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PROTOCOL

TITLE:	**A MULTICENTER, OBSERVATIONAL, 6-MONTH FOLLOW-UP STUDY OF PATIENTS WITH COVID-19 PREVIOUSLY ENROLLED IN A RO7496998 (AT-527) STUDY**
PROTOCOL NUMBER:	CV43140
VERSION NUMBER:	1
EUDRACT NUMBER:	2021-000627-12
IND NUMBER:	149508
NCT NUMBER:	To be determined
TEST PRODUCT:	Not applicable
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSORS:	F. Hoffmann-La Roche Ltd (Ex-United States) Atea Pharmaceuticals, Inc. (United States)
DATE FINAL:	See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Date	Title	Approver's Name	Signature
MAR 3 2021	[redacted], Atea Pharmaceuticals, Inc.	[redacted], M.D.	[redacted]

Date and Time (UTC)	Title	Approver's Name
03-Mar-2021 18:49:39	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OBSERVATIONAL, 6-MONTH FOLLOW-UP STUDY OF PATIENTS WITH COVID-19 PREVIOUSLY ENROLLED IN A RO7496998 (AT-527) STUDY**
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PHASE:	Phase III
INDICATION:	COVID-19
SPONSORS:	F. Hoffmann-La Roche Ltd (Ex-United States) Atea Pharmaceuticals, Inc. (United States)

Objectives and Endpoints

The purpose of this study is to evaluate the long-term sequelae of coronavirus disease 2019 (COVID-19) in patients diagnosed with COVID-19 who previously enrolled in a RO7496998 (AT-527) study (i.e., parent study), for approximately 6 months after the end of the parent study. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the long-term symptoms of patients diagnosed with COVID-19	• Descriptive summaries, over time, of COVID-19 symptoms, as assessed through the COVID-19 Symptom Diary (Items 1–14)
Secondary Objectives	**Corresponding Endpoints**
• To evaluate HRQoL of patients diagnosed with COVID-19	• Impact of dyspnea symptoms on specific activities, as assessed through use of PROMIS-Dyspnea Questionnaire at Day 1 and Months 1, 2, 3, 4, 5, and 6 • Respiratory-specific HRQoL, as assessed through use of SGRQ at Day 1 and Months 1, 2, 3, 4, 5, and 6
• To evaluate medical resource utilization for patients diagnosed with COVID-19	• Proportion of patients with COVID-19–related medically-attended visits through to study end (defined as hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit with the primary reason for the visit being COVID-19 or COVID-19–related symptoms)

Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the long-term outcomes of COVID-19 in patients diagnosed with COVID-19	• Proportion of patients with all-cause mortality • Proportion of patients with death attributable to progression of COVID-19 • Proportion of patients re-infected with SARS-CoV-2 • Proportion of patients with any post-treatment infection including but not limited to bacterial, viral, or fungal pneumonia or sepsis • Frequency of COVID-19–related complications (e.g., death, hospitalization, radiologically-confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis, myocarditis, cardiac failure)
• To evaluate adverse events in patients diagnosed with COVID-19 who previously enrolled in a RO7496998 (AT-527) study	• Incidence and severity of adverse events and serious adverse events, with severity determined according to NCI CTCAE v5.0
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate symptom severity of patients diagnosed with COVID-19	• Self-reported symptom severity, as assessed weekly through use of PGIS
• To evaluate health status and utility scores of patients diagnosed with COVID-19	• Health status utility, as assessed by EQ-5D-5L at Day 1 and Months 1, 2, 3, 4, 5, and 6 • Work or school utility, as assessed through WPAI+CIQ: SHP at Day 1, Months 3 and 6
• To identify and/or evaluate biomarkers that can increase the knowledge and understanding of disease biology	• Prevalence of neutralizing SARS-CoV-2 antibodies over time • Levels of biomarkers in blood and urine samples and their relationship with long-term outcomes or other biomarker endpoints
• To evaluate the effectiveness of a consumer-grade wearable to track changes in physiological and behavioral patterns following COVID-19 infection, as countries permit	• Change in heart rate over time • Change in SpO_2 over time • Change in activity over time • Change in sleep patterns over time

COVID-19 = coronavirus disease 2019; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; HRQoL = health-related quality of life; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PGIS = Patient Global Impression of Severity; PROMIS = Patient Reported Outcomes Measurement Information System; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SGRQ = St. George's Respiratory Questionnaire; SpO_2 = peripheral capillary oxygen saturation; WPAI+CIQ: SHP = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems.

Study Design

Description of Study

This is a Phase III, non-treatment, observational, multicenter, follow-up study to assess long-term outcomes for approximately 6 months in patients diagnosed with COVID-19 who previously enrolled a RO7496998 (AT-527) study, also referred to as the parent study.

There is no study drug or other treatment required in this follow-up study. Throughout this protocol, “study drug” refers to treatment administered in the parent study prior to this study (CV43140).

Any patients previously enrolled in a Phase III RO7496998 (AT-527) study will be informed of the opportunity to participate in this study (CV43140). An attempt will be made, where possible, to consent patients to this study at the same time patients are consented to the parent study. At the latest, patients must provide consent at the Day 1 visit (baseline) of this study (CV43140), prior to the first assessment.

The Day 1 visit (baseline) can coincide with the final visit of the parent study, or as soon as possible after the final visit and within 7 days. Study outcomes will be assessed by measuring specific endpoints in patients at either daily (i.e., continuous measurements via consumer-grade wearable devices), weekly, or monthly time intervals for approximately 6 months. Patients will complete the COVID-19 Symptom Diary and Patient Global Impression of Severity every week; Patient Reported Outcomes Measurement Information System-Dyspnea Questionnaire, St. George's Respiratory Questionnaire, and EuroQol 5-Dimension, 5-Level Questionnaire every month; Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems at the Day 1 visit, Months 3 and 6.

Patients will be assessed through concomitant medication, nasopharyngeal swabs (as clinically indicated), blood samples, and urine samples. Patients will be closely monitored for COVID-19 signs and symptoms and adverse events; adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Patients will be assessed monthly for COVID-19–related medically-attended visits.

In addition, depending on local and country regulations and allowances, patients will use a consumer-grade wearable device (e.g., Apple Watch), provided by the Sponsor, on a continuous basis to capture heart rate, peripheral capillary oxygen saturation, activity, and sleep patterns for the duration of the study. Data stored in the wearable device will be uploaded via a smart device. At the end of this study, patients will be required to return the smart device and the wearable device.

Number of Patients

Approximately 1040 patients diagnosed with COVID-19 who previously enrolled in a Phase III RO7496998 (AT-527) study are expected to enroll in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (signed by patient’s legally authorized representative for patients who have not attained the age of majority)
- Signed Assent Form when appropriate, as determined by patient’s age, individual site, and country standards
- Age $\geq$ 18 years (regardless of weight) at the time of signing Informed Consent Form or age $\geq$ 12 to $<$ 18 years (weight $\geq$ 40 kg) at the time of signing Informed Consent Form (and Assent Form)
- Ability, judged by the investigator, to comply with the study protocol
- Patient was diagnosed with COVID-19 and enrolled in a Phase III RO7496998 (AT-527) COVID-19 study.

