[redacted] **Biostatistics and Programming**

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Shionogi, Inc.**
Protocol Number:	**1812VA323**

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Shionogi

1812VA323

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

26FEB2021

Statistical Analysis Plan

Version *1.2*

Prepared by: [redacted]

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Document History – Changes compared to previous version of SAP:

Version	Date	Author	Changes from Previous Version
1.0	20DEC2019	[redacted]	Original Issue
1.1	26JUN2020	[redacted]	Added section 5.3 to address COVID-19 / SARS-COV-2. Added descriptions of Original and Latest data and handling for Patient Reported Outcomes in section 4.
1.2	22FEB2021	[redacted]	Updated Analysis of Leicester Cough Questionnaire data in section 8.2.4 to account for translation error in Ukrainian. Updated analysis window descriptions in section 4.

TABLE OF CONTENTS

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
C_{max}	maximum plasma drug concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough plasma concentration
CV%	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FU	follow-up
FVC	forced vital capacity
ICIQ-SF	International Consultation on Incontinence Modular Questionnaire-Short Form
ie	that is
IRT	Interactive Response Technology
LCQ	Leicester Cough Questionnaire
MCS	mental components summary
MedDRA	Medical Dictionary for Regulatory Activities
PCS	physical components summary
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PPS	per protocol set
PRO	patient reported outcome
PT	preferred term
PT-INR	prothrombin time international normalized ratio
S-600918	a selective $P2X_3$ receptor antagonist
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36	Short Form (36) Health Survey
SI	International System of Units
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	treatment-emergent adverse events
US	United States Customary Units
VAS	Visual Analog Scale
WHO	World Health Organization
x ULN	times the upper limit of the normal reference range

1. Introduction

This is a Phase 2b study of S-600918 for the treatment of refractory chronic cough. Coughing is a defense mechanism that eliminates sputum and foreign bodies from the airways. Chronic cough is defined as cough that persists for ≥ 8 weeks. Refractory chronic cough is further defined as a chronic cough after the patient is treated for an underlying medical condition, as well as chronic cough for which an underlying medical condition has not been identified despite appropriate patient evaluation. An estimated 2% to 5% of the population of Europe, the United States, and Japan suffers from refractory chronic cough. There are currently no drugs approved for the treatment of refractory chronic cough.

S-600918 is a $P2X_3$ receptor antagonist developed by Shionogi & Co., Ltd that is formulated for once daily oral administration. In previous studies, this class of drugs has shown an effect in suppressing the cough reflex among patients with refractory chronic cough. Four previous studies of S-600918 have been completed, including a phase 1 single ascending dose & food effect study, a phase 1 multiple ascending dose study, a Phase 1 drug-drug interaction study, and a phase 2 crossover study in refractory chronic cough patients. The data from these studies has informed the design of Study 1812VA323 (this VA323 study) and are discussed in further detail in section 1.2.2 of the protocol.

2. 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.

The secondary objectives 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 by the patient 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.

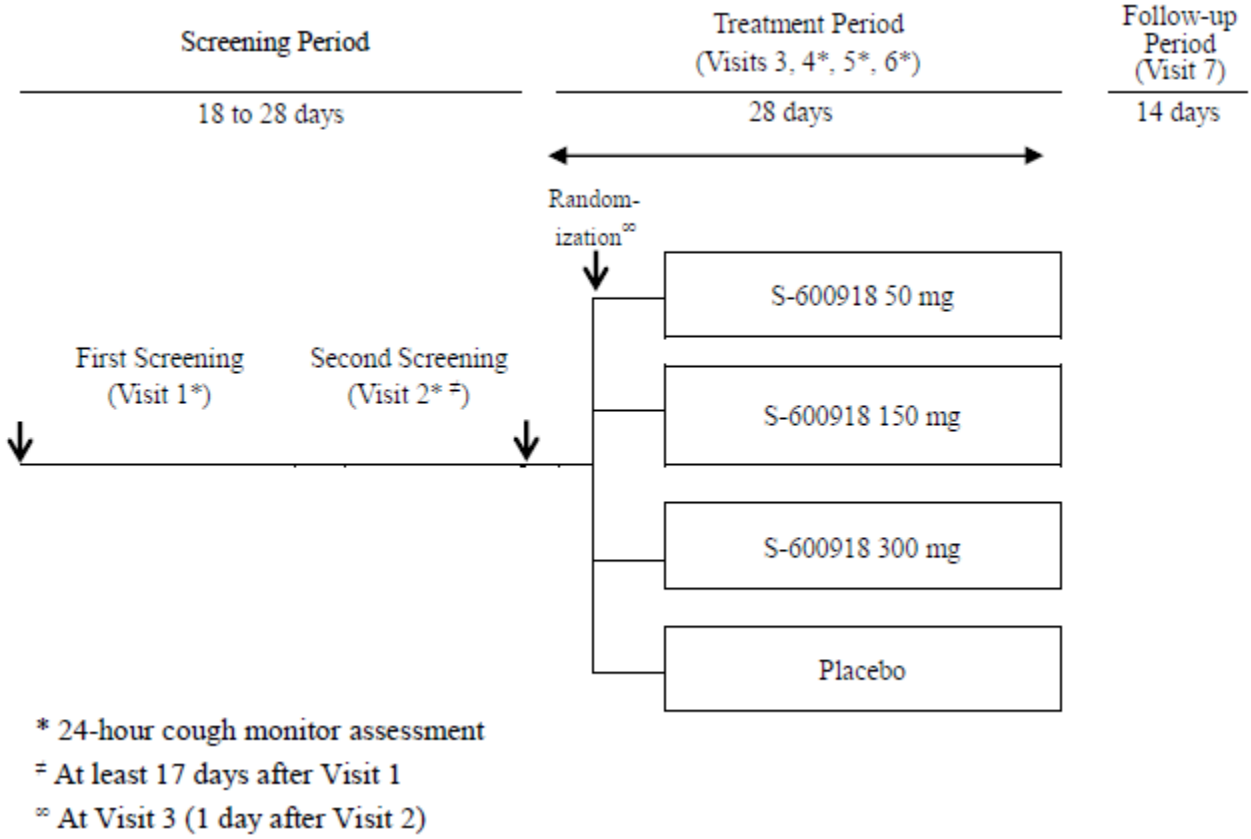
3. Investigational Plan

3.1. Overall Study Design and Plan

This VA323 study is a phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-selection study of 3 doses of S-600918 in patients with refractory chronic cough. A total of 372 patients are planned to be randomized in a 1:1:1:1 manner to either placebo, S-600918 50mg, S-600918 150mg, or S-600918 300mg, stratified by region (United States, Europe, Japan) and by hourly cough count based on the 24-hour cough count recording at Visit 1 (≥30 coughs/hour or <30 coughs/hour). The study duration for each patient is 8-10 weeks, with 18-28 days in screening (Visit 1 and 2), 28 days of treatment (Visit 3, 4, 5, and 6), and 14 days of follow-up (Visit 7) planned. Planned efficacy assessments will be cough counts, as measured by a VitaloJAK cough monitor, and several patient report outcomes & questionnaire responses, including weekly cough severity (VAS), LCQ, ICIQ-SF, SF-36, and PGIC. Further clinical assessments include, but are not limited to laboratory samples, vital signs, electrocardiogram (ECG), physical examinations, adverse events, concomitant medications, and pharmacokinetic samples. A detailed description of study assessments by visit can be found in

