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Covis Pharma B.V.

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Ciclesonide Metered-Dose Inhaler in Non-Hospitalized Patients 12 Years of Age and Older With Symptomatic COVID-19 Infection

Protocol Number: ALV-020-001

Investigational Product: Alvesco® (ciclesonide) Inhalation Aerosol

IND Number: [REDACTED]

Development Phase: Phase 3

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Protocol Date and Version: December 21, 2020; Version 4.0 (Protocol Amendment 3)
August 31, 2020; Version 3.0 (Protocol Amendment 2)
May 18, 2020; Version 2.0 (Protocol Amendment 1)
May 1, 2020; Version 1.0 (Original Protocol)

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Investigator's Statement

I understand that all information concerning the product supplied to me by Covis Pharma B.V. and [REDACTED] in connection with this study and not previously published, is confidential information. This information includes the protocol (and applicable amendments), case report forms, assay methods, technical methodology, and basic scientific data.

I will conduct the study according to the protocol, and I understand that any changes to the protocol must be approved in writing by Covis Pharma B.V., [REDACTED] and the institutional review board/independent ethics committee before implementation, except where necessary to eliminate apparent immediate hazards to the subjects.

I confirm that I will report all adverse events following the regulations referenced in the protocol.

I confirm that I will conduct this study in conformance with the principles of the Declaration of Helsinki, Good Clinical Practice, and United States law and regulations.

I confirm that I am informed of the need for records retention and that no data will be destroyed without the written consent of Covis Pharma B.V.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol, dated December 21, 2020.

Investigator's Signature: _____

_____ Date

Name (printed): _____



1 PROTOCOL SYNOPSIS

Name of Sponsor/Company: Covis Pharma B.V.	Name of Product: Alvesco® Inhalation Aerosol	Name of Active Ingredient: ciclesonide
Title of Study: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Ciclesonide Metered-Dose Inhaler in Non-Hospitalized Patients 12 Years of Age and Older With Symptomatic COVID-19 Infection		
Study Sites: Up to 15 sites in the United States		
Protocol Number: ALV-020-001		Development Phase: Phase 3
Primary Objective: The primary study objective is to assess whether treatment with ciclesonide metered-dose inhaler (MDI) plus standard supportive care results in improved time to alleviation of Coronavirus Disease 2019 (COVID-19)-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection.		
Secondary Objectives: The secondary study objectives are:		
<ul style="list-style-type: none"> • to assess whether treatment with ciclesonide MDI plus standard supportive care reduces the incidence of hospital admissions or death compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection • to assess whether treatment with ciclesonide MDI plus standard supportive care reduces all-cause mortality compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection • to assess whether treatment with ciclesonide MDI plus standard supportive care reduces COVID-19-related mortality compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection • to assess whether treatment with ciclesonide MDI plus standard supportive care reduces the incidence of subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19 compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection • to assess whether treatment with ciclesonide MDI plus standard supportive care increases the percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection • to assess whether treatment with ciclesonide MDI plus standard supportive care increases the time to hospital admission or death compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection • to assess the impact of treatment with ciclesonide MDI plus standard supportive care on oxygen saturation levels compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection 		

Name of Sponsor/Company: Covis Pharma B.V.	Name of Product: Alvesco® Inhalation Aerosol	Name of Active Ingredient: ciclesonide
<ul style="list-style-type: none"> to assess the impact of treatment with ciclesonide MDI plus standard supportive care on COVID-19 viral load compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection to assess the safety of ciclesonide MDI plus standard supportive care compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection 		
<p>Methodology:</p> <p>This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of ciclesonide MDI for the treatment of symptomatic COVID-19 infection. Enrolled patients will be male and female adults and adolescents ≥ 12 years of age with confirmed COVID-19 infection who are currently exhibiting symptoms of the disease and who are not currently hospitalized or under immediate consideration for hospitalization at the time of enrollment. The study will consist of an initial screening/enrollment/randomization visit, a 30-day treatment period, and a follow-up period.</p> <p>Following signature of the informed consent form, patients meeting inclusion/exclusion criteria will be randomly assigned (1:1) to treatment with ciclesonide MDI 320 μg twice daily (BID) (morning [AM] and evening [PM]) plus standard supportive care (hereafter referred to as the ciclesonide arm) or placebo MDI BID (AM and PM) plus standard supportive care (hereafter referred to as the placebo arm). During the initial screening/enrollment/randomization visit, patients will be instructed on how to self-administer a MDI and will be discharged home with a 30-day supply of investigational product (ie, either ciclesonide MDI or placebo MDI), standard supportive care, a pulse oximeter for at-home oxygen saturation level monitoring, and an electronic diary (eDiary). A nasopharyngeal sample for viral load analysis will also be obtained at the initial screening/enrollment/randomization visit. Patients will be instructed to record self-administration of investigational product and oxygen saturation levels in the eDiary. Prior to self-administration of the investigational product (ie, within 1 hour of administration), patients will also complete and record assessments in the eDiary of severity of COVID-19-related symptoms of cough, dyspnea, chills, and feeling feverish (based on a 4-point scale where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe) and the presence/absence of COVID-19-related symptoms of repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell.</p> <p>Qualified healthcare providers will contact patients on days 2, 4, 6, 8, 10, 12, 14, 21 \pm 2 days, and 30 \pm 2 days for a health status check, to collect adverse event and concomitant medication information, and to confirm/clarify information recorded in the eDiary. During these patient contacts, medical advice commensurate with standard of care for reported symptoms or adverse events will be provided. On day 30 (window of + 2 days), the patient will return to the study site for collection of a nasopharyngeal sample for viral load analysis and to return the eDiary and investigational product (ie, used and unused MDIs). Qualified healthcare providers will contact patients on day 37 \pm 4 days and day 60 \pm 7 days to collect follow-up safety and outcome data (the follow-up period).</p> <p>Patients (or their representatives) will be asked to notify study personnel directly in the event they visit an emergency department or are hospitalized during their participation in the study.</p> <p>Patient duration on study is expected to be approximately 60 days, including the screening/enrollment/randomization visit, the 30-day treatment period and the subsequent follow-up period. In the event the patient requires hospitalization during the 30-day treatment period, the patient will discontinue investigational product and scheduled follow-up procedures but will continue to be followed for the outcome of hospitalization and ongoing adverse events.</p> <p>An independent and appropriately constituted Data Monitoring Committee (DMC) will be organized for this study. A charter detailing the purpose of the committee as well as their roles and responsibilities will be put into place and will guide and direct their actions.</p>		

Name of Sponsor/Company: Covis Pharma B.V.	Name of Product: Alvesco® Inhalation Aerosol	Name of Active Ingredient: ciclesonide
Number of Patients: Approximately 400 patients (200 in each arm) will be randomized.		
Diagnosis and Main Criteria for Inclusion:		
<u>Inclusion Criteria</u> Patients eligible for enrollment in the study must meet all the following criteria:		
<ol style="list-style-type: none"> 1. Male and female adults and adolescents \geq 12 years of age. 2. Positive SARS-CoV-2 molecular or antigen diagnostic test within 72 hours prior to enrollment. 3. Patient is not currently hospitalized or under immediate consideration for hospitalization at the time of enrollment. 4. Patient is currently experiencing symptoms of fever, cough, and/or dyspnea. 5. Patient has an oxygen saturation level $>$ 93%. 6. Ability to show adequate use of MDI, including inhalation technique. 7. Patient, parent/legal guardian, or legally-authorized representative must have signed a written informed consent before administration of any study-specific procedures. 		
<u>Exclusion Criteria</u> Patients meeting any of the following criteria are not eligible for participation in the study:		
<ol style="list-style-type: none"> 1. Existence of any life-threatening co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion. 2. History of hypersensitivity to ciclesonide. 3. Treatment with inhaled or intranasal corticosteroids within 14 days of the screening/enrollment/randomization visit. 4. Treatment with oral corticosteroids within 90 days of the screening/enrollment/randomization visit. 5. Participation in any other clinical trial or use of any investigational agent within 30 days of the screening/enrollment/randomization visit. 6. Currently receiving treatment with hydroxychloroquine/chloroquine. 7. Patients with cystic fibrosis. 8. Patients with idiopathic pulmonary fibrosis. 9. Pregnancy (for females of childbearing potential). 		
Test Product, Dose, and Mode of Administration: Ciclesonide 160 μ g/actuation MDI, 320 μ g BID (2 actuations in the AM and 2 actuations in the PM), oral inhalation		
Reference Therapy, Dose, and Mode of Administration: Placebo MDI, BID (2 actuations in the AM and 2 actuations in the PM), oral inhalation		
Duration of Treatment: 30 days		