  Note: Patients who completed all study assessments in the parent study are eligible, regardless of whether patients completed or discontinued early from the study drug.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Participation in an interventional study at the time of enrollment or plans to enroll in an interventional study during this study
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator’s judgment, precludes the patient’s safe participation in and completion of the study

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis is received from the last patient on the study, whichever occurs later. The end of the study is expected to occur approximately 6 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from enrollment of the first patient into this follow-up study to the end of the study, is expected to be approximately 10 months. The total length of the study may be extended if patients from additional Phase III RO7496998 (AT-527) studies roll over into this study.

Investigational Medicinal Products

This is an observational study and there is no investigational medicinal product in the study.

Statistical Methods

Primary Analysis

The primary objective of this study is to evaluate the long-term symptoms of patients diagnosed with COVID-19 who previously enrolled in a RO7496998 (AT-527) study (i.e., parent study), for approximately 6 months after the end of the parent study.

This will be assessed by the following endpoint:

- Descriptive summaries, over time, of COVID-19 symptoms, as assessed through the COVID-19 Symptom Diary (Items 1–14)

This endpoint will be explored using descriptive summary statistics over time and will be specified in the Statistical Analysis Plan (SAP). Because the primary analysis is descriptive in nature, there will be no formal hypothesis testing in the analysis of the primary endpoint. The analysis population will consist of all patients enrolled in the study.

Details of the statistical analysis methods and endpoints will be described in the study SAP which will be finalized prior to study completion.

Determination of Sample Size

This study is observational in nature and designed for estimation and hypothesis-generating purposes. The sample size of approximately 1040 patients is based on site feasibility assessment rather than statistical considerations.

Interim Analysis

While no interim analysis is planned for this study, if necessary, in support of a marketing application to health authorities, interim safety analyses may be conducted.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CDC	Centers for Disease Control
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
EC	Ethics Committee
ER	emergency room
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
FDA	(U.S.) Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MN	mobile nursing
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NP	nasopharyngeal
PGIS	Patient Global Impression of Severity
PRO	patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
RT-PCR	reverse transcriptase-polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus-2
SDV	source data verification
SGRQ	St. George's Respiratory Questionnaire
SOC	standard of care
SpO_2	peripheral capillary oxygen saturation
WPAI+CIQ: SHP	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON COVID-19

While most patients who have an acute infection with Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) and develop coronavirus disease 2019 (COVID-19) recover to their previous health status, some may have persistent or late symptoms. These persistent symptoms are often referred to as “long COVID” and the group of those patients experiencing them are often called “long haulers”. This persistence of symptoms appears to occur often in non-hospitalized patients who experience mild COVID-19 illness (Centers for Disease Control [CDC] 2020) but has presented in more severe patients as well. The most commonly reported long-term symptoms include fatigue, shortness of breath, cough, joint pain, and chest pain (CDC 2020). Two to three weeks after testing positive in the outpatient setting, 35% of persons had not returned to their previous state of health, including 47% of those aged 50 years or older (Tenforde et al. 2020). An increased hazard for psychiatric diagnoses in the three months after the diagnosis of COVID-19 has also been described (Taquet et al. 2020).

Few studies have quantified the frequency or duration of persistent symptoms in this now recognized chronic phase of COVID-19, especially in non-hospitalized patients. Reports to date have revealed mixed findings with regards to frequency, type, and severity of persistent symptoms, possibly as a consequence of presenting self-reported outcomes versus outcomes measured by tests or confirmed diagnoses; measuring outcomes at different time points during the course of the disease; and defining outcomes using different degrees of severity (such as mild fatigue vs. severe fatigue), among other reasons.

Among 143 patients who were hospitalized for COVID-19 in Italy and recovered from the acute phase (mean age, 57 years; 63% men), 87% presented with at least one COVID-19–related symptom in the follow-up visit that took place at a mean of 60 days after onset of first symptom of COVID-19; 32% of 143 patients had 1 or 2 symptoms and 55% had three or more (Carfi et al. 2020). Worsened quality of life was noted in 44% of patients. The most common persistent symptoms were fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (22%). Some symptoms that were common in the acute phase were not as common at the follow-up visit, such as cough, headache, myalgia, dysgeusia, lack of appetite, and anosmia.

A U.S.-based project followed 357 patients who tested positive for SARS-CoV-2 and reported on their health via online surveys (age and sex of this group not reported; 3% hospitalized) (Cirulli et al. 2020). Of the 216 patients who tested positive and provided information after 30 days, 36% reported at least one symptom, whereas the corresponding proportion was 12% among patients who tested negative, and 8% in those who did not undergo tests. Patients reported these predominant symptoms lasting

longer than 30 days associated with COVID-19 as follows: dry cough, difficulty breathing, anosmia, difficulty concentrating, and headache.

In the United Kingdom, United States, and Sweden, 4182 patients reported their symptoms prospectively after testing positive for a SARS-CoV-2 PCR using a mobile application (mean age, 43 years; 29% men; 14% visited a hospital) (Sudre et al. 2020). Of the 4182 patients, the following were reported: 13% with symptoms lasting longer than 4 weeks, 5% with symptoms lasting longer than 8 weeks; and 2% with symptoms lasting longer than 12 weeks. Frequent persistent symptoms were fatigue (98% of patients who had symptoms 28 days after testing positive), headache (91%), dyspnea, and anosmia.

Additionally, a 6-month follow-up study following a cohort of discharged hospitalized patients in China reported that COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression (Huang et al. 2021). The U.K. National Health Service, in March 2020, predicted that 45% of COVID-19 patients who had been hospitalized will need ongoing medical care, 4% will require inpatient rehabilitation, and 1% may permanently require acute care.

It has been reported that outpatient multidisciplinary follow-up research studies will help to improve our understanding of the natural history of COVID-19 sequelae together with factors and mediators involved (Cortinovis et al. 2021).

The widespread utilization of consumer-grade wearable devices has enabled new ways to study disease through continuous patient monitoring and passive collection of data. Physiological and behavioral data from these devices provide rich information to deepen the understanding of the disease itself. Prospective, continuous data collection using consumer-grade wearable devices may provide valuable insight on physiological and behavioral patterns following COVID-19 infection that have been difficult to understand and describe thus far.

Data from consumer-grade wearable devices have been studied previously to develop preliminary digital measures of cognitive impairment (Chen et al. 2019), characterize the impact of chronic pain on daily activities (Tran et al. 2019), and describe population-level response to influenza-like illness using passively collected, daily behavioral data (heart rate, activity, sleep) (Bradshaw et al. 2019). Ongoing studies are examining the extent to which these data relate to real world clinical outcomes and patient-reported outcomes (PROs) in influenza (Study WV42005). Within the COVID-19 indication, a new study recently demonstrated that consumer-grade wearable devices can predict a positive COVID-19 diagnosis up to a week before current PCR-based nasal swab tests (Hirten et al. 2021). In COVID-19 long-term follow-up, however, there is currently a paucity of data from wearable devices, leaving opportunity to examine the physiological and behavioral patterns in patients after the acute phase of their disease.