section 8 of the protocol, with a tabular summary given in Appendix 1 of the protocol which is also available within this SAP as Appendix 1.

Figure 3-1



3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the ratio of the average number of coughs per hour in 24 hours (based on cough counts recorded by the VitaloJAK cough monitor) after administration of study drug for 4 weeks to that at baseline. For cough count data, baseline is defined as the last non-missing observation prior to the initiation of study treatment. As such, a ratio value that is below 1 will represent a reduction in cough, while a value above 1 will represent an increase in cough.

The VitaloJAK cough monitor has European Conformity (CE) marking in the European Union and 510(k) approval from the United States Food and Drug Administration (FDA). It is widely used in global studies and consists of a microphone and a recording device and was designed to acquire, record, and store ambulatory cough sounds for up to 24 hours. The VitaloJAK cough monitor does not measure the intensity or the impact of cough.

In this study, the VitaloJAK cough monitor will be applied to patients at Visit 1 (Screening), Visit 2 (Day -1), Visit 4 (Day 8), Visit 5 (Day 22), and Visit 6 (Day 27). On each of these visit days, patients will be instructed to wear the monitor continuously for 24 hours. Patients will then remove the monitor and return it to the site. The site will upload the data from the cough monitor to Vitalograph, the cough monitor analysis institution. The data will be analyzed by cough analysis technicians and provided for further statistical analysis. The cough data provided for statistical analysis will contain a chronological log of coughs, sleep, wake, and recording times while each of awake and asleep. From this, the average

coughs per hour in the 24 hours following the activation of the cough monitor will be calculated based on the recording time.

3.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include several more representations of the cough counts from the VitaloJAK monitor, as well as scores from several patient-reported outcomes captured via questionnaire or electronic device.

For the cough counts, the secondary efficacy endpoints further explore the ratio of the reduction while awake and while asleep, as well as binary measures of whether patients achieved a 30%, 50%, and 70% reduction threshold. These are:

- 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.
- A reduction from baseline in the number of coughs per hour while awake 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.

Further secondary endpoints draw from the results of several questionnaires or instruments reported during the study. The relevant endpoints are listed below:

- The change from baseline in weekly cough severity as assessed on the Visual Analog Scale (VAS) via the electronic tablet
- The change from baseline through Day 7 in daily cough severity as assessed on the VAS via the eDiary
- The change in Leicester Cough Questionnaire (LCQ) total score from baseline
- Whether or not the patient achieved an increase of ≥ 1.3 points (ie, improvement) in the LCQ total score from baseline
- The change in ICIQ-SF score from baseline
- The change in SF-36 (version 2) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from baseline, and the change from baseline in each of the 8 domain scores.
- The Patient Global Impression of Change (PGIC)

The VAS will be presented as a numerically labelled linear scale from 0-100 mm, where the patient is asked to indicate the severity of the cough. Higher VAS scores correspond to higher cough severity. The weekly cough severity will be captured at Visits 1, 2, 4, 5, and 6, and/or at the time of discontinuation of study drug, via an electronic tablet. The daily cough severity will be captured via an eDiary issued to patients from Visit 1 until Visit 4.

The LCQ is a quality of life measure of chronic cough. The questionnaire contains 19 items across 3 domains (physical, psychological, and social) to which the patient responds on a 7-point Likert response scale. The total score can range from 3 to 21 and domain scores can range from 1 to 7. Higher scores indicate a better quality of life. The LCQ will be completed at Visits 1, 2, 4, 5, and 6, and/or at the time of discontinuation of study drug.

The International Consultation on Incontinence Modular Questionnaire-Short Form (ICIQ-SF) is a questionnaire used to evaluate the frequency, severity, and impact of urinary incontinence on the quality of life. The questionnaire includes 3 items with responses measured on Likert scales, and one item that is measured via a qualitative response. The three nominal responses are summed to give the ICIQ score

(this total ICIQ-SF score can range from 0 to 21). The ICIQ-SF will be completed at Visit 2 and Visit 6, and/or at the time of discontinuation of study drug.

The Short-Form 36 (SF-36) Questionnaire is a widely used patient reported measure of overall health. 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. The SF-36 measurements can be further characterized by 2 summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The SF-36 will be completed at Visit 2 and Visit 6, and/or at the time of discontinuation of study drug.

The Patient Global Impression of Change is a single-item questionnaire based on the Clinical Global Impression – Improvement scale, and it collects the patient's impression of overall improvement at Visit 6 and/or, if applicable, at the time of discontinuation of study drug. Responses are given on a 7-point Likert Scale, with lower scores indicating increasing degrees of improvement (1-3), 4 indicating no change, and higher scores indicating increasing degrees of worsening (5-7).

3.3. Treatments

S-600918 is formulated as a 50-mg orange, film-coated tablet. The placebo used in this study matches the S-600918 50-mg tablet in appearance. Patients will receive study treatment with S-600918 50 mg, S-600918 150 mg, S-600918 300 mg, or matching placebo, as follows:

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

Treatment will be dispensed to patients at Visit 3 (Day 1), Visit 4 (Day 8), and Visit 5 (Day 22). Treatments will be packaged in identical blister cards within a wallet that will each contain 7 days of treatment plus 3 days of extra study drug in the event the patient cannot return for the next visit as scheduled. One wallet will be dispensed at Visit 3 and at Visit 5, and two wallets will be dispensed at Visit 4.

3.4. Dose Adjustment/Modifications

No dose adjustments or modifications are allowed in this study.

4. General Statistical Considerations

Unless otherwise noted, continuous variables will be summarized based on the number of non-missing observations (N), arithmetic mean (Mean), standard deviation (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.

