PT or INR >1.5 (Note: The specified INR threshold does not apply to patients receiving anticoagulant therapy.)
c. AST or ALT >3 × ULN with signs or symptoms consistent with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, eosinophilia of >5%)

2. Action to be Taken by Investigator

If any abnormal liver chemistry criterion is met, the investigator or qualified designee must do the following:

- Report this event to the sponsor as soon as possible, but no later than 72 hours after learning of its occurrence by completing the appropriate eCRF page. If the EDC system is unavailable or technical difficulties are encountered, the event must be reported by completing the paper Liver Event Form and sending it by fax or e-mail to the sponsor. Local fax numbers and the e-mail address are provided in the table in Section 7.6.5.7.2. A sample of the paper Liver Event Form and further instructions are included in the site regulatory binder.
- Patients must be instructed to discontinue study medication if any one of the criteria in Appendix 2, Section 4 (“Drug Discontinuation Criteria Due to Abnormal Liver Chemistry Tests”) is met. Study drug may also be discontinued based on the clinical judgment of the investigator. The investigator or qualified designee should not re-challenge the patient with the investigational product.
- Following the initial observed elevation, every effort should be made to have the patient return to the clinic within 72 hours to repeat liver chemistry tests and for further hepatic evaluation.
- Every effort should be made to have the patients monitored 2 to 3 times per week until abnormal liver chemistry tests (ALT, AST, ALP, total bilirubin) resolve, stabilize, or return to within the normal range or to baseline levels.
- Consultation with a specialist such as a hepatologist should be considered.

- Liver imaging (ie, ultrasound, magnetic resonance imaging, CT scan) should be considered.
- For Criterion b, the case must be reported as an SAE if the criterion is met after initiation of study drug administration.

3. Follow-up Examination

When any of the abnormal liver chemistry criteria are met, the following assessments should be performed at the follow-up visit(s) and reported by completing the appropriate eCRF page:

- Clinical symptoms course
- Alcohol use
- Risk factors for nonalcoholic steatohepatitis (NASH), such as diabetes, obesity, and hypertriglyceridemia
- Autoimmune hepatitis/cholangitis
- Wilson's disease
- Laboratory assessments
  - Viral hepatitis serology
    - Hepatitis A IgM antibody
    - Hepatitis B surface antigen (HBs antigen) and Hepatitis B core antibody (HBc antibody)
    - Hepatitis C RNA
    - Hepatitis E IgA antibody
    - Cytomegalovirus IgM antibody
    - Epstein-Barr viral capsid antigen IgM antibody
  - For patients with total bilirubin >1.5 × ULN, conjugated bilirubin
  - Complete blood count with differential to assess for eosinophilia