There is limited evidence on the long-term effects of COVID-19 infection, particularly for non-hospitalized patients with mild or moderate COVID-19. Therefore, additional evaluation of COVID-19 long-term symptoms, including frequency and time to resolution, is warranted in patients with mild to moderate COVID-19, utilizing clinical follow-up, PROs, and consumer-grade wearable devices.

1.2 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The main benefit of this study will be an improved understanding of the long-term sequelae of COVID-19 by following patients diagnosed with COVID-19 who previously enrolled in a RO7496998 (AT-527) study (i.e., parent study). Close monitoring of these long-term COVID-19–related symptoms will be beneficial in determining recovery post-infection in these patients. For the individual patient, there is a potential benefit of additional medical oversight.

Potential risks of a patient's involvement in this study include risks common to clinical trials, such as the inconvenience of clinical assessments, blood draws, and urine samples. Nasopharyngeal (NP) swabs may be collected if clinically indicated, such as by worsening of symptoms. Collection of blood and urine samples from patients will provide vital information on the clinical manifestation or cessation of biomarkers related to viral infection and immune response mounted by patients over time. Blood and urine sampling is routine with biomarker surveillance studies in the clinical trial setting. The risk to patients regarding the blood sampling venipuncture procedure will be low, no greater than blood collected as part of standard of care (SOC), and the procedure will be conducted by a trained professional. The volume of blood collected during the study will be minimized to mitigate unnecessary blood sampling and visits scheduled for the patient. Symptom driven NP swabs during this study will help to confirm infection as clinically indicated and correlate virology with study biomarkers also being followed. NP swabs are synonymous with virology studies and the swab procedure will be conducted by site personnel well versed in the procedure.

Based on the wide number and differing clinical observations reported by authors for convalescent COVID-19 patients, this follow-up study will employ a multi-faceted approach for collecting clinical measures to observe the patient cohort over an approximately 6-month period, including PROs and activity and physiological data from wearable devices. This will enable future clinical studies to have a clinically meaningful suite of tools at their disposal to assess the long-term COVID-19 sequelae, particularly in those patients diagnosed with mild to moderate COVID-19.

Although the use of PROs and wearable devices are not considered to be part of the SOC in the treatment or follow-up of COVID-19 patients, associated risks with the use of these devices by patients are considered to be minimal. A potential risk of the wearable device is a rash from the armband due to sensitivities or allergies. The use of a consumer-grade wearable device will be purely exploratory in this study but the technology may provide data (e.g., heart rate, pulse oximetry, activity, and sleep) about

the long-term recovery in patients with COVID-19 through employing a less invasive and less burdensome approach to patient follow-up.

Considering the above, the benefit-risk balance for this study is considered favorable.

2. OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the long-term sequelae of COVID-19 in patients diagnosed with COVID-19 who previously enrolled in a RO7496998 (AT-527) study (i.e., parent study), for approximately 6 months after the end of the parent study. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the long-term symptoms of patients diagnosed with COVID-19	• Descriptive summaries, over time, of COVID-19 symptoms, as assessed through the COVID-19 Symptom Diary (Items 1–14)
Secondary Objectives	**Corresponding Endpoints**
• To evaluate HRQoL of patients diagnosed with COVID-19	• Impact of dyspnea symptoms on specific activities, as assessed through use of PROMIS-Dyspnea Questionnaire at Day 1 and Months 1, 2, 3, 4, 5, and 6 • Respiratory-specific HRQoL, as assessed through use of SGRQ at Day 1 and Months 1, 2, 3, 4, 5, and 6
• To evaluate medical resource utilization for patients diagnosed with COVID-19	• Proportion of patients with COVID-19–related medically-attended visits through to study end (defined as hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit with the primary reason for the visit being COVID-19 or COVID-19–related symptoms)
• To evaluate the long-term outcomes of COVID-19 in patients diagnosed with COVID-19	• Proportion of patients with all-cause mortality • Proportion of patients with death attributable to progression of COVID-19 • Proportion of patients re-infected with SARS-CoV-2 • Proportion of patients with any post-treatment infection including but not limited to bacterial, viral, or fungal pneumonia or sepsis • Frequency of COVID-19–related complications (e.g., death, hospitalization, radiologically-confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis, myocarditis, cardiac failure)
• To evaluate adverse events in patients diagnosed with COVID-19 who previously enrolled in a RO7496998 (AT-527) study	• Incidence and severity of adverse events and serious adverse events, with severity determined according to NCI CTCAE v5.0

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To evaluate symptom severity of patients diagnosed with COVID-19	• Self-reported symptom severity, as assessed weekly through use of PGIS
• To evaluate health status and utility scores of patients diagnosed with COVID-19	• Health status utility, as assessed by EQ-5D-5L at Day 1 and Months 1, 2, 3, 4, 5, and 6 • Work or school utility, as assessed through WPAI+CIQ: SHP at Day 1, Months 3 and 6
• To identify and/or evaluate biomarkers that can increase the knowledge and understanding of disease biology	• Prevalence of neutralizing SARS-CoV-2 antibodies over time • Levels of biomarkers in blood and urine samples and their relationship with long-term outcomes or other biomarker endpoints
• To evaluate the effectiveness of a consumer-grade wearable to track changes in physiological and behavioral patterns following COVID-19 infection, as countries permit	• Change in heart rate over time • Change in SpO_2 over time • Change in activity over time • Change in sleep patterns over time

COVID-19 = coronavirus disease 2019; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; HRQoL = health-related quality of life; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PGIS = Patient Global Impression of Severity; PROMIS = Patient Reported Outcomes Measurement Information System; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SGRQ = St. George's Respiratory Questionnaire; SpO_2 = peripheral capillary oxygen saturation; WPAI+CIQ: SHP = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, non-treatment, observational, multicenter, follow-up study to assess long-term outcomes for approximately 6 months in patients diagnosed with COVID-19 who previously enrolled a RO7496998 (AT-527) study, also referred to as the parent study.

There is no study drug or other treatment required in this follow-up study. Throughout this protocol, “study drug” refers to treatment administered in the parent study prior to this study (CV43140).

Any patients previously enrolled in a Phase III RO7496998 (AT-527) study will be informed of the opportunity to participate in this study (CV43140). An attempt will be made, where possible, to consent patients to this study at the same time patients are consented to the parent study. At the latest, patients must provide consent at the Day 1 visit (baseline) of this study (CV43140), prior to the first assessment.