Name of Sponsor/Company: Covis Pharma B.V.	Name of Product: Alvesco® Inhalation Aerosol	Name of Active Ingredient: ciclesonide
<p>Criteria for Evaluation:</p> <p>Efficacy:</p> <p><u>Primary Efficacy Endpoint</u></p> <ul style="list-style-type: none"> • Time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30 <p><u>Secondary Efficacy Endpoints</u></p> <ul style="list-style-type: none"> • Percentage of patients with hospital admission or death by day 30 • All-cause mortality by day 30 • COVID-19-related mortality by day 30 • Percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30 • Percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 7, by day 14, and by day 30 • Time to hospital admission or death • Change from baseline in oxygen saturation levels • Change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30 <p>Safety: Safety will be assessed based on adverse events.</p>		

Name of Sponsor/Company: Covis Pharma B.V.	Name of Product: Alvesco® Inhalation Aerosol	Name of Active Ingredient: ciclesonide
<p>Statistical Methods:</p> <p><u>Efficacy</u></p> <p>The primary efficacy variable is time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30. The primary analysis will be based on the intent-to-treat population (all randomized patients). To increase precision of treatment effect estimation and inference, a Cox proportional hazards model will be used to allow for inclusion of additional prespecified prognostic baseline covariates. The median time to event and 95% confidence intervals will be summarized by treatment arm, and Kaplan-Meier estimates of the survival curves will also be generated. The secondary efficacy endpoints of percentage of patients with hospital admission or death by day 30; all-cause mortality by day 30; COVID-19-related mortality by day 30; percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30; and percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 7, by day 14, and by day 30 will be analyzed using a logistic regression model. This will improve the precision of treatment effect estimation and inference by allowing for baseline covariate adjustments to be included in the model. Analysis of the secondary efficacy endpoint of time to hospital admission or death will be performed using the same method as that used for the primary efficacy endpoint. The secondary efficacy endpoint of change from baseline in oxygen saturation levels will be summarized descriptively at all timepoints captured in the eDiary. The secondary efficacy endpoint of change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30 will be summarized descriptively.</p> <p><u>Safety</u></p> <p>The safety population will include all randomized patients who receive at least 1 dose of double-blind study medication. Safety will be evaluated by summarizing the incidence of adverse events. Comparative analyses will be done on adverse events of special interest (eg, oral candidiasis).</p> <p><u>Interim Safety Review</u></p> <p>The DMC will conduct a review of blinded safety data once 100 subjects have been enrolled. Details of the interim safety review will be described in detail in the DMC charter.</p>		
<p>Sample Size and Power:</p> <p>This study is designed to assess the efficacy and safety of ciclesonide MDI plus standard supportive care compared with placebo MDI plus standard supportive care. The primary endpoint is time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30. Assuming a median time to alleviation of 7 days for the ciclesonide arm and 11 days for the placebo arm (hazard ratio of approximately 1.58) with a total study duration of 30 days and a total of 201 events observed in the 2 arms combined, a sample size of approximately 232 patients (116 in each arm) is required to achieve 90% power at $\alpha = 0.05$ for the study. To account for an unknown drop-out rate in this patient population as well as other factors that may impact the overall power of the study, the planned sample size was increased to 400 patients (200 in each arm) for this study. Note that these are best estimates at this point as there is still much uncertainty regarding COVID-19.</p>		

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2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AM	morning
BID	twice daily
CDC	Centers for Disease Control and Prevention
C _{max}	maximum concentration
COVID-19	coronavirus disease 2019
DDC	direct data capture
DMC	data monitoring committee
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MDI	metered-dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
PM	evening
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	World Health Organization

3 INTRODUCTION

3.1 Background Information on Coronavirus Disease 2019 (COVID-19)

There is currently an outbreak of respiratory disease caused by a novel coronavirus that was first detected in Wuhan City, Hubei Province, China, and that has now been detected in many locations internationally, including cases in the United States. The virus has been named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the disease it causes has been named Coronavirus Disease 2019 (COVID-19). On January 31, 2020, the Department of Health and Human Services issued a declaration of a public health emergency related to COVID-19 and on March 13, 2020, the President declared a national emergency in response to COVID-19.

The United States Centers for Disease Control and Prevention (CDC) has stated that symptoms compatible with COVID-19 include subjective or measured fever, cough, or difficulty breathing, and may present within 2 to 14 days after exposure. Reported illnesses have ranged from mild symptoms to severe illness and death for confirmed COVID-19 cases.

Currently there are no approved treatments for COVID-19. Innovators are looking at products in a variety of areas, including the assessment of antiviral drugs that might treat the specific virus, as well as host targets, such as interleukin-6 receptor inhibitors that may be helpful in reducing lung inflammation and improving lung function in COVID-19 patients, thereby potentially slowing the progression of severe respiratory symptoms.

3.2 Background Information on Ciclesonide and Rationale for Use in COVID-19

Alvesco[®] (ciclesonide) Inhalation Aerosol is an inhaled corticosteroid that has been approved in the United States for the indication of maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older ([Alvesco[®] Inhalation Aerosol US prescribing information, 2019](#)). Alvesco (ciclesonide) Inhalation Aerosol is administered by oral inhalation employing a pressurized metered-dose inhaler (MDI) and is available in 2 strengths (80 µg/actuation and 160 µg/actuation). Additional summary information regarding Alvesco (ciclesonide) Inhalation Aerosol is provided in the product labeling ([Alvesco[®] Inhalation Aerosol US prescribing information, 2019](#)).

Systemic glucocorticoid therapy is not currently indicated in patients with pneumonia or COVID-19 because of the potential for prolonging viral replication, as observed in patients with Middle East Respiratory Syndrome Coronavirus ([CDC, 2020](#)). However, inhaled glucocorticoids, such as ciclesonide, may demonstrate clinical benefit in patients with less severe symptoms of COVID-19 ([Fu et al, 2020](#); [Zhai et al, 2020](#)).

Institut Pasteur Korea has recently identified ciclesonide as a potential candidate against COVID-19 infection based on a screening of approximately 3000 drugs. A total of 48 drugs were initially pre-selected based on an assay of SARS-CoV and were further tested for antiviral activity against SARS-CoV-2. Of these, 24 drugs (including ciclesonide) showed antiviral activity against SARS-CoV-2 ([Jeon et al, 2020](#)). This finding was corroborated in a recent publication by [Matsuyama et al, 2020](#), in which it was reported that ciclesonide blocked SARS-CoV-2 replication in cultured cells at low concentrations. Furthermore, a small number

(n = 3) of patients in Japan with confirmed COVID-19 infection, all over 65 years of age and receiving supplemental oxygen, were treated with ciclesonide and demonstrated clinical improvement in 2 days (Puiu, 2020), providing additional support for continued study of ciclesonide in the treatment of COVID-19. Interestingly, an underlying mechanism for the suppression of viral infection by ciclesonide has been revealed by the isolation of a drug-resistant mutant. Isolation of this mutant indicated that NSP15, a viral ribonuclease, is a molecular target of ciclesonide (Matsuyama et al, 2020). Thus, it is reasonable to consider that ciclesonide may exhibit a direct-acting antiviral activity in addition to its intrinsic anti-inflammatory function and, therefore, has the potential to manifest dual roles (antiviral and anti-inflammatory) in the treatment of COVID-19 infection.