Baseline will be defined as the last valid assessment recorded prior to the first administration of study drug unless otherwise specified.

For summaries, patients will be counted only once within each planned visit. In these summaries, the visit windows will follow the windows given in the protocol, which are repeated in Appendix 1 of this SAP. However, +1 day will be allowed at the end of the Visit 6 time window for analysis.

Table 4-1: General Analysis Visit Windows

Visit	Target Day	Window Start Day	Window End Day
Visit 1 / Screening	-18	-28	-18
Visit 2 / Day -1	-1	-1	-1
Visit 3 / Day 1	1	1	1
Visit 4 / Day 8	8	6	10
Visit 5 / Week 3	22	20	24
Visit 6 / Week 4	27	25	28

In the event that more than one observation is recorded within one of these windows, then, among these records within the window, the record occurring at the planned visit in the CRF will be used. If no records occurred at the planned visit within the window, then records occurring at any unplanned visits within the visit window will be considered, and the record occurring closest in time to the target visit day will be used. Results that are recorded at an Early Discontinuation visit may be summarized at a planned visit if the Early Discontinuation visit falls within the window for the planned visit, and the planned visit has not occurred.

Study days will be calculated using the date of the first administration of study drug as follows:

- If the assessment occurs on or after the date of the first administration of study drug,
  study day = (date of assessment – date of first administration of study drug) + 1
- If the assessment occurs prior to the date of the first administration of study drug,
  study day = date of assessment – date of first administration of study drug

Summaries presented by visit will only present the visits for which the parameter was planned to be collected. Listings of data collected at study visits will include all such data, regardless of whether it was planned to be collected during that visit.

Certain regional guidelines provide that patient reported outcomes (PROs) can be re-entered, or corrected, by the patient after the initial entry. This study uses several PROs, such as VAS, LCQ, ICIQ-SF, SF-36, PGIC, and Taste Questionnaire. As such when the original data are corrected, analyses will be conducted that use the latest available corrected data. For patients who did not correct their original entry, their original entry will be used in these analyses of corrected data. Additional analyses of only the original data will also be performed.

The following conventions define how the original data and corrected data will be analyzed. If there are no data corrections, then these conventions do not apply.

Analyses on the full analysis Set will use the latest corrected data, regardless of when the correction was obtained. A footnote to all tables containing corrected data will note how many instances of corrected data were included. These analyses will be included in the body of the CSR and will be the basis of hypothesis testing.

These analyses will be repeated using the original entries. Any differences in inference between the analysis of the corrected data and analysis of the original data will be noted in the CSR.

There is no plan for analyzing the PRO data using a Per Protocol Set. However, if this plan changes during or after the study, the Per Protocol Set will use corrected data only if the corrected data falls within the protocol defined window for a visit. Corrected data collected outside a visit window will not be

included in the Per Protocol Set population. A supplemental Per Protocol Set analysis will be conducted using only the original collected data. Any difference in the conclusions based on the Per Protocol Set between the use of the original and corrected data will be noted in the CSR if the CSR has not yet been completed.

In principle, missing data will not be imputed.

4.1. Sample Size

The sample size has been determined using the results of the VA322 proof-of-concept study. In that VA322 study, 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 patients per treatment group. Allowing for exclusion of 10% of patients per treatment group, 93 patients per treatment group will be needed. Therefore, the planned sample size at randomization was determined to be a total of 372 patients. [redacted]

4.2. Randomization, Stratification, and Blinding

Patients who meet screening criteria at Visit 3 will be randomized in a 1:1:1:1 allocation to the 4 treatment groups (described in detail in section 3.3). The randomization will be stratified based on 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).

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. Section 3.3 of this SAP describes how treatment is packaged to achieve the dose-levels of S-600918 used in this study.

The randomization schedule will be maintained by IRT until data lock, as specified in the IRT User Manual. Except for unblinded sponsor staff (e.g., 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.

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 after unblinding, even if treatment is discontinued.

Patients who are unblinded at the request of an investigator will be summarized and listed and described in the Clinical Study Report (CSR).

4.3. Analysis Sets

The analysis sets define the groups of patients that will be analyzed and presented in the tables, listings, and figures that are described in this SAP. Patients will be listed along with their inclusion or exclusion in each of the analysis sets defined in this section.

4.3.1. All Randomized Population

The all randomized population will include all patients who are randomized to a treatment. Presentations based on this set of patients will group patients according to their randomized treatment.

4.3.2. Full Analysis Set (FAS)

The FAS will include all randomized patients who receive at least 1 dose of study drug and who have accepted cough monitor assessment at both baseline and at least 1 visit after initiation of study drug. Presentations based on this set of patients will group them according to their randomized treatment. The primary efficacy analysis will be performed on the full analysis set as well as the per protocol set (below). The primary hypothesis will be tested using the FAS. Patients in the all randomized population who fail to meet these criteria for entry in to the FAS will be listed with their reason(s) for exclusion from the FAS.

4.3.3. Per Protocol Set (PPS)

The PPS will include all randomized patients who are included in the FAS, provided they:

- Meet all inclusion criteria affecting the evaluation of efficacy
- Meet no exclusion criteria affecting the evaluation of efficacy
- Do not have any major protocol deviations affecting the evaluation of efficacy (as defined in the Study Deviation Rules Document)
- Do not use any prohibited therapy affecting the evaluation of efficacy during the study

The criteria above represent an adherence to the specifications of the protocol with regards to efficacy assessments. The details of the rules used to make the determination of which criteria affect the evaluation of efficacy will be provided in a separate document that will be reviewed by study personnel at the sponsor. The first version of this Study Deviation Rules Document will be completed and signed off prior to the first patient being randomized. This document will be finalized prior to unblinding. Patients who receive any dose of the incorrect study drug will not be included in the PPS. Prohibited therapies will be assessed by a medical review to determine whether they affect the evaluation of efficacy. This review will be finalized prior to final unblinding.

Presentations based on this set of patients will group them according to their randomized treatment. Supplementary analyses will be performed on the PPS. Patients in the FAS who fail to meet these criteria for entry in to the PPS will be listed with their reason(s) for exclusion from the PPS.

4.3.4. Safety Population

The safety population will include all randomized patients who receive at least 1 dose of study drug. Presentations based on this set of patients will group them according to the first study treatment they are administered.

4.3.5. PK Concentration Population

The PK concentration population will include all patients who receive at least 1 dose of S-600918 and have at least 1 evaluable concentration. Presentations based on this set of patients will group them according to the treatment received.