The Day 1 visit (baseline) can coincide with the final visit of the parent study, or as soon as possible after the final visit and within 7 days. Study outcomes will be assessed by measuring specific endpoints in patients at either daily (i.e., continuous measurements via consumer-grade wearable devices), weekly, or monthly time intervals for approximately 6 months. Patients will complete the COVID-19 Symptom Diary and Patient Global Impression of Severity (PGIS) every week; Patient Reported Outcomes Measurement Information System (PROMIS)-Dyspnea Questionnaire, St. George's Respiratory Questionnaire (SGRQ), and EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) every month; Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems (WPAI+CIQ: SHP) at the Day 1 visit, Months 3 and 6.

Patients will be assessed through concomitant medication, NP swabs (as clinically indicated), blood samples, and urine samples (see Appendix 1 for details regarding the timing of these assessments). Patients will be closely monitored for COVID-19 signs and symptoms and adverse events; adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Patients will be assessed monthly for COVID-19–related medically-attended visits.

In addition, depending on local and country regulations and allowances, patients will use a consumer-grade wearable device (e.g., Apple Watch), provided by the Sponsor, on a continuous basis to capture heart rate, peripheral capillary oxygen saturation (SpO_2), activity, and sleep patterns for the duration of the study (see Section 4.5.3). Data stored in the wearable device will be uploaded via a smart device. At the end of this study, patients will be required to return the smart device and the wearable device.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis is received from the last patient on the study, whichever occurs later. The end of the study is expected to occur approximately 6 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from enrollment of the first patient into this follow-up study to the end of the study, is expected to be approximately 10 months. The total length of the study may be extended if patients from additional Phase III RO7496998 (AT-527) studies roll over into this study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Non-Standard Clinical Outcome Assessments

At the onset of the global emergency, there was limited understanding of what constituted disease progression in COVID-19 and how the symptoms experienced by patients manifested themselves and affected their lives. Given the heterogeneous

nature of COVID-19–related symptoms in outpatients, key COVID-19–related symptoms should be assessed systematically to provide an accurate evaluation. For this reason, the example U.S. FDA COVID-19 PRO instrument has been used as a basis for the COVID-19 Symptom Diary assessing 14 key symptoms and will be used for this study. The symptom items used in this PRO are derived from information provided by the Centers for Disease Control and Prevention as of 28 August 2020.

3.3.2 Rationale for Biomarker Assessments

COVID-19 is a heterogeneous disease, and expression of certain biomarkers has been shown to vary with disease severity (Arunachalam et al. 2020; Su et al. 2020). Exploratory biomarkers during the long-term observational study may allow for identification of patients at higher risk of sustained or worse outcomes to COVID-19. Blood biomarkers will include, but are not limited to, markers of inflammation and those with known associations to tissue damage and repair (e.g., wound healing/fibrotic remodeling of the lung) to explore their associations to persistent lung anomalies induced by COVID-19 (Dressen et al. 2018; Neighbors et al. 2018). Biomarkers for non–lung-related outcomes may also be measured to understand the progression of COVID-19. The changes in biomarkers and their relationship to long-term clinical and other biomarker endpoints will be assessed to further the understanding of disease biology of COVID-19.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1040 patients diagnosed with COVID-19 who previously enrolled in a Phase III RO7496998 (AT-527) study are expected to enroll in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (signed by patient's legally authorized representative for patients who have not attained the age of majority)
- Signed Assent Form when appropriate, as determined by patient's age, individual site, and country standards
- Age $\geq$ 18 years (regardless of weight) at the time of signing Informed Consent Form or age $\geq$ 12 to $<$ 18 years (weight $\geq$ 40 kg) at the time of signing Informed Consent Form (and Assent Form)
- Ability, judged by the investigator, to comply with the study protocol
- Patient was diagnosed with COVID-19 and enrolled in a Phase III RO7496998 (AT-527) COVID-19 study.

  Note: Patients who completed all study assessments in the parent study are eligible, regardless of whether patients completed or discontinued early from the study drug.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Participation in an interventional study at the time of enrollment or plans to enroll in an interventional study during this study
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a non-randomized, observational, and non-treatment study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will set up the patient in the electronic data capture (EDC) system with the same patient identification number as from the parent study.

The treatment arm to which patients were assigned in the parent study will not be disclosed until the final analysis of the parent study is reported, which may occur during this study (CV43140).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

This is an observational study. No study drug will be administered.

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and supplemental oxygen used by a patient from the Day 1 visit of this study to the end of this study (CV43140). Concomitant therapy data may be transferred from the parent study. There are no food, alcohol, herbal therapy, or smoking restrictions during this study.

Although there are no restrictions on concomitant therapies in this study, all such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

At applicable sites, certain study assessments and visits may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating

sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1) will specify the assessments that may be performed by an MN professional.

Assessments at Unscheduled Visits

Assessments listed in Appendix 1, as deemed necessary by the investigator and/or the Sponsor (e.g., for evaluation of an adverse event), may be performed at unscheduled visits.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent and assent (where appropriate) for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms (and Assent Forms where appropriate) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, demographic data, concomitant medications, and resolved adverse events may be transferred from the parent study. Ongoing adverse events at the end of the parent study will be reopened in this study (CV43140) (see Section 5.1).

In addition, all concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and supplemental oxygen used by the patient during the study will be recorded. At each visit, changes in concomitant medication and allergies will be recorded.

Any COVID-19 vaccination that has occurred before the patient enrolls into the study or during the study will be recorded on the Concomitant Medications eCRF, including the report product or brand/trade or company manufacturer, if available (examples: Pfizer COVID-19 vaccine, Moderna COVID-19 vaccine), and date(s) administered if known. If not available, report as COVID-19 vaccine.

4.5.3 Wearable Device

At the Day 1 visit, depending on local and country regulations and allowances, patients will be provided with a consumer-grade wearable device (e.g., Apple Watch) where possible and detailed instructions on the correct use of the device to track their health data continuously (e.g., heart rate, SpO_2, activity, and sleep pattern). Data stored in the consumer-grade wearable device will be uploaded through a smart device, preferably on a daily basis. Data are not available to the Sponsor in real-time; therefore, are not medically actionable. Data captured from this consumer-grade wearable device are not considered medical-grade and are for exploratory analysis only.

At the end of this study, patients will be required to return the consumer-grade wearable device and the smart device. All patient identifiers and personal information will be removed from these devices at the end of the study.

4.5.4 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to designated central laboratories or the Sponsor or a designee for analysis:

- Symptom-guided NP swab for SARS-CoV-2 reverse-transcriptase (RT)-PCR, genotypic analysis, and respiratory pathogen co-infections panel (multiplex BioFire® assay) (see Appendix 2 for example symptoms)
- Serum samples for exploratory biomarker research and SARS-CoV-2 antibodies
- Symptom guided serum samples for exploratory biomarker research and SARS-CoV-2 antibodies (see Appendix 2 for example symptoms)
- Blood PAXgene™ RNA for RNA sequencing or quantitative PCR
- Blood sample for hemoglobin A1c
- Urine sample for exploratory biomarker research

NP swabs (symptom-guided; as clinically indicated), blood, and urine sample collection may be performed by an MN professional.