The systemic bioavailability is low for inhaled glucocorticoids (mean maximum concentration [C_{max}] of des-ciclesonide [pharmacologically active metabolite of ciclesonide prodrug] in plasma following once daily 320 µg inhaled ciclesonide was 0.369 ng/mL), whereas oral glucocorticoids such as prednisone and prednisolone have a mean C_{max} of 2.4 and 18.1 µg/L/1 mg dose, respectively (Czock et al, 2005). Therefore, it is hypothesized that use of Alvesco (ciclesonide) Inhalation Aerosol will reduce inflammation and viral replication in the lung in patients with COVID-19 while limiting the risk of systemic toxicities. These effects have the potential to decrease symptom burden and shorten disease duration.

From data available to date, it appears that patients with comorbidities of hypertension and diabetes mellitus are at most risk when exposed to COVID-19 (Yang et al, 2020; Zhang et al, 2020). There is currently limited data describing how COVID-19 affects people with asthma. In a study of 140 cases of COVID-19 patients no link to asthma was observed (Zhang et al, 2020). The data reported thus far may support the hypothesis that inhaled corticosteroids could provide a protective effect for these patients against COVID-19.

Covis Pharma B.V. (Covis) is assessing the safety and efficacy of Alvesco (ciclesonide) Inhalation Aerosol in non-hospitalized patients with symptomatic COVID-19 infection in this multicenter, randomized, double-blind, placebo-controlled study.

3.3 Rationale for Dose Selection and Treatment Duration

The dose of ciclesonide selected for use in this study is 320 µg twice daily (BID), which is the currently approved highest recommended starting dose for Alvesco Inhalation Aerosol (Alvesco® Inhalation Aerosol US prescribing information, 2019). Patients will be instructed to self-administer Alvesco Inhalation Aerosol (hereafter referred to as ciclesonide MDI) or placebo MDI at a frequency of BID concurrently with standard supportive care for 30 days. The duration of treatment is consistent with the limited information available regarding time to discharge for patients in China without hypoxemia or respiratory distress (mean time to discharge 17 ± 4 days) (Pan et al, 2020).

Because there are no proven or approved treatments for COVID-19, all patients will also receive standard supportive care according to the treating facility's standard.



3.4 Rationale for Subject Population

Patients with confirmed COVID-19 infection who are not hospitalized and presenting with mild to moderate disease represent the largest population (80%; [Verity et al, 2020](#)) and have been determined as the population with the highest likelihood of benefit from ciclesonide treatment due to earlier intervention potentially decreasing viral replication and, therefore, viral load. It is hypothesized that treatment with ciclesonide will decrease duration of clinical symptoms, thereby decreasing the severity of disease.

The study will enroll male and female patients 12 years of age or older, the population for which Alvesco has been determined to be safe. Furthermore, patients who have been treated with inhaled or intranasal corticosteroids within 14 days of screening/enrollment/randomization or any patient who has received oral corticosteroids within 90 days of screening/enrollment/randomization will be excluded from the study in order to minimize potential confounding of data from background steroid use.



4 STUDY OBJECTIVES

4.1 Primary Objective

The primary study objective is to assess whether treatment with ciclesonide MDI plus standard supportive care results in improved time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection.

4.2 Secondary Objectives

The secondary study objectives are:

- to assess whether treatment with ciclesonide MDI plus standard supportive care reduces the incidence of hospital admissions or death compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection
- to assess whether treatment with ciclesonide MDI plus standard supportive care reduces all-cause mortality compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection
- to assess whether treatment with ciclesonide MDI plus standard supportive care reduces COVID-19-related mortality compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection
- to assess whether treatment with ciclesonide MDI plus standard supportive care reduces the incidence of subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19 compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection
- to assess whether treatment with ciclesonide MDI plus standard supportive care increases the percentage of patients with alleviation of COVID 19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection
- to assess whether treatment with ciclesonide MDI plus standard supportive care increases the time to hospital admission or death compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection
- to assess the impact of treatment with ciclesonide MDI plus standard supportive care on oxygen saturation levels compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection
- to assess the impact of treatment with ciclesonide MDI plus standard supportive care on COVID-19 viral load compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection



- to assess the safety of ciclesonide MDI plus standard supportive care compared with placebo plus standard supportive care in non-hospitalized patients with symptomatic COVID-19 infection

4.3 Estimands

The International Council for Harmonization (ICH) *Guidance: Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials E9(R1)* was adopted on 20 November 2019. This section will describe the planned analyses for this protocol in the context of this guideline.

An estimand is a description of the treatment effect to address the clinical/scientific question of interest posed by the trial objective.

4.3.1 Primary Endpoint Estimand

The attributes of the estimand for the primary endpoint of this trial are:

1. Treatment regimens: ciclesonide and placebo
2. Populations of interest: patients meeting inclusion/exclusion criteria grouped according to randomized treatment assignment reflect the target population
3. Patient-level outcome: time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30
4. Intercurrent events: regardless of the use of rescue medications, protocol violations, or investigational product discontinuation
5. Population-level summary measure: difference in survival distributions between treatment regimens

The **treatment-policy strategy** for this estimand is the difference in survival distributions of time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30 between those assigned to ciclesonide and those assigned to placebo, regardless of patient's use of rescue medications, protocol violations, or investigational product discontinuation. Therefore, for all patients in the intent-to-treat (ITT) analysis set, all observed on-study data will be analyzed in accordance with the definition set forth above for intercurrent events.

Since death and hospitalization are not part of the primary endpoint patient level-outcome definition, a composite strategy will be used to handle these situations. If a patient dies or is hospitalized, regardless of when it occurs, the value attributed in that scenario would be a failure to respond or achieve alleviation of COVID-19-related symptoms by the end of the study (day 30). This ascribes a sufficiently unfavorable outcome under these scenarios.



4.3.2 Key Secondary Endpoint Estimand

The attributes of the estimand for the key secondary endpoint included in the multiplicity control procedure of this trial are:

1. Treatment regimens: ciclesonide and placebo
2. Populations of interest: patients meeting inclusion/exclusion criteria grouped according to randomized treatment assignment reflect the target population
3. Patient-level outcome: binary indicator of alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 14
4. Intercurrent events: regardless of the use of rescue medications, protocol violations, or investigational product discontinuation
5. Population-level summary measure: difference in response probabilities between treatment regimens

The **treatment-policy strategy** for this estimand is the difference in probabilities of alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 14 between those assigned to ciclesonide and those assigned to placebo, regardless of patient's use of rescue medications, protocol violations, or investigational product discontinuation. Therefore, for all patients in the ITT analysis set, all observed on-study data will be analyzed in accordance with the definition set forth above for intercurrent events.

Since death and hospitalization are not part of this key secondary endpoint patient level-outcome definition, a composite strategy will be used to handle these situations. If a patient dies or is hospitalized, then the value attributed in that scenario would be failure to achieve alleviation of COVID-19-related symptoms which ascribes the most unfavorable value.

Estimands for other secondary efficacy endpoints included in the multiplicity control procedure ([section 10.7.3](#)) will be described in the Statistical Analysis Plan (SAP).

5 STUDY DESCRIPTION

5.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy, and safety study of ciclesonide MDI for the treatment of symptomatic COVID-19 infection. Enrolled patients will be male and female adults and adolescents ≥ 12 years of age with confirmed COVID-19 infection who are currently exhibiting symptoms of the disease and who are not currently hospitalized or under immediate consideration for hospitalization at the time of enrollment. The study will consist of an initial screening/enrollment/randomization visit, a 30-day treatment period, and a follow-up period.