5. Patient Disposition

5.1. 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. Also, among all randomized patients, the number of patients included in each analysis population defined in section 4.3 will be summarized by treatment group, as well as overall. As well as randomized patients, patients withdrawn from the study during screening period will be tabulated by reason of withdrawal and listed.

5.2. Protocol Deviations

Protocol deviations that are relevant to the analyses will be identified in a separate protocol deviations rules document that will be reviewed by study personnel. During the study, these rules will be reviewed and instances where patients met any of the conditions will be logged in a database that will be finalized and locked prior to final unblinding. Major deviations, that is those that are related to efficacy, will inform the per protocol set (PPS) as described in section 4.3.3. In addition to these major deviations that result in the removal of patients from the PPS, the significant protocol deviations, that are required for CSR reporting, will be summarized and listed.

5.3. COVID-19 / SARS-COV-2

Shortly after this study began enrolling patients, the SARS-COV-2 virus, which causes coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization. In accordance with guidances issued by regulatory agencies, study data collection has been amended for randomization patients to capture visits missed due to COVID-19 related reasons, and discontinuations due to COVID-19 related reasons. COVID-19 related adverse events, concomitant medications, and medical history are collected using existing CRFs.

Listings of patients who missed visits due to COVID-19 related reasons will be listed for the All Randomized Population. Patients who withdraw from the study due to COVID-19 related reasons will be summarized and listed as described in section 5.1 Disposition, of this SAP.

The anticipated impact of COVID-19 is widely regarded as unknown. If the impact of COVID-19 on the conduct of this study is observed to be significant, further summaries and listings of the impact will be explored.

6. Demographics and Baseline Characteristics

All summaries of demographics and baseline characteristics described in this section will be presented for the FAS and for the Safety Population.

6.1. Demographics

A summary of demographics and baseline information will be presented by treatment group. The demographic characteristics consist of age (years) at informed consent, sex, race, and ethnicity. The

baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2). Body mass index is calculated as (body weight in kilograms) / (height in meters)^2.

Age, along with height, weight, and BMI at baseline, will be summarized using descriptive statistics. The number and percentage of patients by age category (<45, ≥45 - <65, ≥ 65), sex (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino), and region (Japan, Europe, and United States) will also be summarized.

Patient demographic and baseline characteristics will also be presented via listings.

6.2. Baseline Disease Characteristics

Average cough counts per hour in 24 hours at Visit 1 and Visit 2 and baseline will be summarized using descriptive statistics by treatment group. In addition, the weekly severity of cough (VAS) at baseline, the LCQ at baseline, and baseline pulmonary function test results, including FVC (L), FEV1 (L), and FEV1/FVC ratio will be summarized using descriptive statistics. As well, the duration of chronic cough (months; ((date of screening – reported start date of chronic cough) + 1) / 30.4375) will be summarized using descriptive statistics by treatment group. When part of the start date or end date is missing, 15th of the month for missing day and July 1st when month and day are missing will be used.

Cough-related history will be recorded on the eCRF and coded using MedDRA v22.1. The number and percentage of patients with any cough-related history will be summarized by treatment and overall for each preferred term. Cough-related history will also be listed with the calculated duration of each history. For the calculation of duration, partial dates will be handled as above, using the 15th of the month for missing day and July 1st when month and day are missing. Ongoing histories will use the date of enrollment as the end date for calculating duration.

6.3. Smoking History

Smoking history (pack-years) will be summarized categorically (0 pack-years, > 0 pack-years, > 5 pack-years, >10 pack-years, and >15 pack-years), and using descriptive statistics by treatment group.

6.4. Medical History

Medical history, including prior and current conditions, surgeries, cough-related history, alcohol use, smoking, and marijuana use will be recorded on the eCRF and coded using MedDRA v22.1. The number and percentage of patients with any medical history will be summarized by treatment and overall for each system organ class and preferred term. Medical history data will also be presented in a listing.

6.5. Inclusion and Exclusion Criteria

Randomized patients that fail to meet eligibility criteria will be listed with the inclusion or exclusion criteria that was not met.

7. Treatments and Medications

7.1. Prior, Concomitant, and Restricted Medications

Prior, concomitant, and restricted medications and therapies will be coded using the WHO Drug Dictionary. Prior medications will be classified as those medications that begin prior to the first

administration of study drug. Concomitant medications are those medications that may have been taken during study treatment. This principle applies to medications for which partial or missing start or end dates are recorded. Restricted therapy is defined as any concomitant therapy for which use is permitted only with restrictions.

For the purposes of classifying a course of treatment as prior and/or concomitant, partial start dates will be presumed as the earliest possible recorded date. Start dates that are entirely missing will be presumed as the date of informed consent.

For the purposes of classifying a course of treatment as prior and/or concomitant, partial end dates will be presumed as the latest possible recorded date. Records with end dates that are entirely missing will be considered as prior and concomitant if the start date occurs before study treatment. Such records with start dates occurring after the first dose of study treatment will be considered concomitant.

7.1.1. Prior Medications

The number and percentage of patients using any prior medications and by preferred term will be summarized by treatment for the FAS and the Safety Population. Prior medications will be listed for the Safety Population.

7.1.2. Concomitant Medications

The number and percentage of patients using any concomitant medications and by preferred term will be summarized by treatment for the FAS and the Safety Population. Concomitant medications will be listed for the Safety Population.

7.1.3. Restricted Medications

The number and percentage of patients using any restricted medications and by preferred term will be summarized by treatment for the FAS and the Safety Population. Restricted medications will be listed for the Safety Population.

7.2. Study Treatments

7.2.1. Study Drug Exposure

Duration of exposure is defined as the total number of days a patient is exposed to any study drug and will be presented as the total number of days from the first dose date (Day 1) to the last dose date (date of last dose minus the date of first dose + 1) as recorded in the clinical database. If a patient is lost to follow-up, but the drug accountability log confirms that the patient has taken study drug, the visit date following the last completed drug accountability log will be used. If drug accountability log is missing for some reason, the patients will be regarded as not dosed for such duration.

The duration of exposure to study drug by treatment will be summarized by treatment for the FAS and the Safety Population using descriptive statistics. The duration of exposure will then be classified into one of the following categories: > 1 day, >= 7 days, >= 14 days, >= 21 days and >= 25 days and will be presented as the number and percentage of patients in each duration category.

The cumulative dose will be defined as the sum of the actual dose across all study days on which study drug was taken. Patients who take more or less than the planned 6 tablets of study drug in a day will be considered to have received actual dose of (# of tablets taken / 6) for that day. Average daily dose is the cumulative dose divided by the duration of exposure. The average daily dose and cumulative dose will be summarized by descriptive summary statistics.