Exploratory biomarker research and virology tests may include, but will not be limited to, analysis of SARS-CoV-2 antibody titer, inflammatory mediators and/or cytokines, immune cells, viral load, viral titer, virus drug susceptibility and virus genotypic analysis (e.g., next-generation sequencing [NGS]). Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exception:

- NP swabs, serum, blood PAXgene™ RNA, blood, and urine samples collected for virology and biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the Institutional Review Board/ Ethics Committee (IRB/EC)–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.5 Clinical Outcome Assessments

Clinical outcome assessments in this study will be completed by patients via PROs to evaluate long-term outcomes of patients with COVID-19 who previously enrolled in a RO7496998 (AT-527) study. In addition, PRO instruments will enable the capture of each patient's direct experience with any long-term symptoms of COVID-19.

PRO data will be collected through use of the following instruments: COVID-19 Symptom Diary, PGIS, PROMIS-Dyspnea Questionnaire, SGRQ, EQ-5D-5L, and WPAI+CIQ: SHP.

4.5.5.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at home at specified timepoints during the study (see schedule of activities in Appendix 1).

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the instrument to be administered at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Patients should be given the following instructions for completing PRO instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.5.2 Description of Clinical Outcome Assessment Instruments

COVID-19 Symptom Diary

The COVID-19 Symptom Diary (see Appendix 2) will be used to characterize key symptoms recognized as part of COVID-19 illness per FDA guidance (FDA 2020). The COVID-19 Symptom Diary is composed of 14 individual symptom questions, each with a 3- or 4-point Likert response option. The content of the COVID-19 Symptom Diary remains unchanged from the parent study (Study CV43043), but the recall period and administration schedule are modified for the long-term study design.

The COVID-19 Symptom Diary will be completed in its entirety by the patient once a week (see Appendix 1). To ensure that data standards meet health authority requirements, the COVID-19 Symptom Diary will be completed as per schedule of assessment for the duration of the study.

Patient Global Impression of Severity

The PGIS (see Appendix 3) is a single item assessment of a patient's impression of the severity of his or her COVID-19 symptoms during the course of the study. Change in COVID-19 symptoms are rated on a 4-point Likert scale from "none" (0) to "severe" (3). The PGIS will be completed by the patient once a week for the duration of the study.

PROMIS-Dyspnea Questionnaire

The PROMIS Short Form Dyspnea Severity Questionnaire is a 10-item questionnaire selected from the PROMIS Item Bank v1.0–Dyspnea Severity (Choi et al. 2011). The item bank assesses the severity of shortness of breath and difficulty of breathing in response to specific activities. Patients will be asked to self-report their severity of shortness of breath over the past seven days (see Appendix 4). The PROMIS Short Form Dyspnea Severity instrument is scored on a 4-point Likert scale, with an option to indicate that an activity had not been performed. A higher score indicates a higher symptom severity of dyspnea.

St. George's Respiratory Questionnaire

The SGRQ is a 50-item respiratory-specific quality-of-life questionnaire initially developed and validated for use in chronic obstructive pulmonary disease (COPD) (Jones et al. 1992) (see Appendix 5). It includes questions that assess the impact of disease on symptoms, activity, and functionality. Each scale is scored from 0 to 100,

and a total score represents the weighted average of these three subscores. Items are assessed on various response scales, including a 5-point Likert scale and a true/false scale. The SGRQ has a recall period of the past 4 weeks. Recently, the SGRQ has been applied more broadly to assess patients with airflow limitation due to causes other than COPD, including asthma (Ortega et al. 2014). The SGRQ will be administered once a month.

EuroQol-5D-5L

The EQ-5D-5L, is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 6). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems

The WPAI+CIQ: SHP is a 10-item scale (see Appendix 7) adapted from the WPAI: General Health v2 (Reilly et al. 1993) to assess both work and classroom environments. Patients will be asked to estimate the amount of time that their work, school work and daily activities were affected by their COVID-19 symptoms over the previous 7 days (Reilly et al. 1996). The WPAI+CIQ: SHP assesses absenteeism as well as “presenteeism,” which accounts for the time when patients were present for work or school, but believed their health had a negative effect on their ability to perform at the usual level. A higher score represents greater impairment in productivity.

4.5.5.3 Additional COVID-19–Related Assessments

COVID-19–Related Medically-Attended Visit(s) Assessment

A COVID-19–related medically-attended visit will be defined as follows: hospitalization, emergency room (ER) visit, urgent care visit, physician’s office visit, or telemedicine visit, with the primary reason for the visit being COVID-19 or COVID-19–related symptoms.

Only medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF. Details will include at minimum:

- Type of visit (hospitalization, ER visit, urgent care visit, physician’s office visit, or telemedicine visit)
- Date of visit
- Primary reason for COVID-19–related medically-attended visit

- Treatments given for COVID-19 (including, but not limited to, concomitant medications and supplemental oxygen)
- If hospitalization due to COVID-19 was required, include length of visit, whether intensive care unit care was given, or whether mechanical ventilation was required

Any adverse events or concomitant therapies reported to the investigator should be recorded on the respective Adverse Events eCRF or Concomitant Medications eCRF.

4.5.6 Optional Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, optional blood samples will be collected from consenting patients for DNA extraction to enable Whole Genome Sequencing (WGS) or whole exome sequencing (WES) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Of note, at participating sites, blood samples will only be collected from consenting patients who have not previously provided a WGS sample in the parent study. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.6) will not be applicable at that site.

The Informed Consent Form will contain a separate section that addresses optional blood samples for WGS or WES. A separate, specific signature will be required to document a patient's agreement to provide optional blood samples. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Whole Genome Sequencing or Whole Exome Sequencing Informed Consent/Withdrawal eCRF.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored for up to 15 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.4 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation from the Study

Patients are required to complete an early termination visit as soon as possible after they decide to withdraw from the study or the investigator withdraws the patient from the study. This visit can be performed remotely.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.2 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.3 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Any adverse events that occur during this study should be reported as outlined below.

For ongoing adverse events starting in the parent study, any follow-up of the adverse event will be reported in this study (Study CV43140). The adverse event severity, according to NCI CTCAE v5.0 (Table 2), should be evaluated by the investigator at the Day 1 visit of this study and recorded in the "adverse event initial NCI CTCAE grade" field of the Adverse Event eCRF for Study CV43140. The most extreme NCI CTCAE grade for the adverse event should also be recorded, taking into account the severity of the event since it was first reported during the parent study.