Following signature of the informed consent form (ICF), patients meeting inclusion/exclusion criteria will be randomly assigned (1:1) to treatment with ciclesonide MDI 320 μg BID (AM and PM) plus standard supportive care (hereafter referred to as the ciclesonide arm) or placebo MDI BID (AM and PM) plus standard supportive care (hereafter referred to as the placebo arm). During the initial screening/enrollment/randomization visit, patients will be instructed on how to self-administer a MDI and will be discharged home with a 30-day supply of investigational product (ie, either ciclesonide MDI or placebo MDI), standard supportive care, a pulse oximeter for at-home oxygen saturation level monitoring, and an electronic diary (eDiary). A nasopharyngeal sample for viral load analysis will also be obtained at the initial screening/enrollment/randomization visit. Patients will be instructed to record self-administration of investigational product and oxygen saturation levels in the eDiary. Prior to self-administration of the investigational product (ie, within 1 hour of administration), patients will also complete and record assessments in the eDiary of severity of COVID-19-related symptoms of cough, dyspnea, chills, and feeling feverish (based on a 4-point scale where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe) and the presence/absence of COVID-19-related symptoms of repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell. Qualified healthcare providers will contact patients on days 2, 4, 6, 8, 10, 12, 14, 21 ± 2 days, and 30 ± 2 days for a health status check, to collect adverse event and concomitant medication information, and to confirm/clarify information recorded in the eDiary. During these patient contacts, medical advice commensurate with standard of care for reported symptoms or adverse events will be provided. On day 30 (window of $+ 2$ days), the patient will return to the study site for collection of a nasopharyngeal sample for viral load analysis and to return the eDiary and investigational product (ie, used and unused MDIs). Qualified healthcare providers will contact patients on day 37 ± 4 days and day 60 ± 7 days to collect follow-up safety and outcome data (the follow-up period).

Patients (or their representatives) will be asked to notify study personnel directly in the event they visit an emergency department or are hospitalized during their participation in the study.

Patient duration on study is expected to be approximately 60 days, including the screening/enrollment/randomization visit, the 30-day treatment period and the subsequent follow-up period. In the event the patient requires hospitalization during the 30-day treatment period, the patient will discontinue investigational product and scheduled follow-up procedures but will continue to be followed for the outcome of hospitalization and ongoing adverse events (see [section 5.3.4](#)).



5.2 Study Schedule

The time and events schedule for this study is provided in [Table 1](#).



Table 1. Schedule of Events				
	Screening/Enrollment/Randomization Visit (Day 1)	Treatment Period (Day 1 through Day 30)	Follow-up Period (Through Day 60)	Early Termination
Informed consent	X (before administration of any study-specific procedures)			
Inclusion/exclusion criteria review	X (predose)			
Prior/concomitant medication review	X (predose)	X (collected during patient contacts)		
Demographic data and medical history ^a	X (predose)			
Physical examination, vital signs, height, weight, and calculation of body mass index	X (predose)			
Urine pregnancy test (for females of childbearing potential only)	X (predose, within 48 hours prior to enrollment)			
Confirm positive COVID-19 diagnostic test ^b	X (predose)			
Randomization	X (predose)			
Dispensing of IP, eDiary, and pulse oximeter	X (predose)			
Training on MDI inhalation technique (including rinsing of mouth with water following inhalation of IP), use of eDiary, and use of pulse oximeter	X (predose)			
Assess severity of COVID-19-related symptoms of cough, dyspnea, chills, and feeling feverish using a 4-point scale	X (predose)	X (BID [AM and PM] ≤ 1 hour prior to IP administration, record in eDiary) ^c		
Assess presence/absence of COVID-19-related symptoms of repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell	X (predose)	X (BID [AM and PM] ≤ 1 hour prior to IP administration, record in eDiary) ^c		
Oxygen saturation levels	X (predose)	X (BID [AM and PM] ≤ 1 hour prior to IP administration, record in eDiary) ^c		
Collection of nasopharyngeal sample for viral load analysis	X (predose)	X (day 30 [window of + 2 days]) ^d		
IP administration	X	X (BID [AM and PM], record in eDiary) ^c		
Adverse events	X (record any adverse events that occur following signing of informed consent)	X (collected during patient contacts)	X (collected during patient contacts)	X ^f



Table 1. Schedule of Events				
Screening/Enrollment/Randomization Visit (Day 1)		Treatment Period (Day 1 through Day 30)	Follow-up Period (Through Day 60)	Early Termination
HCP to contact patient for health status check, to collect adverse event and concomitant medication information, and to confirm/clarify information recorded in eDiary ^e		X (days 2, 4, 6, 8, 10, 12, 14, 21 ± 2 days, and 30 ± 2 days)		
Return of eDiary and investigational product (ie, used and unused MDIs)		X (day 30 [window of + 2 days]) ^d		X
HCP to contact patient to collect follow-up safety and outcome data			X (day 37 ± 4 days and day 60 ± 7 days)	X ^f
<p>AM = morning (prior to noon); BID = twice a day; COVID-19 = coronavirus disease 2019; eDiary = electronic diary; HCP = healthcare provider; IP = investigational product; MDI = metered-dose inhaler; PM = evening (prior to midnight); SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.</p> <p>^a = To include date of onset of COVID-19 symptoms.</p> <p>^b = To meet criteria for inclusion, patient must have a positive SARS-CoV-2 molecular or antigen diagnostic test within 72 hours prior to enrollment.</p> <p>^c = Note on day 1 dosing: In the event the patient receives the initial dose of IP at or before noon during the screening/enrollment/randomization visit, this will be considered to be the day 1 AM dose and the patient will be instructed to perform symptom assessments and oxygen saturation level monitoring, and to self-administer the day 1 PM dose prior to midnight. In the event the patient receives the initial dose of IP any time after noon during the screening/enrollment/randomization visit, this will be considered to be the day 1 PM dose and the patient will be instructed to wait until morning to perform symptom assessments, oxygen saturation level monitoring, and to self-administer the next dose (ie, day 2 AM dose). Note on day 30 dosing: Patients will be instructed to continue dosing through day 30. In the event the patient has their day 30 (window of + 2 days) visit on day 30, they will be instructed to perform symptom assessments and oxygen saturation level monitoring, and to self-administer the day 30 doses as per their typical schedule/routine. Thus, depending upon the time of day that the day 30 visit occurs, patients may or may not receive both doses on day 30. For patients that have their day 30 visit on day 31 or day 32, they will be instructed to complete through the day 30 PM dose and then discontinue investigational product dosing, symptom assessments, and oxygen saturation level monitoring.</p> <p>^d = On day 30 (window of + 2 days) the patient will return to the study site for collection of a nasopharyngeal sample for viral load analysis and to return the eDiary and investigational product (ie, used and unused MDIs).</p> <p>^e = During these patient contacts, medical advice commensurate with standard of care for reported symptoms or adverse events will be provided.</p> <p>^f = In the event of early termination, all ongoing non-serious adverse events will be followed until resolution, stabilization, or study day 60, whichever comes first; all ongoing serious adverse events will be followed until resolution or resolution with sequelae.</p> <p>Note: Patients (or their representatives) will be asked to notify study personnel directly in the event they visit an emergency department or are hospitalized during their participation in the study.</p>				



5.3 Study Visits and Procedures

For each patient, 3 study periods are planned: the screening/enrollment/randomization visit, the 30-day treatment period, and the follow-up period. The procedures and assessments to be performed during each study period are indicated in [Table 1](#). Further relevant details of the evaluations to be performed at each study period are described below.

5.3.1 Screening/Enrollment/Randomization Visit

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see [section 12.2](#)).

The following procedures will be conducted prior to administration of investigational product (ie, predose):

- Review inclusion/exclusion criteria.
- Confirm positive SARS-CoV-2 molecular or antigen diagnostic test (Note: patient must have a positive SARS-CoV-2 molecular or antigen diagnostic test within 72 hours prior to enrollment).
- Review demographics, medical history, and medication history (including prior [within 90 days before screening/enrollment/randomization visit] and current medications). Date of onset of COVID-19 symptoms should be recorded.
- Perform full physical examination, including measurements of vital signs (blood pressure [mm Hg], respiratory rate [breaths per minute], temperature [°F], and heart rate [beats per minute]), oxygen saturation level, height, weight, and calculation of body mass index.
- Perform urine pregnancy test for females of childbearing potential within 48 hours prior to enrollment.
- Collect nasopharyngeal sample for COVID-19 viral load analysis.
- Provide patient with the eDiary and instruct on usage.
- Provide patient with pulse oximeter and instruct on usage. **Instruct patient to seek medical attention immediately should oxygen saturation levels fall to 93% or below.**
- Instruct patient on recording severity of COVID-19-related symptoms of cough, dyspnea, chills, and feeling feverish using a 4-point scale where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe, and have patient record baseline results in the eDiary.
- Instruct patient on recording presence/absence of COVID-19-related symptoms of repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, and have patient record baseline results in the eDiary.
- Provide patient with study personnel contact information and instruct patient (or their representative) to notify study personnel directly in the event they visit an emergency department or are hospitalized during their participation in the study.
- Dispense investigational product according to treatment assignment.