A summary of each patient's exposure will be presented in a listing.

7.2.2. Treatment Compliance

Overall study drug compliance will be calculated for each patient by evaluating how many days a patient takes study drug as directed while on study treatment up to and including Day 28. For each day on treatment, the number of tablets taken will be directly captured on the eCRF. Days where 6 tablets are recorded as taken will be counted as the number of days of compliant dosing until the earliest date of day after the date of V6, Day 28 or date prior to the date of discontinuation. For patients who complete treatment, the number of days on treatment will be calculated as (day after the date of Visit 6 – date of Visit 3) + 1. For patients who prematurely discontinue treatment, the number of days on treatment will be calculated as (date prior to the date of discontinuation – date of Visit 3) + 1. The number of days on treatment will be considered up to Day 28 – that is, the number of days on treatment will have a maximum value of 28.

Thus, the overall study drug compliance (%) will be calculated as:

$$Compliance = 100\ x\ \frac{Number\ of\ Days\ of\ Compliant\ Dosing}{Number\ of\ Days\ on\ Treatment}$$

Where number of days on treatment is defined as in section 7.2.1. A patient is considered to have demonstrated adequate compliance if overall study drug compliance is between 80% and 100%, inclusive.

A categorical summary of whether patients were compliant (yes/no) will be presented by treatment group for the safety population. Summary statistics on percentage of treatment compliance as well as the number and percentage of patients in each compliance category (>=70%, >=80%, >=90%, 100%) will be presented by treatment group for the safety population.

8. Efficacy Analysis

For all efficacy analyses, baseline is defined the last assessment before first dose of study drug, unless otherwise noted. All efficacy analyses will be presented for FAS, and, where noted, for the PPS. When the framework described for the primary analysis (which is also used in several subsequent analyses) is applied to cough count data, if any patient has an average coughs per hour at any baseline or post-baseline measurement that is zero, a correction factor of 0.1 will be added to all observed average coughs per hour values for all patients. A correction factor of 0.1 is necessary because these counts are log-transformed for the purposes of analysis, and $\log_{10}(0)$ is undefined. This handling is applied in the same manner to average coughs per hour in 24 hours, while asleep, and while awake. In principle, efficacy analyses will be based on data compliant with the analysis visit window at each visit in the treatment period for both of FAS and PPS (see section 4 of this SAP). For this reason, data outside the analysis visit windows will be regarded as missing.

8.1. Primary Efficacy Endpoint

As described in section 3.2.1, the primary efficacy endpoint is the ratio of coughs per hour in the 24 hours following administration of study drug. The cough counts will be provided based on the VitaloJAK recordings, following evaluation by the cough analysis technicians. This ratio of the cough count observed at Visit 4, Visit 5, and Visit 6 to the cough count observed at baseline will be transformed using the common logarithm for the purposes of analysis. The last planned cough recording prior to the first dose of study drug should occur at Visit 2, however, if the cough count at Visit 2 is missing, then according to the general conventions for baseline, the cough count from Visit 1 will be used as the baseline. As well, in some instances, the cough recording at Visit 2 may span Visit 3 and include time

after the first dose of study drug. If the end date and time of the Visit 2 cough recording is after the date and time of the first dose of study drug, then the cough count from Visit 1 will be used as the baseline.

8.1.1. Primary Analysis

The null hypotheses of equality between the treatment and placebo effects will be tested using a mixed model, containing treatment group, week (as a classification term), and the interaction between treatment group and week as fixed effects; patient as random effect; and region and the common logarithm of the frequency of coughs per hour at baseline as covariates. In this model, the covariance structure will be given as unstructured, and the degrees of freedom will be derived using the Kenward-Roger method. Should the model fail to converge using the unstructured covariance, compound symmetry will be used. Using this model, the log-transformed ratio of the number of coughs per hour in 24 hours after 4 weeks of administration of study drug will be used to evaluate the null hypothesis at each dose level of S-600918 at the 2-sided alpha level of 0.05 among the FAS.

The primary analysis will summarize each of these three 2-way comparisons, presenting the estimate for the difference of the effects of treatment at Visit 6, the 95% confidence interval for this difference, and the p-value based on the hypothesis and model described above. Furthermore, the time course of the treatment effect for each treatment group will be plotted with the mean and 95% confidence interval.

8.1.2. Sensitivity Analyses of the Primary Endpoint

A sensitivity analysis of the primary efficacy endpoint will be performed on the FAS using an analysis of covariance containing treatment group, as factor; and region and the common logarithm of the frequency of coughs per hour at baseline as covariates. It is expected that this ANCOVA will perform similarly as the primary analysis, using the observed data. Thus, two sensitivity analyses using this ANCOVA model on the FAS will be performed: one that imputes missing observations with the last post-baseline observation, and that imputes the baseline cough counts per hour for missing observations.

Furthermore, the primary analysis will be repeated for the FAS using 1) the protocol visit windows found in Table 7-2 of the Protocol, and 2) the nominal visit analysis windows presented below in Table 8-1.

Table 8-1: Analysis Visit Windows for Sensitivity Analysis

Visit	Target Day	Window Start Day	Window End Day
Visit 1	-18	-28	-18
Visit 2	-1	-1	-1
Visit 3	1	1	1
Visit 4	8	2	14
Visit 5	22	15	24
Visit 6	27	25	Latest of Day 28, Day of Visit 6, and Day of Last Dose of Study Drug

8.1.3. Supplementary Analyses of the Primary Endpoint

The Primary Analysis described in section 8.1.1 and the Sensitivity Analyses described in section 8.1.2 will be repeated on the PPS as supplementary analyses.

8.1.4. Other Analyses of the Primary Endpoint

Summary statistics for the average number of coughs per hour in 24 hours at each visit will be presented by treatment group using the geometric mean and its 95% confidence interval for the FAS.

Subgroup analyses will be performed to evaluate the primary efficacy endpoint among subgroups of patients for the FAS. For these subgroup analyses, the primary analysis method mentioned in the section 8.1.1 will be repeated. Within this framework, the subgroups below will be analyzed:

1. Region (1-1: Japan, Europe, United States, 1-2: Japan, Europe and United States)
2. Hourly cough count at baseline (≥30 coughs/hour, <30 coughs/hour)
3. Cough count at Visit 1 (≥30 coughs/hour, <30 coughs/hour)
4. Pulmonary/Cough History (Asthma, Cough variant asthma [CVA], Gastroesophageal reflux disease [GERD], Upper airway cough syndrome including postnasal drip, rhinosinusitis, and rhinitis [UACS], Eosinophilic bronchitis including atopic cough [EB], Sinobronchial syndrome [SBS], Unexplained cough, Other, and Refractory cough, i.e., other than Unexplained cough and Other). A patient may have more than one pulmonary history. Such patients will be included in each category by pulmonary history.