Please note that “study drug” refers to the treatment administered in the parent study prior to this follow-up study.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a

pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.5 and 5.3.5.6 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Adverse events that are related to a protocol-mandated intervention

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.7)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.
The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained, all adverse events should be reported from Day 1 visit of this study until the end of the study. For ongoing adverse events which occurred before the Day 1 visit of this study, the adverse event will be reported as outlined in Section 5.1.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug administered in the parent study, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (Table 3):

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug administered in the parent study on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the procedure (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to the initiation of a study procedure.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of COVID-19.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of COVID-19, “COVID-19 progression” should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.5 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for the parent study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF and where possible, will be transferred from the parent study.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.6 Lack of Efficacy or Worsening of COVID-19

Medical occurrences or symptoms of deterioration that are anticipated as part of COVID-19, such as fluctuations in symptoms should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of COVID-19 on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of COVID-19").

5.3.5.7 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

5.3.5.8 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

PPD 24-Hour Safety Hotline:

- North America: +1 (888) 483-7729
- EMEA/APAC: +44 (0) 1223 374 240
- Latin America: +55 11 4504 4801

Roche Medical Monitor/ Medical Responsible: [redacted], M.D., Ph.D.
Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events

After informed consent has been obtained, serious adverse events will be reported from Day 1 visit of this study. For ongoing serious adverse events since the parent study, the adverse event will be reported as outlined in Section 5.1. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the

EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, the wearable monitor (e.g., Apple Watch) is considered a medical device. The investigator must report all medical device complaints to the Sponsor.
The investigator should document as much information as possible and forward the complaints to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

For complaints and adverse events associated with the wearable monitor (e.g., Apple Watch), the Sponsor will forward the complaint to the manufacturer. The manufacturer will report all adverse events according to the regulatory requirements for reporting of medical device-related adverse events (21 CFR 803).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
AT-527	AT-527 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final analysis of the study will occur at the end of the study (see Section 3.2).

Differential loss to follow-up may introduce bias into the study. Patients may be lost to follow-up because they are fully recovered or they experience an adverse outcome.

Details of the statistical analysis methods and endpoints will be described in the study Statistical Analysis Plan (SAP) which will be finalized prior to study completion.

6.1 DETERMINATION OF SAMPLE SIZE

This study is observational in nature and designed for estimation and hypothesis-generating purposes. The sample size of approximately 1040 patients is based on site feasibility assessment rather than statistical considerations.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient disposition (i.e., the number of patients who enroll, discontinue, or complete the study) will be summarized descriptively. Reasons for premature study discontinuation will also be summarized and may be listed if appropriate. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

A patient disposition figure will show the flow of patients starting with the parent study and finishing with the number of patients contributing data to this study.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, region, treatment group in the parent study, RT-PCR status, seropositive status, presence of

risk factors, preexisting symptoms and other patient characteristics of interest) will be summarized using descriptive statistics including means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall. Demographic and baseline characteristics may be obtained from data collected in the parent study.

Patient characteristics will be displayed in a tabular format (number and percentage), including demographics, medical history before COVID-19, and treatments received for COVID-19.

To evaluate the potential for selection bias, patient characteristics will be compared between the parent study and the follow-up study to examine for systematic differences.

6.4 STATISTICAL ANALYSES

The analysis population will consist of all patients enrolled in the study. Long-term clinical and PROs will be summarized descriptively and trends over time will be explored. Outcomes may also be explored by patient characteristics (e.g., treatment received in the parent study), as appropriate.

6.4.1 Primary Endpoint

The primary objective of this study is to evaluate the long-term symptoms of patients diagnosed with COVID-19 who previously enrolled in a RO7496998 (AT-527) study (i.e., parent study), for approximately 6 months after the end of the parent study.

This will be assessed by the following endpoint:

- Descriptive summaries, over time, of COVID-19 symptoms, as assessed through the COVID-19 Symptom Diary (Items 1–14)

This endpoint will be explored using descriptive summary statistics over time and will be specified in the SAP. Because the primary analysis is descriptive in nature, there will be no formal hypothesis testing in the analysis of the primary endpoint.

6.4.2 Secondary Endpoints

The secondary endpoints are as follows:

- Impact of dyspnea symptoms on specific activities, as assessed through use of PROMIS-Dyspnea Questionnaire at Day 1 and Months 1, 2, 3, 4, 5, and 6
- Respiratory-specific health-related quality of life, as assessed through use of SGRQ at Day 1 and Months 1, 2, 3, 4, 5, and 6
- Proportion of patients with COVID-19–related medically-attended visits through to study end (defined as hospitalization, ER visit, urgent care visit, physician's office visit, or telemedicine visit with the primary reason for the visit being COVID-19 or COVID-19–related symptoms)
- Proportion of patients with all-cause mortality

- Proportion of patients with death attributable to progression of COVID-19
- Proportion of patients re-infected with SARS-CoV-2
- Proportion of patients with any post-treatment infection including but not limited to bacterial, viral, or fungal pneumonia or sepsis
- Frequency of COVID-19–related complications (e.g., death, hospitalization, radiologically-confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis, myocarditis, cardiac failure)
- Incidence and severity of adverse events and serious adverse events, with severity determined according to NCI CTCAE v5.0

Observed absolute values will be summarized by means, standard deviations, medians, and ranges for continuous endpoints, as appropriate, while count and percentages will be tabulated for categorical endpoints by study timepoints. Longitudinal modeling of endpoints may also be explored, as appropriate.

All endpoints will be summarized descriptively and no p-values will be presented.

6.4.3 Exploratory Endpoints

The exploratory endpoints are as follows:

- Self-reported symptom severity, as assessed weekly through use of PGIS
- Health status utility, as assessed by EQ-5D-5L at Day 1 and Months 1, 2, 3, 4, 5, and 6
- Work or school utility, as assessed through WPAI+CIQ: SHP at Day 1, Months 3 and 6
- Prevalence of neutralizing SARS-CoV-2 antibodies over time
- Levels of biomarkers in blood and urine samples and their relationship with long-term outcomes or other biomarker endpoints
- Changes in physiological and behavioral patterns, as measured by consumer-grade wearables outputs, such as:
  - Change in heart rate over time
  - Change in SpO_2 over time
  - Change in activity over time
  - Change in sleep patterns over time

Observed absolute values will be summarized by means, standard deviations, medians, and ranges for continuous endpoints, as appropriate, while count and percentages will be tabulated for categorical endpoints by study timepoints. Longitudinal modeling of endpoints may also be explored, as appropriate.

All endpoints will be summarized descriptively and no p-values will be presented.

6.5 SAFETY ANALYSES

The safety analyses will include all enrolled patients in the study.

Safety will be assessed through descriptive summaries of serious adverse events (nature, frequency, and severity) and vital signs. Serious adverse events will also be listed. Safety may be explored by study treatment received in the parent study, as appropriate.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, including serious adverse events that are continuing/persisting from the parent study (regardless of causal association with the study drug administered in the parent study) or any new adverse event with an onset date on or after the first day of enrollment and during this follow-up study, will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

6.6 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.7 INTERIM ANALYSIS

While no interim analysis is planned for this study, if necessary, in support of a marketing application to health authorities, interim safety analyses may be conducted.