- Train patient on appropriate MDI inhalation technique and instruct patient to rinse their mouth with water following inhalation of investigational product.

Following completion of the above procedures, study personnel will observe patient self-administration of the first dose of investigational product, and the patient will record administration in the eDiary.

Study personnel will record any adverse events occurring following signing of the informed consent in the eSource direct data capture (DDC) system.

Patients will be instructed to seek medical attention immediately in the event they experience any of the emergency warning signs for COVID-19 as listed on the CDC website.

5.3.2 Double-Blind Treatment Period

- Patient to self-administer investigational product at a frequency of BID (AM [prior to noon] and PM [prior to midnight]) and record in the eDiary.
- Patient to assess severity of COVID-19-related symptoms of cough, dyspnea, chills, and feeling feverish using a 4-point scale at a frequency of BID (AM and PM) \leq 1 hour prior to investigational product administration and record results in the eDiary.
- Patient to assess presence/absence of COVID-19-related symptoms of repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell at a frequency of BID (AM and PM) \leq 1 hour prior to investigational product administration and record results in the eDiary.
- Patient to check oxygen saturation levels using provided pulse oximeter at a frequency of BID (AM and PM) \leq 1 hour prior to investigational product administration and record in the eDiary.
- Qualified healthcare providers will contact each patient on days 2, 4, 6, 8, 10, 12, 14, 21 ± 2 days, and 30 ± 2 days for a health status check, to collect adverse event and concomitant medication information, and to confirm/clarify information recorded in the eDiary. During these patient contacts, medical advice commensurate with standard of care for reported symptoms or adverse events will be provided.
- Patient to return to the study site on day 30 (window of + 2 days) for collection of nasopharyngeal sample for viral load analysis and to return the eDiary and investigational product (ie, used and unused MDIs).

Note on day 1 dosing: In the event the patient receives the initial dose of investigational product at or before noon during the screening/enrollment/randomization visit, this will be considered to be the day 1 AM dose and the patient will be instructed to perform symptom assessments and oxygen saturation level monitoring, and to self-administer the day 1 PM dose prior to midnight. In the event the patient receives the initial dose of investigational product any time after noon during the screening/enrollment/randomization visit, this will be considered to be the day 1 PM dose and the patient will be instructed to wait until morning to perform symptom

assessments, oxygen saturation level monitoring, and to self-administer the next dose (ie, day 2 AM dose).

Note on day 30 dosing: Patients will be instructed to continue dosing through day 30. In the event the patient has their day 30 (window of + 2 days) visit on day 30, they will be instructed to perform symptom assessments and oxygen saturation level monitoring, and to self-administer the day 30 doses as per their typical schedule/routine. Thus, depending upon the time of day that the day 30 visit occurs, patients may or may not receive both doses on day 30. For patients that have their day 30 visit on day 31 or day 32, they will be instructed to complete through the day 30 PM dose and then discontinue investigational product dosing, symptom assessments, and oxygen saturation level monitoring.

5.3.3 *Follow-Up Period*

- Qualified healthcare providers to contact patient to collect follow-up safety and outcome data on day 37 \pm 4 days and day 60 \pm 7 days.

5.3.4 *Early Termination Procedures*

In the event of early termination, all ongoing non-serious adverse events will be followed until resolution, stabilization, or study day 60, whichever comes first; all ongoing serious adverse events will be followed until resolution or resolution with sequelae. Patients should be instructed to return the eDiary and investigational product (ie, used and unused MDIs) to the study site in a timely manner.



6 PATIENT ELIGIBILITY AND WITHDRAWAL CRITERIA

6.1 Number of Patients

Approximately 400 patients (200 in each arm) will be randomized. A sample size justification is provided in [section 10.1](#).

It is anticipated that patients will be enrolled at up to 15 study sites in the United States.

6.2 Inclusion Criteria

Patients eligible for enrollment in the study must meet all the following criteria:

1. Male and female adults and adolescents ≥ 12 years of age.
2. Positive SARS-CoV-2 molecular or antigen diagnostic test within 72 hours prior to enrollment.
3. Patient is not currently hospitalized or under immediate consideration for hospitalization at the time of enrollment.
4. Patient is currently experiencing symptoms of fever, cough, and/or dyspnea.
5. Patient has an oxygen saturation level $> 93\%$.
6. Ability to show adequate use of MDI, including inhalation technique.
7. Patient, parent/legal guardian, or legally-authorized representative must have signed a written informed consent before administration of any study-specific procedures. In the event the patient is a minor under the age of 18, assent by the patient to participate in the study must also be obtained.

6.3 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for participation in the study:

1. Existence of any life-threatening co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion.
2. History of hypersensitivity to ciclesonide.
3. Treatment with inhaled or intranasal corticosteroids within 14 days of the screening/enrollment/randomization visit.
4. Treatment with oral corticosteroids within 90 days of the screening/enrollment/randomization visit.
5. Participation in any other clinical trial or use of any investigational agent within 30 days of the screening/enrollment/randomization visit.
6. Currently receiving treatment with hydroxychloroquine/chloroquine.
7. Patients with cystic fibrosis.



8. Patients with idiopathic pulmonary fibrosis.
9. Pregnancy (for females of childbearing potential).

6.4 Withdrawal Criteria

Patients have the right to withdraw from the study at any time for any reason. Patients may also be withdrawn by the investigator at any time during the study for any of the following reasons:

- Patient, parent/legal guardian, or legally-authorized representative requests withdrawal.
- Patient experiences an adverse event requiring withdrawal from the study.
- Patient is noncompliant with the study schedule.
- Investigator believes it is in the best interest of the patient's health.

The medical monitor must be notified immediately for any of these instances to discuss follow-up plans. The data monitoring committee (DMC) (see [section 7.3](#)) should also be notified of patient withdrawals for any reason. When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the eSource. Early termination procedures should be completed (see [section 5.3.4](#)).

Patients who are withdrawn from the study will not be replaced.



7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Efficacy

7.1.1 Efficacy Endpoints

The primary efficacy endpoint is:

- Time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30

The secondary efficacy endpoints for the study are:

- Percentage of patients with hospital admission or death by day 30
- All-cause mortality by day 30
- COVID-19-related mortality by day 30
- Percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30
- Percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 7, by day 14, and by day 30
- Time to hospital admission or death
- Change from baseline in oxygen saturation levels
- Change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30

7.1.2 Efficacy Assessments

7.1.2.1 Assessment of COVID-19-Related Symptoms of Cough, Dyspnea, Chills, and Feeling Feverish

Patients will assess severity of COVID-19-related symptoms of cough, dyspnea, chills, and feeling feverish using a 4-point scale where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. Assessment of these symptoms will be performed predose during the screening/enrollment/randomization visit. During the 30-day treatment period, patients will be instructed to assess these 4 symptoms using a 4-point scale at a frequency of BID prior to self-administration of the investigational product (ie, within 1 hour of administration). The patient will record results in the eDiary.



7.1.2.2 Presence/Absence of COVID-19-Related Symptoms of Repeated Shaking with Chills, Muscle Pain, Headache, Sore Throat, and New Loss of Taste or Smell

Patients will assess the presence/absence of COVID-19-related symptoms of repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell. Assessment of these symptoms will be performed predose during the screening/enrollment/randomization visit. During the 30-day treatment period, patients will be instructed to assess presence/absence of these symptoms at a frequency of BID prior to self-administration of the investigational product (ie, within 1 hour of administration). The patient will record results in the eDiary.