A forest plot will also be provided based on the estimates for the difference of the effects of treatment at Visit 6 and its 95% Confidence Interval for the subgroups above.

The primary analysis framework will be used to assess characteristics of the dose-response relationship on the primary efficacy endpoint. The framework will be applied as originally described as well as to the log-transformed ratio of average coughs per hour in 24 hours following 4 weeks of treatment to that at baseline. The below comparisons will be presented for each of these models.

- Placebo versus 50 mg, 150 mg, and 300 mg S-600918
- Placebo and 50 mg S-600918 versus 150 mg and 300 mg S-600918
- Placebo, 50 mg, and 150 mg S-600918 versus 300 mg S-600918
- Linear Trend Test across all Treatment Groups

This framework above will be applied to the log-transformed ratio of average coughs per hour in 24 hours following 3 weeks of treatment to that at baseline, as well.

Furthermore, a three-parameter Emax model will be fitted for the ratio of the average cough count per hour in 24 hours at Visit 6 to that at baseline minus 1 to estimate the minimum, maximum, and median effect of dose on response. In this Emax model, dose will be handled in the original scale. As well, a similar Emax model will be fitted for the ratio of the average cough count per hour in 24 hours at Visit 5 to that at baseline minus 1. Responses will be plotted on a scatterplot and the fitted curve will be presented on the plot. If this Emax model fails in convergence, other models, including a linear model may be fitted.

8.2. Analysis of Secondary Efficacy Endpoints

The model for the primary analysis described in section 8.1.1 provides the framework for the analysis of many of the secondary efficacy endpoints. In such cases, the only difference will be response being modelled, unless otherwise noted. For the sake of brevity, this framework will be referenced as the primary analysis framework. Wherever this framework is referenced, the corresponding 95% confidence intervals and p-values will be presented.

8.2.1. Analysis of Cough Counts while Awake / Asleep

The cough counts while awake and while asleep will be provided based on the VitaloJAK recordings, following evaluation by the cough analysis technicians. Like the primary efficacy endpoint, the ratio of the coughs per hour while awake at Visit 4, Visit 5, and Visit 6 to that at baseline, will be transformed using the common logarithm. This transformed ratio of coughs per hour while awake will be analyzed using the primary analysis framework. As well, the similarly transformed ration of coughs per her while asleep will be analyzed using the primary analysis framework for the FAS.

Average hourly cough counts while awake and while asleep will be presented by treatment group at each visit using the geometric mean and its 95% confidence interval for the FAS.

8.2.2. Analysis of Cough Count Reduction Thresholds

The proportion of patients who achieved a reduction from baseline in the number of coughs per hour in 24 hours and while awake at Visit 6 of ≥30%, ≥50%, ≥70% will be summarized descriptively for each treatment group and compared between each dose level of S-600918 and placebo using a Cochran-Mantel-Haenszel (CMH) test with strata by region (Japan, Europe, United States) and cough count at baseline (≥30 coughs/hour, <30 coughs/hour) for the FAS. The odds ratio and its 95% confidence interval will be presented, as well.

In addition, the proportion of patients who achieved a reduction from baseline in the number of coughs per hour in 24 hours and while awake at Visit 6 of ≥30%, ≥50%, ≥70% will be summarized descriptively for each treatment group by region and cough count at baseline (≥30 coughs/hour, <30 coughs/hour) for the FAS.

8.2.3. Analysis of Cough Severity (VAS)

The change in weekly cough severity at Visit 4, Visit 5, and Visit 6 to that at baseline will be analyzed using the primary analysis framework for the FAS. Similarly, the change in daily cough severity from Day 1 through Day 7 will be analyzed using the primary analysis framework for the FAS, only using Day 7 in place of Visit 6.

Both weekly and daily cough severity will also be summarized using descriptive statistics at each planned assessment by treatment group for the FAS.

8.2.4. Analysis of Leicester Cough Questionnaire (LCQ) Score

The change from baseline at Visit 4, Visit 5, and Visit 6 of the LCQ score of each domain (Physical, Psychological, and Social) and the LCQ total score will be analyzed using the primary analysis framework for the FAS. The proportion of patients who achieved an improvement from baseline in the LCQ Total Score of ≥1.3 at Visit 6 will be summarized descriptively for each treatment group and compared between each dose level of S-600918 and placebo using a CMH test with strata by region (Japan, Europe, United States) and cough count at baseline (≥30 coughs/hour, <30 coughs/hour) for the FAS. The odds ratio and its 95% confidence interval will be presented, as well. In addition, the proportion of patients who achieved this improvement from baseline in the LCQ Total Score will be summarized descriptively for each treatment group by region and cough count at baseline (≥30 coughs/hour, <30 coughs/hour) for the FAS.

As well, LCQ domain scores and total score will be summarized by treatment at each visit using descriptive statistics for the FAS.

During the course of the study, while still fully blinded, it was discovered that a translation error occurred in the Ukrainian translation of the LCQ. This error only affected the response options for question 16 and question 17, both of which are used in the calculation of the Psychological domain score and the Total score. As a result, the handling of the Psychological domain score and LCQ total score data for Ukrainian patients will be different, as described below.

(1) All data will be listed. (2) The analyses of Psychological domain score and LCQ Total score data described in this section will be performed excluding these patients. (3) Additional analyses of the Psychological domain score and LCQ Total score will be added where the responses for these Ukrainian patients to question 16 and question 17 are replaced by the observed mean response to the other questions within the Psychological Domain (questions 4, 5, 6, 12, and 13) within each patient and visit. These analyses will mirror those described in this section, with this added convention for these patients.

8.2.5. Analysis of International Consultation on Incontinence Modular Questionnaire-Short Form (ICIQ-SF) Score

The change from baseline to in the ICIQ-SF Score will be summarized using the primary analysis framework for the FAS. Given that ICIQ-SF is only collected at baseline and at Visit 6, it is not necessary to include the fixed effect of week and the interaction between treatment group and week as fixed effects.

The 3 ordinal responses to the ICIQ-SF will be summarized using descriptive statistics at each visit by treatment group for the FAS. Subgroup analyses of 1) female patients and male patients and 2) patients with at least 1 symptom at baseline and patients with no symptoms at baseline will be conducted.