6.8 SUBGROUP ANALYSES

The main analyses may be performed for groups of patients with certain characteristics. Some characteristics that may denote groups with different results will be identified during the course of the parent study. At this point, it is anticipated that such characteristics may be related to age, sex, morbidity before COVID-19 (e.g., obesity, diabetes, asthma), severity of acute COVID-19 before receiving treatment in the parent study and/or having completed the treatment of RO7496998 (AT-527) during the parent study. Subgroup analyses will be specified in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and electronic PRO will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device or application installed on the patient’s personal device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Where permitted, study monitors will perform targeted source data verification and review to confirm that critical protocol data as defined in the Monitoring Plan and entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Due to the COVID-19 pandemic, access to clinical trial sites may be restricted. In such cases, remote source data verification (SDV) (if permitted by the site and by local law) and remote data review will be performed. Study monitors will perform ongoing remote data review to confirm that critical protocol data (i.e., source data) entered on the eCRFs by authorized site personnel are accurate and complete.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

In addition to SDV or remote SDV on targeted critical data, ongoing remote data monitoring will be performed for this study. Study monitors will perform ongoing remote data review (defined in the Monitoring Plan and Centralized Monitoring Plan) to confirm that critical protocol data are entered into the eCRF by authorized site personnel are accurate and complete. Centralized monitoring tools will be implemented in order to support the remote data monitoring activity.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, and images, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or MN Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the

local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other

processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity.

Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan and a Centralized Monitoring Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by F. Hoffmann-La Roche Ltd (outside the United States) and Atea Pharmaceuticals, Inc. (in the United States). F. Hoffmann-La Roche Ltd will provide clinical operations management and data management, and both, F. Hoffmann-La Roche Ltd and Atea Pharmaceuticals, Inc. will provide medical monitoring.

Approximately 180 sites globally will participate to enroll approximately 1040 patients.

A contract research organization will be used for site management and monitoring, medical monitoring, and select regulatory submissions.

An MN vendor will be used to facilitate study visits being performed within the patient’s home.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, virology, biomarker analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon

request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an investigational medicinal product (IMP) for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Activities

Month	Day 1 [a]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	
(Visit Window)		±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	ET/UV [b]
Informed consent [a]	x							
PROs [c]								
COVID-19 Symptom Diary [d]	To be collected weekly							x
PGIS [d]	To be collected weekly							x
PROMIS-Dyspnea Questionnaire	x	x	x	x	x	x	x	x
St. George's Respiratory Questionnaire	x	x	x	x	x	x	x	x
EQ-5D-5L	x	x	x	x	x	x	x	x
WPAI+CIQ: SHP	x			x			x	x
Medically-attended visit(s) assessment [e]	x	x	x	x	x	x	x	x
NP swab for SARS-CoV-2 RT-PCR, genetic analysis, and BioFire® assay (symptom-guided) [f, g]	As clinically indicated							
Serum sample for biomarkers and SARS-CoV-2 antibodies	x			x			x	x
Serum sample for biomarkers and SARS-CoV-2 antibodies (symptom-guided) [h]	As clinically indicated							

Appendix 1: Schedule of Activities (cont.)

Month	Day 1 [a]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	
(Visit Window)		±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	ET/UV [b]
Blood sample for RNA	x			x			x	x
Blood sample for HbA_{1c}	x							
Urine sample for exploratory biomarker research	x			x			x	
Blood sample for WGS or WES (optional) [i]	x							
Collection of heart rate, SpO_2, activity, and sleep pattern–wearable device [j]	Continuous							
Concomitant medications [k]	←	―	―	―	―	―	―	→
Adverse Events [l]	←	―	―	―	―	―	―	→

COVID-19 = coronavirus disease 2019; EQ-5D-5L = Euro-QoL-5D-5-L; ET = early termination; HbA_{1c} = hemoglobin A1c; NP = nasopharyngeal; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; PROMIS = Patient Reported Outcomes Measurement Information System; RT-PCR = reverse-transcriptase polymerase chain reaction; SpO_2 = peripheral capillary oxygen saturation; UV = unscheduled visit; WES = whole exome sequencing; WGS = whole genome sequencing; WPAI+CIQ: SHP = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems.

Note: All assessments at each visit, except sample collections, can be conducted remotely (e.g., via telephone or computer). For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, select assessments or procedures (e.g., sample collection) may be performed by a trained nursing professional at the patient's home or another suitable location.

[a] The Day 1 visit (baseline) can coincide with the final visit of the parent study, or as soon as possible after the final visit and within 7 days Informed consent must be documented before any study assessment is performed. An attempt will be made, where possible, to consent patients to this study at the same time patients are consented to the parent study.

[b] An UV represents a visit that is not specified by the protocol but is determined to be necessary by the investigator or Sponsor (e.g., for evaluation of an adverse event). Assessments should be performed as clinically indicated.

[c] PRO questionnaires are to be completed by the patient before the patient receives any information on disease status, prior to the performance of non-PRO assessments. The assessments are to be conducted in the order listed in the schedule above.

[d] The COVID-19 Symptom Diary will be completed by the patient every week, with a 7-day recall of symptoms at worst. This questionnaire should be completed within 48 hours when the window for completion opens every 7 days. The PGIS will be completed every week at the same time as the COVID-19 Symptom Diary for the duration of the study.

[e] All details to be recorded in the eCRF at all visits. For details of the assessment, see Section 4.5.5.3.

[f] The symptom-guided NP swab for COVID-19 RT-PCR, genetic analysis, and BioFire® assay is to be conducted at any visit or UV, when the investigator determines it is warranted. Symptom-guided defined as patient with any "COVID-19 like" symptom(s) (see Appendix 2 for example symptoms). Patients should immediately contact the site upon onset of any "COVID-19 like" symptom(s) to ensure timely collection of appropriate samples.

[g] At least two NP swabs, one from each nostril, will be taken and sent to a central laboratory, as clinically indicated. Results from NP swabs will not be available during the study. Therefore, if a COVID-19 re-infection is suspected, it is under investigator's discretion to perform a local diagnostic test.

[h] The symptom-guided serum sample for biomarkers and SARS-CoV-2 antibodies is to be conducted at any visit or UV, when the investigator determines it is warranted. Symptom-guided defined as patient with any "COVID-19 like" symptom(s) (see Appendix 2 for example symptoms). Patients should immediately contact the site upon onset of any "COVID-19 like" symptom(s) to ensure timely collection of appropriate samples.

[i] Not applicable for a site that has not been granted approval for WGS or WES. Performed only for patients at participating sites who have provided written informed consent to participate and have not previously provided a blood sample for WGS in the parent study. If the sample is not collected at the Day 1 visit for any reason, it may be collected at any later timepoint.

[j] Depending on local and country regulations and allowances, patients will be provided with a consumer-grade wearable device (e.g., Apple Watch) where possible at the Day 1 visit to use on a continuous basis. Patients will be provided information regarding the use of the device (e.g., charging, waterproof properties, and support). Data stored in the wearable device will be uploaded through a smart device preferably on a daily basis.