7.1.2.3 Oxygen Saturation Levels

Oxygen saturation levels will be measured predose during the screening/enrollment/randomization visit. During the 30-day treatment period, patients will be instructed to measure oxygen saturation levels (using the provided pulse oximeter) at a frequency of BID. The patient will record results of all assessments in the eDiary. **The patient will be instructed to seek medical attention immediately should oxygen saturation levels fall to 93% or below.**

7.1.2.4 Viral Load Analysis

A nasopharyngeal swab for viral load analysis will be collected by study personnel predose during the screening/enrollment/randomization visit and on day 30 (window of + 2 days). For each patient, the same nostril should be used for collection of samples at both time points, if possible. Sample collection, handling, labeling, storage, shipping, and methods of analysis will be performed according to procedures specified in separate documents.

7.2 Safety

7.2.1 Safety Endpoint

Safety will be assessed based on adverse events.

7.2.2 Safety Assessments

Adverse events will be recorded starting with the signing of the ICF. Adverse events occurring during the screening/enrollment/randomization visit will be recorded by study personnel in the eSource. Information regarding adverse events occurring during the 30-day treatment period and post-treatment adverse events occurring during the follow-up period will be collected by qualified healthcare providers during the scheduled patient contacts and recorded in the eSource.

Any new infection that occurs on study, regardless of the infecting agent (ie, viral or non-viral) should be captured as an adverse event. In these cases, the site of infection and source of culture (eg, bronchoalveolar lavage, tracheal aspirate, sputum, blood, urine) should be recorded.

[Section 9](#) contains additional information regarding to adverse events.



7.3 Data Monitoring Committee

An independent and appropriately constituted DMC will be organized for this study. A charter detailing the purpose of the committee as well as their roles and responsibilities will be put into place and will guide and direct their actions.



8 STUDY CONDUCT

8.1 Treatments to be Administered

The investigational product in this study is ciclesonide MDI (supplied as Alvesco Inhalation Aerosol, 160 µg) or a matching placebo MDI; all patients will also receive standard supportive COVID-19 care. The investigational product will be self-administered by the patient BID (2 actuations in the AM and 2 actuations in the PM) for 30 days. During the initial screening/enrollment/randomization visit, patients will be provided with investigational product for the duration of the 30-day treatment period and will be instructed on how to appropriately self-administer a MDI. For patients in the ciclesonide arm, the total daily dose will be 640 µg (320 µg BID). Patients will be instructed to rinse their mouth with water following inhalation of investigational product.

8.2 Method of Assigning Patients to Treatment Groups

Following signature of the ICF, patients meeting inclusion/exclusion criteria will be randomly assigned (1:1) to treatment with ciclesonide MDI 320 µg BID plus standard supportive care or placebo MDI BID plus standard supportive care. The randomization schedule will be generated by the contract manufacturing organization and incorporated into the labeling of kits. Randomization will be done in blocks of 6 with 3 active and 3 placebo kits randomized within each block. Sites will be supplied with kits in groups of 6 according to these predetermined blocks. Assignment of kits to patients at a site will be done sequentially with patients receiving the next available kit in the block of kits when they have met the necessary criteria and are ready to be randomized.

All patients will be assigned a unique patient number during the screening/enrollment/randomization visit. After a patient number has been assigned, the number will not be reused even if the patient withdraws before receiving any study drug.

8.3 Blinding

Patients and investigators/study personnel will be blinded to study treatment assignment.

8.4 Treatment Compliance

The first dose of investigational product will be administered following randomization during the screening/enrollment/randomization visit and recorded by the patient in the eDiary. During the 30-day treatment period, patients will enter the dosing regimen taken (number of actuations, date, and time) BID in the eDiary. Patients should make every attempt to maintain consistency in the dosing schedule.

Qualified healthcare providers will contact patients on days 2, 4, 6, 8, 10, 12, 14, 21 ± 2 days, and 30 ± 2 days for a health status check, to collect adverse event and concomitant medication information, and to confirm/clarify information recorded in the eDiary (including treatment compliance). Based on these compliance checks, the patient may be counseled about the importance of taking the investigational product as instructed.



8.5 Investigational Product Materials and Management

8.5.1 Description of Investigational Product

Ciclesonide is a white to yellow-white powder. It is soluble in dehydrated alcohol, acetone, dichloromethane, and chloroform. The molecular formula of ciclesonide is C₃₂H₄₄O₇.

Ciclesonide will be supplied by the sponsor as commercially available Alvesco Inhalation Aerosol, 160 µg. Alvesco 160 µg Inhalation Aerosol is a pressurized, metered-dose aerosol unit fitted with a dose indicator. The 160 µg/actuation strength contains 60 actuations fill/canister. Alvesco is intended for oral inhalation only. Each unit contains a solution of ciclesonide in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. After priming, Alvesco 160 µg delivers 160 µg of ciclesonide from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

A matching placebo MDI will also be provided.

8.5.2 Investigational Product Packaging and Labeling

Investigational product will be supplied as commercially available Alvesco Inhalation Aerosol, 160 µg or a matching placebo MDI. Two inhalers will be provided per patient in a patient kit. The investigational product label will include the protocol number and notice that the contents are for research use only. A unique identifier on the label will provide traceability of the investigational product to the lot number, batch number, and retest date.

8.5.3 Investigational Product Storage

Investigational product should be stored per Alvesco Inhalation Aerosol labeling (ie, 25°C [77°F] with excursions permitted between 15°C and 30°C [59°F to 86°F]) ([Alvesco Inhalation Aerosol US prescribing information, 2019](#)).

Until dispensing, investigational products must be stored in a securely locked area, accessible only to authorized site personnel and the study monitor.

8.5.4 Investigational Product Handling and Disposal

The sponsor will supply investigational products only to the investigator or designee. The investigator or designee (eg, site pharmacist) is responsible for inventory, storage, and dispensing of investigational products. The investigator will not allow use of the investigational products other than as directed by this protocol.

The patient will return investigational product (ie, used and unused MDIs) to the study site during their visit on day 30 (window of + 2 days). In the event the patient is withdrawn from the study, they should be instructed to return the investigational product to the study site in a timely manner.



All used and unused MDIs must be returned to the sponsor according to instructions provided to the site by the sponsor, site monitor, or designee.

8.6 Procedure for Breaking the Randomization Code

Under normal circumstances, the blind will not be broken. In the event of a medical emergency, when management of a patient's condition requires knowledge of the treatment assignment, the blind may be broken. Should emergency unblinding be necessary, the investigator will contact the contract manufacturing organization for unblinding information and will notify the sponsor immediately. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Reasons for unblinding will be documented in the eSource. The date and the identity of the person responsible for breaking the blind must be also documented.

8.7 Investigational Product Accountability

The investigator must ensure that all investigational product supplies are kept in a secure locked area, under controlled temperature, with access limited to those authorized by the investigator. The investigator must maintain accurate records of the receipt of all investigational product shipped by the sponsor or the sponsor's representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all investigational product.

8.8 Concomitant and Prohibited Medications

Investigators may prescribe concomitant medications as standard supportive COVID-19 care.

Concomitant medications (including prescription medications, over-the-counter medications, herbal medications, vitamins, and nutritional supplements) taken by the patient and the reasons for use will be recorded during the screening/enrollment/randomization visit. Patients should continue to take these medications as directed during their participation in the study.

Concomitant medication use occurring during the 30-day treatment period will be collected by qualified healthcare providers during the scheduled patient contacts on days 2, 4, 6, 8, 10, 12, 14, 21 ± 2 days, and 30 ± 2 days and recorded in the eSource.



Patients who received treatment with inhaled or intranasal corticosteroids within 14 days or oral corticosteroids within 90 days of the screening/enrollment/randomization visit are excluded from study participation. Patients are also excluded from study participation if they are participating in any other clinical study or have used any investigational agent within 30 days of the screening/enrollment/randomization visit or if they are currently receiving treatment with hydroxychloroquine/chloroquine. These medications are also prohibited for the duration of the study.