As well, the non-ordinal responses to the ICIQ-SF (question 6) will be summarized by the number and percent of patients experiencing symptoms at each visit for the FAS. This summary will be repeated within the following subgroups 1) female patients and male patients and 2) patients with at least 1 symptom at baseline and patients with no symptoms at baseline.

8.2.6. Analysis of Short Form 36, Version 2 (SF-36v2) Scores

The analyses of SF-36v2 scores will use normalized scores provided by Optum, which are based on the 2009 standard normalization scores.

The change from baseline in the Physical Component Summary (PCS) score from the SF-36 responses will be summarized using the primary analysis framework for the FAS. As well, the Mental Component Summary (MCS) score, and the 8 domain scores (see section 3.2.2) will be analyzed in the same manner. Given that SF-36 is only collected at baseline and at Visit 6, it is not necessary to include the fixed effect of week and the interaction between treatment group and week as fixed effects.

The PCS, MCS, and 8 domain scores will be summarized using descriptive statistics at baseline and at Visit 6 by treatment group for the FAS.

8.2.7. Analysis of Patient Global Impression of Change (PGIC)

The PGIC at Visit 6 will be summarized using descriptive statistics and the Van Elteren test will be applied to compare the PGIC at each dose level of S-600918 to placebo, with strata by region (Japan, Europe, United States) and cough count at baseline (≥30 coughs/hour, <30 coughs/hour). And, proportion of patients with either of “Very much improved”, “Much improved” or “Minimally improved” will be compared between each dose level of S-600918 and placebo using a Cochran-Mantel-Haenszel (CMH) test with strata by region (Japan, Europe, United States) and cough count at baseline (⩾30 coughs/hour, <30 coughs/hour) for the FAS. The odds ratio and its 95% confidence interval will be presented, as well.

8.3. Other Efficacy Analyses

8.3.1. Analysis of Cough Recording Completeness

The duration of recording time (hours) within each patient’s cough recording will be summarized using descriptive statistics at each visit by treatment for the FAS. As well, the number and percentage of patients with a duration of recording time that is >=20 hours, >=22 hours, >=23 hours, and 24 hours will be summarized at each treatment by visit for the FAS.

9. Safety Analysis

All summaries of safety will be performed on the safety population.

9.1. Adverse Events

Treatment Emergent Adverse Events (TEAEs) will be defined as an adverse event that may have an onset following administration of study drug. For the purposes of classifying adverse events according to this definition, events with partial onset dates will be considered as the closest possible date to the last day of study drug dosing. In general, summaries will be provided by treatment group, and by MedDRA system organ class (SOC) and preferred term (PT).

9.1.1. Incidence of Adverse Events

An overall summary of TEAEs will be presented by treatment group and will include the number and percentage of patients with at least one TEAE, any serious TEAEs, any fatal TEAEs, and any TEAEs leading to discontinuation of study drug. The 95% confidence intervals for these percentages by the Clopper-Pearson method will be presented. Similarly, the number of patients experiencing these events will be compared at each level of active S-600918 dosing to placebo using Fisher's exact test.

The number and percentage of patients with TEAEs will be summarized by SOC and PT for each treatment. All AEs will be presented in a listing.

9.1.2. Relationship of Adverse Events to Study Drug

An overall summary of treatment-related TEAEs will be presented by treatment group and will include the number and percentage of patients with at least one treatment-related TEAE, any serious treatment-related TEAEs, any fatal treatment-related TEAEs, and any treatment-related TEAEs leading to discontinuation of study drug. The 95% confidence intervals for these percentages by the Clopper-Pearson method will be presented.

The number and percentage of patients with treatment-related TEAEs will be summarized by SOC and PT for each treatment.

9.1.3. Severity of Adverse Event

The number and percentage of patients with TEAEs by severity will be presented by MedDRA system organ class and preferred term for each treatment group. Each patient will be counted only once within a preferred term or system organ class at the most extreme observed level of severity.

9.1.4. Serious Adverse Events

The number and percentage of patients with serious TEAEs at any time will be summarized by SOC and PT for each treatment. All serious TEAEs will be presented in a separate listing.

9.1.5. Adverse Events Leading to Treatment Discontinuation

The number and percentage of patients with TEAEs leading to discontinuation of study drug will be summarized by SOC and PT for each treatment. All TEAEs leading to discontinuation of study drug will be presented in a separate listing.

9.1.6. Death

All TEAEs with an outcome of death will be presented in a separate listing.

9.1.7. Subgroup Analyses for Adverse Events

The number and percentage of patients with TEAEs will be similarly summarized for each treatment by Region (United States, Europe, Japan).

Forest plots of the relative risk and its 95% confidence interval of TEAEs between each active treatment group and placebo will be presented for the subgroups above for TEAEs.

9.1.8. Taste Changes

The number and percentage of patients with any treatment-emergent adverse events that reflect taste change as defined using the Standardized MedDRA Query (SMQ) category of "Taste and smell disorders" will be summarized by SOC and PT for each treatment group.

As well, the number and percentage of patients with any treatment-emergent adverse events shown in Table 9-1 will be summarized by SOC and PT for each treatment group.

Table 9-1: Adverse Events Reflecting Taste Change

Preferred Terms Code	System Organ Class Code	Preferred Terms Name	System Organ Class Name
10001480	10029205	Ageusia	Nervous system disorders
10013911	10029205	Dysgeusia	Nervous system disorders
10019071	10037175	Hallucination, gustatory	Psychiatric disorders
10020989	10029205	Hypogeusia	Nervous system disorders
10064480	10022891	Gustometry abnormal	Investigations
10069147	10029205	Hypergeusia	Nervous system disorders
10082490	10029205	Taste disorder	Nervous system disorders

Responses to the taste questionnaire will be summarized descriptively and listed.

[redacted]

9.2. Clinical Laboratory Evaluations

Clinical laboratory samples will be analyzed using a central laboratory, and results will be provided in SI and US units with the appropriate normal ranges. All laboratory results will be listed.

The results from the samples collected at Visit 2, Visit 4, Visit 6, and Visit 7 will be summarized using at each visit. For continuous results, both the results and change from baseline of the results will be summarized. Continuous chemistry, hematology, and urinalysis results will be summarized using SI units and US units.

Chemistry results except for blood urea nitrogen and total protein and hematology results except for hematocrit, erythrocytes (red blood cells), basophil count, and monocyte count will be categorized according to CTCAE version 5 and listed. Cross tables of these grades at Visit 2 and each of Visit 4, Visit 6 and Visit 7 will be prepared by each parameter. For the cross tables, grades will be summarized using SI units for patients enrolled at sites outside the United States and using US units for patients enrolled at sites within the United States.