4. Drug Discontinuation Criteria Due to Abnormal Liver Chemistry Tests

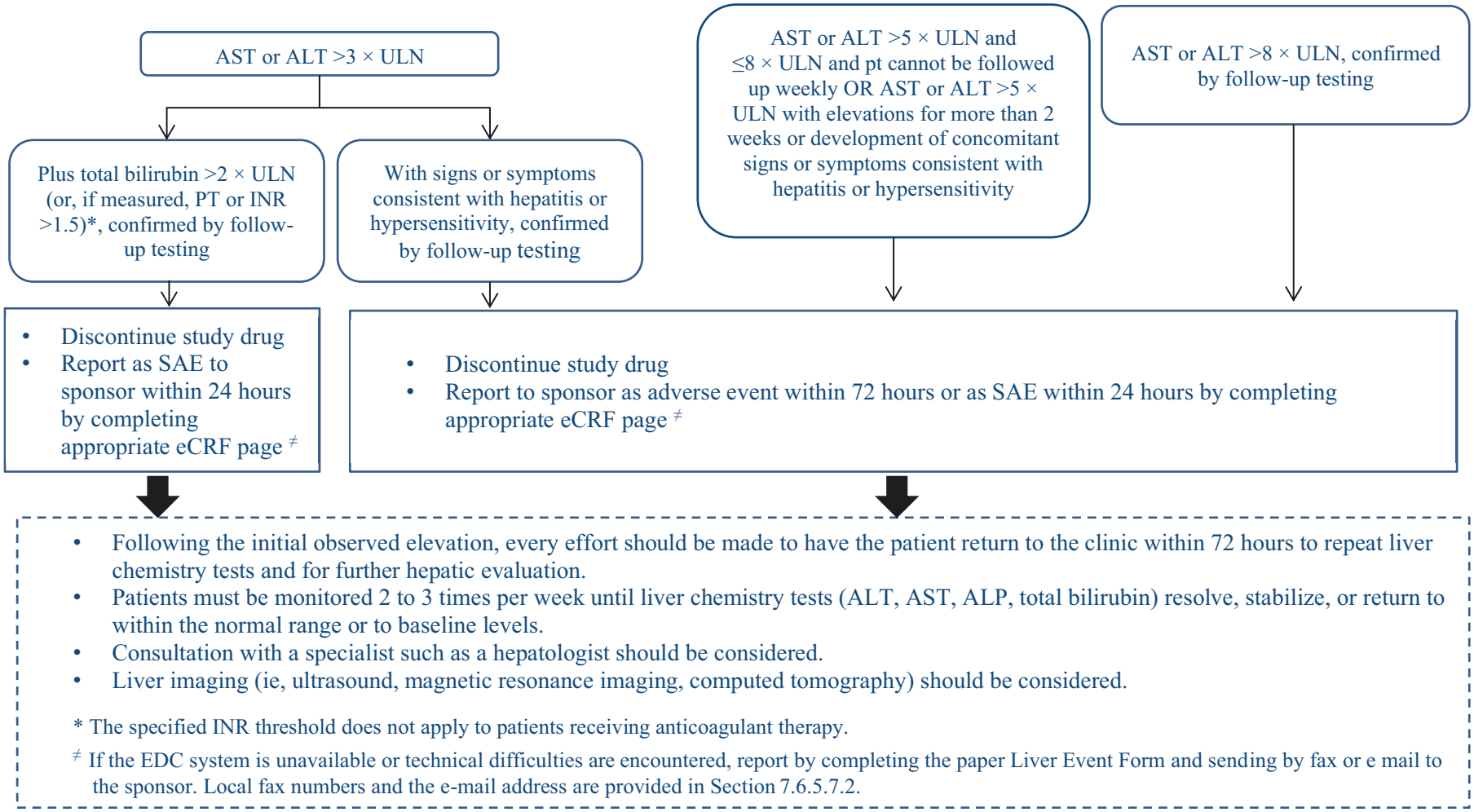
Study drug must be discontinued if any one of the following criteria is met:

- AST or ALT >8 × ULN, confirmed by follow-up testing (ie, initial abnormality is confirmed on subsequent testing), regardless of medical history or physical examination findings
- AST or ALT >5 × ULN, with elevations for more than 2 weeks or development of concomitant signs or symptoms consistent with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, or eosinophilia of >5%)
- AST or ALT >3 × ULN and total bilirubin >2 × ULN or, if measured, PT or INR >1.5, confirmed by follow-up testing (ie, initial abnormality is confirmed on subsequent testing), regardless of medical history or physical examination

findings. (Note: The specified INR threshold does not apply to patients receiving anticoagulant therapy.)

- AST or ALT >3 × ULN, with signs or symptoms consistent with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, or eosinophilia of >5%), confirmed by follow-up testing (ie, initial laboratory abnormality is confirmed upon subsequent testing)
- AST or ALT >5 × ULN and ≤8 × ULN and the patient cannot be followed up weekly

Appendix Figure 2-1 Management and Discontinuation Criteria for Abnormal Liver Chemistry Tests: Algorithm



* The specified INR threshold does not apply to patients receiving anticoagulant therapy.

≠ If the EDC system is unavailable or technical difficulties are encountered, report by completing the paper Liver Event Form and sending by fax or e mail to the sponsor. Local fax numbers and the e-mail address are provided in Section 7.6.5.7.2.

Appendix 3 Sponsor's Signature

Product Name:	S-600918
Study Title:	A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-selection study of S-600918 in patients with refractory chronic cough
Study Number:	1812VA323
Date of Original:	04 Sep 2019
Date of Latest Amendment:	10 Sep 2020

This clinical study protocol was subject to critical review and has been approved by the sponsor:

Refer to electronic signature page

[redacted]
Shionogi & Co., Ltd.
ID: [redacted]

Refer to electronic signature page

Date: day-month-year

Appendix 4 Investigator's Signature

Product Name:	S-600918
Study Title:	A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-selection study of S-600918 in patients with refractory chronic cough
Study Number:	1812VA323
Date of Original:	04 Sep 2019
Date of Latest Amendment:	10 Sep 2020

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>