9 ADVERSE EVENTS

9.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have to have a causal relationship with the pharmaceutical product. An adverse event can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Any worsening of the patient's disease under study or other medical conditions will also be considered to be an adverse event, unless it is within the normal range of disease fluctuation for that patient.

Any new infection that occurs on study, regardless of the infecting agent (ie, viral or non-viral) should be captured as an adverse event. In these cases, the site of infection and source of culture (eg, bronchoalveolar lavage, tracheal aspirate, sputum, blood, urine) should be recorded.

9.2 Reporting of Adverse Events

Adverse events will be recorded starting with the signing of the ICF. Adverse events occurring during the screening/enrollment/randomization visit will be recorded by study personnel in the eSource. Information regarding adverse events occurring during the 30-day treatment period and post-treatment adverse events occurring during the follow-up period will be collected by qualified healthcare providers during the scheduled patient contacts and recorded in the eSource.

Investigators will review the reported adverse events on a regular basis during the course of the study. A DMC will conduct a review of blinded safety data once 100 subjects have been enrolled (see [section 10.9](#)).

9.2.1 *Severity of Adverse Events*

Adverse events will be graded for severity as follows:

- Mild is defined as causing no limitation of usual activities.
- Moderate is defined as causing some limitation of usual activities.
- Severe is defined as causing inability to carry out usual activities.

Severity of adverse events occurring during the screening/enrollment/randomization visit will be recorded by study personnel in the eSource. Severity information for each adverse event occurring during the 30-day treatment period and post-treatment adverse events occurring during the follow-up period will be obtained by qualified healthcare providers during the scheduled patient contacts and recorded in the eSource.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.



9.2.2 Relationship to Investigational Product

The investigator will be asked to document his/her opinion of the relationship of the adverse event to the investigational product as follows:

- Not related - The event can be readily explained by the patient's underlying medical condition or concomitant therapy, and no relationship exists between the investigational product and the event.
- Unlikely related - The temporal relationship between the event and the administration of the investigational product is uncertain, and the event can most likely be explained by the patient's medical condition or other therapies.
- Possibly related - There is some logical temporal relationship between the event and the administration of the investigational product, and the event is unlikely to be explained by the patient's medical condition or other therapies.
- Related - The temporal relationship is compelling between the administration of the investigational product, and the event cannot be explained by the patient's medical condition or other therapies.

9.2.3 Action Taken with Investigational Product

For each recorded adverse event, the action taken with investigational product will be documented as follows:

- No change
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

9.2.4 Outcome

The outcome of the adverse event will be documented as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal
- Unknown



Outcome data will be obtained by qualified healthcare providers during the scheduled patient contacts and recorded in the eSource.

9.3 Serious Adverse Event Definition

A serious adverse event is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability and/or incapacity
- Results in a congenital anomaly or birth defect

The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at immediate risk of death at the time of the serious adverse event. It does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered to be serious adverse events.

9.4 Reporting Serious Adverse Events

All serious adverse events that occur during the course of the study from the time informed consent is signed and up to the patient’s study completion or discontinuation, whether or not the event is considered causally related to the investigational product, must be reported by the investigator to the sponsor’s safety reporting group as described in the Safety Reporting Instructions. In the event that the investigator becomes aware of a serious adverse event that occurred after the patient completes or discontinues from the study, and the serious adverse event is suspected to be related to investigational product, it must be reported to the sponsor’s safety reporting group. Any special reporting requirements are described in the Safety Reporting Instructions.

All serious adverse events must be reported **within 24 hours** from the time when the investigator first becomes aware of the event. Serious Adverse Event Report Forms will be provided to each study site. Details on the process of reporting can be found in the Safety Reporting Instructions. The completed Serious Adverse Event Form should be sent to Premier Research by one of the following methods:





For all serious, unexpected adverse events potentially related to the use of the investigational product, Covis or its designee will notify the appropriate regulatory authorities and all participating investigators in accordance with ICH guidelines and local safety reporting requirements. It is the responsibility of the investigator to notify the Institutional Review Board (IRB) of all unexpected serious adverse drug reactions involving risk to human subjects in compliance with their IRB reporting requirements.

Each serious adverse event must be followed until its resolution or its resolution with sequelae. Any follow-up information to a serious adverse event must be reported to the sponsor within 24 hours of receipt of the new information.

The investigator must determine whether the clinical seriousness of the event warrants removal of the patient from the study. The investigator should, in any case, institute appropriate diagnostic and therapeutic measures and keep the patient under observation for as long as is medically indicated.



10 STATISTICAL EVALUATION

As a companion to this protocol and in an effort to provide a more detailed explanation of the statistical methodology to be used for this study, a SAP will be finalized prior to locking the database and before unblinding the randomization. Any changes in the statistical methods described in this protocol that occur prior to unblinding will be documented in the SAP and will not require a protocol amendment.

10.1 Sample Size and Power

This study is designed to assess the efficacy and safety of ciclesonide MDI plus standard supportive care compared with placebo MDI plus standard supportive care. The primary endpoint is time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30. The Cox proportional hazards model will be used to compare treatment arms with respect to time to alleviation (or recovery) of COVID-19-related symptoms as defined in the primary endpoint. Total number of events (recoveries) as well as the expected rate of recovery (or hazard ratio) for treatment compared to placebo are key determinants of power. The expected median survival time is approximately 7 days for the ciclesonide arm and approximately 11 days for the placebo arm (hazard ratio of approximately 1.58) with a total study duration of 30 days. For 90% power, approximately 201 events (recoveries) are required to detect this anticipated increase in rate of recovery between ciclesonide and placebo. A sample size of 232 patients (116 per arm) is required to achieve the specified 90% power at an $\alpha = 0.05$ for this study. To account for an unknown drop-out rate in this patient population as well as other factors that may impact the overall power of the study, the planned sample size was increased to 400 patients (200 in each arm) for this study. Note that these are best estimates at this point as there is still much uncertainty regarding COVID-19.

10.2 Statistical Analysis Sets

The safety population will include all patients who received at least 1 dose of investigational product (either ciclesonide MDI or placebo MDI). Safety analyses will compare groups defined by the treatment they received. The ITT population will include all randomized patients. Analyses conducted on the efficacy dataset will be on an ITT basis where the treatment groups are defined by the treatment to which patients were randomized.

Any additional analysis sets will be defined in the SAP.

10.3 Statistical Methods

10.3.1 General Principles

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, standard deviation, median, and range will be provided. For categorical variables, the number and percentage in each category will be determined.



10.3.2 Missing Data

All attempts will be made to minimize the amount of missing data. Sensitivity analyses may be conducted to evaluate the potential impact of the missing data.

10.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics, medical history, baseline physical examination findings, baseline vital sign data, baseline height, baseline weight, and baseline body mass index will be summarized descriptively by treatment group.

10.5 Patient Disposition

Patient disposition will be summarized, including the reasons for discontinuation. The number of patients in each analysis population will be displayed and an accounting of exclusions from each study population will be provided.

10.6 Concomitant Medications

Concomitant medications will be tabulated by Anatomical and Therapeutic Class of World Health Organization (WHO) drug, preferred term, and treatment group. A medication's usage will be considered concomitant if it was started or continued after administration of investigational product. If the start date is missing, it will be assumed that the medication was used concomitantly.

10.7 Analysis of Efficacy Data

10.7.1 Primary Efficacy Endpoint

The primary efficacy variable is time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30. The primary analysis will be based on the ITT population (all randomized patients). To improve the precision of treatment effect estimation and inference, baseline covariate adjustments will be made for gender, age, race, and body mass index, as these are known COVID-19 risk factors. A Cox proportional hazards model will be used to allow for inclusion of these additional covariates. The median time to event and 95% confidence intervals will be summarized by treatment arm, and Kaplan-Meier estimates of the survival curves will also be generated.