[k] Medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and supplemental oxygen used by a patient during the study will be recorded. Any COVID-19 vaccination which has occurred before the patient enrolls into the study or during the study will be recorded in the concomitant medications eCRF, including the report product or brand/trade or company manufacturer, if available (examples: Pfizer COVID-19 vaccine, Moderna COVID-19 vaccine), and date(s) administered if known. If not available, report as COVID-19 vaccine.

[l] After informed consent has been obtained, all adverse events should be collected from the Day 1 visit of this study through the end of the study . For ongoing adverse events which occurred before the Day 1 visit of this study, the adverse event will be reported as outlined in Section 5.1.

Appendix 2
COVID-19 Symptom Diary

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Note that the following is a sample. Sites will be provided with separate versions of the diary for in-clinic assessment and patient at-home assessment.

COVID-19 Symptom Diary

This diary will keep track of your COVID-19 symptoms during the study. Please complete one time each week.

Please rate the severity of each symptom at its worst over the past 7 days.

	None 0	Mild 1	Moderate 2	Severe 3
1. Nasal Congestion or runny nose				
2. Sore Throat				
3. Cough				
4. Shortness of breath (difficulty breathing)				
5. Muscle or body aches				
6. Fatigue (tiredness)				
7. Headache				
8. Chills/Sweats				
9. Feeling hot or feverish				
10. Nausea (wanting to throw up)				
11. Vomiting (thrown up)				
12. Diarrhea (mostly or completely liquid bowel movements)				

	Same as usual **0**	**Less than usual** **1**	**No sense** **2**
13. Rate your sense of **smell** over the past 7 days.			
14. Rate your sense of **taste** over the past 7 days.			

Appendix 3
Patient Global Impression of Severity

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Patient Global Impression of Severity

Please rate your overall COVID-19 symptoms at their worst over the past 7 days.

☐ None

☐ Mild

☐ Moderate

☐ Severe

Appendix 4
Patient Reported Outcomes Measurement Information System (PROMIS)-Dyspnea Questionnaire

<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.

PROMIS Item Bank v1.0 – Dyspnea Severity – Short Form 10a

Dyspnea Severity – Short Form 10a

Please respond to each question or statement by marking one box per row.

	<u>Over the past 7 days</u>, how short of breath did you get with each of these activities?…	**No shortness of breath**	**Mildly short of breath**	**Moderately short of breath**	**Severely short of breath**	**I did not do this in the past 7 days**
DYSSV001	Dressing yourself without help	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV002	Walking 50 steps/paces on flat ground at a normal speed without stopping.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV003	Walking up 20 stairs (2 flights) without stopping.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV004	Preparing meals.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV005	Washing dishes	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV006	Sweeping or mopping	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV007	Making a bed.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV008	Lifting something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries).....	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV009	Carrying something weighing 10-20 lbs (about 4.5-9kg, like a large bag of groceries) from one room to another.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ X
DYSSV010	Walking (faster than your usual speed) for ½ mile (almost 1 km) without stopping	☐ 0	☐ 1	☐ 2	☐ 3	☐ X

Last Updated: 1 August 2016

Appendix 5
St. George's Respiratory Questionnaire

<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one*:

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days*:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in *each box* that applies to you *these days*: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in *each box* that applies to you *these days*: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in *each box* that applies to you *these days*: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✓) in *each box* that applies to you *because of your breathing*:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✓) in *each box* that applies to you *because of your chest trouble*:

	True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog
Doing things at home or in the garden
Sexual intercourse
Going out to church, pub, club or place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

.....
.....
.....
.....

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐
It stops me doing one or two things I would like to do ☐
It stops me doing most of the things I would like to do ☐
It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Appendix 6
EuroQol 5-Dimension, 5-Level Questionnaire

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Health Questionnaire

English version for the USA

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

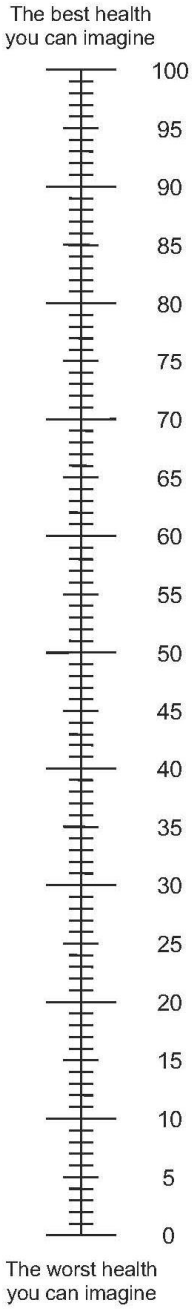
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Appendix 7
Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Specific Health Problems

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: SHP, Version 2 (WPAI+CIQ:SHP, V 2)

The following questions ask about the effect of your **problem** on your ability to work, attend classes, and perform regular daily activities. *Please fill in the blanks or circle a number, as indicated.*

1) Are you currently employed (working for pay)? ____NO ___YES

If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2) During the past seven days, how many hours did you miss from work because of problems associated with your **problem**? *Include hours you missed on sick days, times you went in late, left early, etc. because of **problem**. Do not include time you missed to participate in this study.*

_____HOURS

3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

4) During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6)*

5) During the past seven days, how much did **problem** affect your productivity <u>while you were working?</u>

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If **problem** affected your work only a little, choose a low number. Choose a high number if **problem** affected your work a great deal.*

Consider only how much **problem** affected productivity <u>while you were working</u>.

Problem had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	**Problem** completely prevented me from working

Circle a number

6) Do you currently attend classes in an academic setting (middle school, high school, college, graduate school, additional course work, etc.)? _____NO _____YES

If NO, check "NO" and skip to question 10.

7) During the past seven days, how many hours did you miss from class or school because of problems <u>associated with your **problem**</u>? *Do not include time you missed to participate in this study.*

_____ HOURS

8) During the past seven days, how many hours did you actually attend class or school?

_____ HOURS *(If "0", skip to question 10.)*

9) During the past seven days, how much did your **problem** affect your productivity while in school or attending classes in an academic setting?

*Think about days your attention span was limited, you had trouble with comprehension or days in which you could not take tests as effectively as usual. If **problem** affected your productivity at school or in class only a little, choose a low number. Choose a high number if **problem** affected your productivity at school or in class a great deal.*

Consider only how much **problem** affected productivity while in school or attending classes.

Problem had no effect on my class work	0 1 2 3 4 5 6 7 8 9 10	**Problem** completely prevented me from doing my class work

10) During the past seven days, how much did **problem** affect your ability to do your regular daily activities, other than work at a job or attending classes?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If **problem** affected your activities only a little, choose a low number. Choose a high number if **problem** affected your activities a great deal.*

Consider only how much **problem** affected your ability to do your regular daily activities, other than work at a job or attending classes.

Problem had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	**Problem** completely prevented me from doing my daily activities

Circle a number

Adapted from: Reilly MC, Tanner A, Meltzer EO: Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. Clin Drug Invest 1996; 11(5):278-288.