Qualitative results for urinalysis will be summarized by the number and percentage of patients with results in each category by treatment group at each visit.

Significant abnormalities will be defined for ALT, AST, and Total Bilirubin. An AST or ALT result >3 x ULN and a total bilirubin value >2 x ULN will be considered an abnormality. The number and percentage of patients experiencing either and both of these abnormalities after the first dose of study drug up through the follow-up visit will be summarized by treatment group. As well, the number and percentage of patients experiencing an AST results >3 x ULN, an ALT results >3 x ULN, an AST or ALT results >5 x

ULN, prothrombin time international normalized ratio (PT-INR) >1.5, and (an AST or ALT result >3 x ULN) and (a total bilirubin value >2 x ULN or PT-INR >1.5) will be summarized. A separate listing will present all ALT, AST, and total bilirubin results for any patients with either abnormality.

Numbers of patients and their proportions whose creatinine increased more than 0.3 mg/dL for patients enrolled in the United States or more than 26 umol/L for patients enrolled outside of the United States from Visit 2 at each of Visits 4, 6, 7 and any time point during treatment period and follow-up period will be summarized. A separate listing will present all creatinine results for any patients with an increase greater than 0.3 mg/dL from Visit 2.

9.3. Vital Sign Measurements

Blood pressure and pulse rate will be recorded at each visit in the study. Observations at Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 will be summarized using descriptive statistics. The change from baseline will also be summarized for these Visit 4, Visit 5, Visit 6, and Visit 7, with baseline defined as the last observation prior to the first administration of study drug. All vital signs data will be listed.

9.4. Physical Examination

A physical examination will be performed at each visit, except for Visit 5. All physical examinations after Visit 1 will be abbreviated and limited to the respiratory system only. All physical exam data will be listed.

9.5. Electrocardiogram

Qualitative assessments of electrocardiograms (ECG) conducted at Visit 1, Visit 2, Visit 6, and Visit 7 will be summarized by treatment group and by visit according to the number and percentage of patients reporting an ECG result in each result category. These assessments will be reported as normal, abnormal-not clinically significant, or abnormal-clinically significant.

10. Pharmacokinetics

All presentations of data related to pharmacokinetics will be presented for the PK Concentration Population.

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} and dose will be presented graphically by scheduled visit (Visit 4 and Visit 6) for S-600918 and for S-600918 acyl glucuronide. 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.

Plasma drug and metabolite concentrations determined in blood samples obtained outside of allowable time windows will be included in PK analyses and will not be handled as missing data.
Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the PK analyst. Any such exclusion will be communicated to the sponsor and clearly represented in the study report along with justification for exclusion.

Descriptive statistics for C_{trough} will be presented as follows:
- N: no decimal place
- Mean, Geometric Mean, SD, median, Min, and Max: same precision as per the observed values.
- CV% and CV% Geometric Mean: one decimal place

11. Pharmacodynamics

There are no pharmacodynamic analyses planned for this study.

12. Interim Analysis

No Interim analysis is planned for this study.

13. Changes in the Planned Analysis

There are no changes in the planned analyses described in the protocol within this SAP.

14. Appendices

14.1. Appendix 1: Schedule of Study Procedures

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

	Screening Period		Treatment Period (Day 1 to 28)				Follow-up Period	
Visit	**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
Measure FEV_1 and FVC; assess pt vs Exclusion Criterion #19 [bb]	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
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			◄	———	———	———	►	
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				

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 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		
Collect study drug wallet; assess pt compliance/drug accountability and record number of tablets of study *(continued next page)*				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
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]								
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 [dd]		X [dd]	X	X [ee]
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] 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.

[ee] 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.

14.2. Appendix 2: Handling of Cough Counts

The number of coughs per hour is used in the following situations in the efficacy analyses:

- in 24 hours
- while awake
- while asleep

The number is commonly derived by the formula given below:

$$Number\ of\ coughs\ per\ hour = \frac{Total\ number\ of\ coughs\ measured\ in\ evaluation\ session}{Total\ length\ of\ evaluation\ session\ in\ hours}$$

Each evaluation session is, at most, 24 hours. The above formula applies even when the total length of evaluation is less than 24 hours. There is no minimum length required to apply the formula above. MILLI in Events dataset stands for millisecond in the event time, and it is handled in the formula above, too. MILLI is always missing when FACAT is “SESSION”, corresponding to start date and time of session and expected end date and time of session, respectively. MILLI whose FACAT is “SESSION” will be imputed with 0 when MILLI in the last record in the current session is missing, otherwise with the same value of MILLI in the last record in the current session, respectively. Any counts of coughs after 24 hours since cough monitoring has started will not be considered for evaluation. The evaluation session starts while patient is awake. The evaluation session is curtailed to last observable time of the measured data if there is no record after 24 hours since cough monitoring has started.

The above termination of session has exception in the following three cases 1) Termination for some reason including due to battery exhaustion in monitoring device or artificial termination (FAOBJ=”Early Termination”), 2) Intermittent removal (where FAOBJ=”Removal”) without any records with FAOBJ to be either of “Restore”, “Cough”, “Sleep” or “Wake” after the appearance of record. The time in these records is regarded as the end of the evaluation session.

The evaluation session excludes interruptions as below

1) between removal time (FAOBJ=”Removal”) and its restoration time (FAOBJ=”Restore”) by device removal.
2) between flagged area started (FAOBJ=”Flagged Area Start”) to its end (FAOBJ=”Flagged Area End”) in case of unintentional missing count due to noise.
3) between mute started (FAOBJ=”Mute Start”) to its end (FAOBJ=”Mute End”) during pressing Mute button by subject.

The number of coughs in such interrupted sessions will not be used even if recorded due to its unreliability.

If either counting is rejected or device is unassigned, then the number of coughs is considered as missing. If under 1 hour of data exists, it will not be analyzed by Vitalograph, and it will be rejected on the portal provided by Vitalograph, as per “Cough Analysis Plan: S2019323_0001, Project No. S2019323” prepared by Vitalograph. Otherwise if there is no record of cough, then the number of coughs is set to be 0.

The length of awake of 20 minutes or less will not be handled as awake session, as such a record will not be included in the database.

When any of the number of coughs per hour in 24 hours at baseline or during treatment period is 0, 0.1 will be added to all of the number of coughs per hour in 24 hours in order to apply the mixed effect model. Likewise, this handling is applied to those while awake and asleep, too.