The SAP will describe how missing data will be handled in the primary analysis. In addition, a sensitivity analysis for the primary endpoint will be conducted using a tipping point analysis that will systematically and comprehensively vary assumptions about the missing outcomes on the treatment arms. Details will be provided in the SAP.



10.7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of percentage of patients with hospital admission or death by day 30; all-cause mortality by day 30; COVID-19-related mortality by day 30; percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30; and percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 7, by day 14, and by day 30 will be analyzed using a logistic regression model. To improve the precisions on treatment effect estimation and inference, baseline covariate adjustments will be made for gender, age, race, and body mass index, as these are known COVID-19 risk factors. Analysis of the secondary efficacy endpoint of time to hospital admission or death will be performed using the same method as that used for the primary efficacy endpoint. The secondary efficacy endpoint of change from baseline in oxygen saturation levels will be summarized descriptively at all time points captured in the eDiary. The secondary efficacy endpoint of change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30 will be summarized descriptively.

10.7.3 Multiple Comparisons

In order to control the overall Type I error rate for the analyses of the planned primary and secondary endpoints, a fixed-sequence method will be utilized. Under this methodology, all endpoints will be ordered sequentially; testing will begin with the first endpoint (primary endpoint) at the full alpha level and continue through the sequence only until an endpoint is not statistically significant. The sequence of testing will be as follows:

1. Time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30
2. Percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 14
3. Percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 7
4. Percentage of patients with alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of ≥ 24 hours (ie, ≥ 3 AM/PM assessments) by day 30
5. Change from baseline in oxygen saturation levels at day 7
6. Change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30

7. Percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30
8. Time to hospital admission or death
9. Percentage of patients with hospital admission or death by day 30
10. All-cause mortality by day 30
11. COVID-19-related mortality by day 30

10.8 Analysis of Safety Data

The incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) body system classification and preferred term. All treatment-emergent adverse events will be summarized overall and for each body system and preferred term by treatment group, relationship to investigational product, and severity. For tabulations by severity, only a patient's most severe event within the category (eg, overall, body system, or preferred term) will be counted. "Treatment-emergent" will be defined as starting or worsening after the first dose of investigational product. If the start date is missing, the event is assumed to be treatment-emergent. All serious adverse events will be tabulated.

In order to understand specific adverse events of special interest (eg, oral candidiasis), analyses will be conducted to compare the treatment arms with respect to differences in cumulative incidence rates with accompanying confidence intervals. Details will be provided in the SAP.

10.9 Interim Safety Review

The DMC will conduct a review of blinded safety data once 100 subjects have been enrolled. Details of the interim safety review will be described in detail in the DMC charter.



11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Conduct of the Study

Covis shall implement and maintain quality control and quality assurance procedures with written Standard Operating Procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH Good Clinical Practice (GCP), and applicable regulatory requirements.

This study is to be conducted according to globally accepted standards of GCP (as defined in the ICH E6 Guideline for GCP, 1 May 1996), in agreement with the latest revision of the Declaration of Helsinki and in keeping with local regulations.

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate Independent Ethics Committee (IEC)/IRB, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the patient having to be withdrawn from the study and render that patient nonevaluable.

11.2 Study Monitoring

Monitoring and auditing procedures, developed or endorsed by the sponsor, will be followed to comply with GCP guidelines. Access to the study documentation and medical records will be ensured.

The study will be monitored by the sponsor or its designee. Throughout the course of the study, the study monitor will make frequent contact with the investigator. This will include telephone/web calls, e-mails, and video conferences, if appropriate. During the remote interim monitoring visits, the status of the site will be discussed including, but not limited to the following: enrollment status, review of study data, and ICF process for newly enrolled patients.

As part of the data monitoring, source documents must be made available to the study monitor for remote review. Remote source data verification will be performed as specified in the clinical monitoring plan. The study monitor will also perform remote investigational product drug accountability and will perform reviews of the electronic investigator study file to ensure completeness of documentation in all respects of clinical study conduct and safety oversight.

Upon completion of the study, the study monitor will conduct a final review of the study files, after which the files should be secured for the appropriate time period. The investigator, or appointed delegate, will make themselves available over the phone or web, if needed, and will



cooperate in making documents available for inspection and responding to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the sponsor or regulatory agencies.



12 ETHICS

12.1 Independent Ethics Committee/Institutional Review Board

Prior to initiation of the study, the investigator will submit the study protocol, sample ICF, and any other documents that pertain to patient information, recruitment methods, and advertisements, to the IRB/IEC. The investigator must also submit any other information that may be requested to the IRB/IEC for review and approval. The investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. A letter confirming the approval must be forwarded to the study monitor prior to initiation of this study. This letter will be forwarded to the sponsor prior to the initiation of the study.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site, as well as other adverse event reports received by the sponsor, in accordance with local procedures.

The investigator will be responsible for obtaining annual IRB/IEC approval or renewal throughout the duration of the study.

12.2 Written Informed Consent and Assent

Potential patients, their parent/legal guardian, or their legally-authorized representative must provide written consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An ICF that includes information about the study will be prepared and given to the patient. This document will contain all the elements required by the ICH *Guidance: Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice E6(R2)* (2016). The document must be in a language understandable to the patient and must specify who informed the potential patient. After reading the ICF, the potential patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

A copy of the signed ICF must be given to the patient. The original signed ICFs will be retained by the Investigator.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

In the event the patient is a minor under the age of 18, assent by the patient to participate in the study must also be obtained.



13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms/Source Data Handling

Source documents and source data will be captured electronically in this trial and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a DDC system also known as the eSource that is fully validated according to 21 Code of Federal Regulations Part 11. Changes to the data will be captured by an automatic audit trail. The study site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, adverse events, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the study site for data collected directly into the application; rather, the electronic source record directly populates the trial database. At the end of the study, the investigator must certify that the data entered into the eSource system are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

The investigator, or designee, will enter study data required by the protocol into the eSource system. The eSource system has a variety of validations programmed which direct the site user to collect clean and complete data in the moment as well as clear indicators of incomplete forms so that they can be followed up on in a timely manner. Clinical research associates will also remotely monitor the collected data via an online portal to review for completeness and accuracy. Any questions about the collected data can be queried within the eSource system by the clinical research associate or data manager. Appropriate study site personnel should then address those queries within the eSource system which will maintain a comprehensive audit trail. Uniform procedures for addressing queries will be discussed during system training as well as the study site initiation visits and will be documented in a data management plan.

Designated data captured in the eSource system will automatically be included into the clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Computerized and manual procedures should be used to review and check data within the eSource system for omissions, apparent errors, and values that may require further clarification. Data queries requiring clarification should be initiated within the eSource system for the study site to review and resolve. Only authorized personnel can make corrections to the clinical database, and all corrections will be documented in the system audit trail.

Adverse events will be coded using the most current MedDRA version. Prior and concomitant medications will be coded according to the WHO Drug Dictionary.



13.2 Retention of Essential Documents

The following records must be retained by the investigator for a minimum of 2 years after the sponsor has notified FDA that investigations have been discontinued, or after FDA has approved the new drug application:

- Signed ICFs for all patients
- Patient identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the investigator and the IRB/IEC
- Composition of the IRB/IEC or other applicable statement
- Record of relevant communications between the investigator and sponsor (or contract research organization)
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- Copies of the eSource records and of documentation of corrections for all patients
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (eDiaries, patient records, hospital records, laboratory records, etc.)
- All other documents as listed in section 8 of the ICH *Guidance: Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice E6(R2)* (2016) (Essential Documents for the Conduct of a Clinical Trial)

However, due to international regulatory requirements, the sponsor may request retention for a longer period of time. The investigator must therefore obtain approval in writing from the sponsor prior to destruction of any records.

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.



14 FINANCING AND INSURANCE





15 PUBLICATION POLICY

The sponsor will retain the ownership of all data. When the study is complete, the sponsor will arrange the analysis and tabulation of data. A clinical study report will then be prepared, which may be used for publication, presentation at scientific meetings, or submission to regulatory authorities. All proposed publications based on this study must be subject to the sponsor's approval requirements.



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