MILD- CONTAIN CICLESONIDE CLINICAL TRIAL COVID-19 TREATMENT

2021-6696

Short Title: Mild-CONTAIN

Health Canada Submission Protocol – Version 5.2 July 27, 2021

Canadian Sponsor:

Research Institute of the McGill University Health Centre

Canadian Principal Investigator:

Nicole Ezer MD MPH
Assistant Professor of Medicine, McGill University

Draft or Version Number: 6.1

August 23, 2021

STATEMENT OF COMPLIANCE

This protocol will receive independent institutional review board (IRB) permission in each participating province. For the purposes of regulatory compliance, the sponsor institution is the Research Institute of the McGill University Health Center for the operations in Canada.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable Canadian law and ICH guidelines.

Principal Investigator:

Signed:  Date: August 23, 2021

Nicole Ezer
Assistant Professor of Medicine, Research Institute of the McGill University Health Center

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience	
CFR	Code of Federal Regulations	
CONSORT	Consolidated Standards of Reporting Trials	
COVID-19	coronavirus disease 2019	
SRS-CoV	SARS coronavirus	(i.e. circa 2003)
SARS-CoV-2	SARS coronavirus 2	(i.e. circa 2019)
CRF	Case Report Form	
CRO	Contract Research Organization	
DCC	Data Coordinating Center	
DSMB	Data and Safety Monitoring Board	
eCRF	Electronic Case Report Form	
GCP	Good Clinical Practice	
ICF	Informed Consent Form	
ICH	International Conference on Harmonization	
IEC	Independent or Institutional Ethics Committee	
IRB	Institutional Review Board	
MERS-CoV	Middle East respiratory syndrome coronavirus	
MUHC	McGill University Health Center	
N	Number (typically refers to subjects)	
PHI	Protected Health Information	
PI	Principal Investigator	
RI-MUHC	Research Institute of the McGill University Health Centre	
SAE	Serious Adverse Event	
SOP	Standard Operating Procedure	
WHO	World Health Organization	

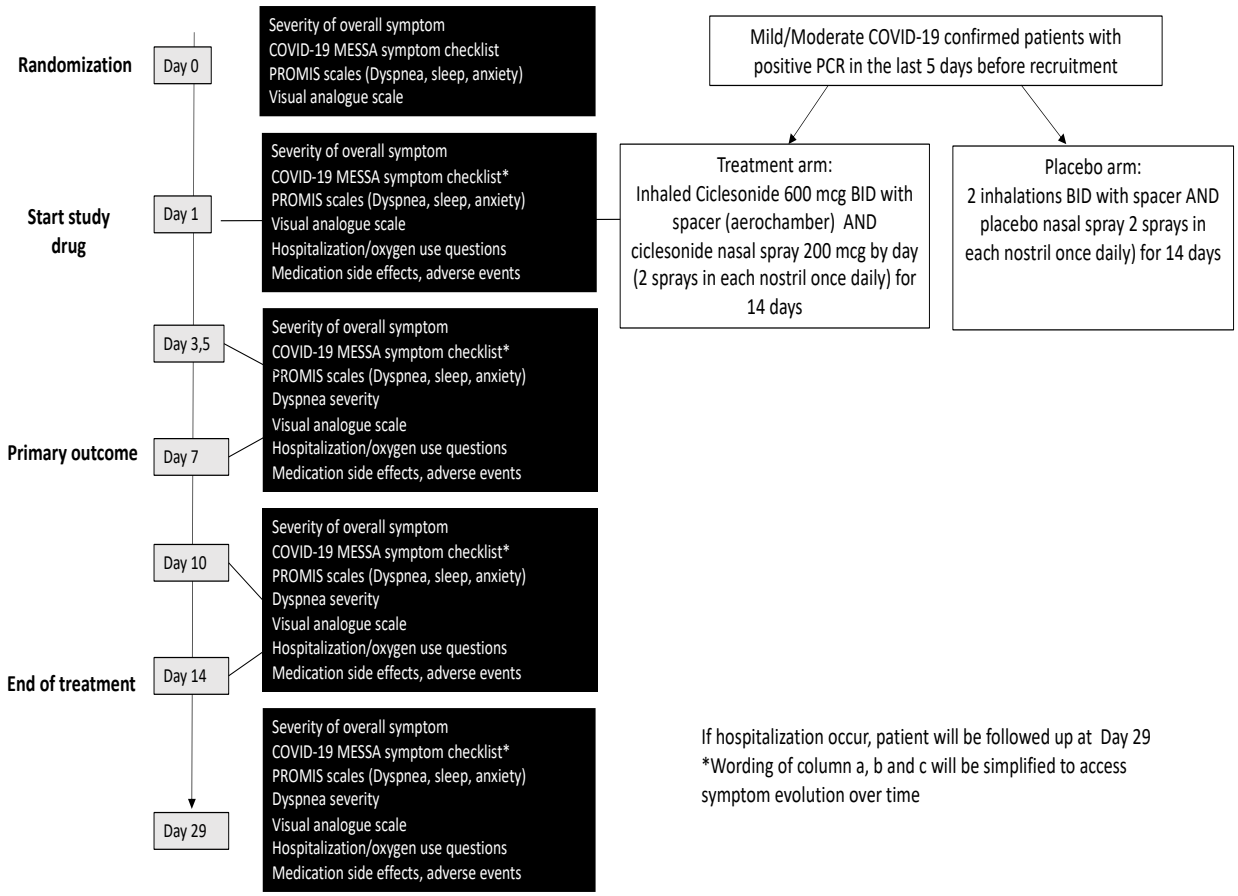
Summary

Full Title:	Mild - CONTAIN CiclesOnide cliNical TriAl covId-19 treatmeNt
Short Title:	Mild - CONTAIN
Clinical Phase:	II
Sponsor:	Research Institute of the McGill University Health Centre
Principal Investigator:	Nicole Ezer MDCM, MPH, FRCPC
Co-Investigators	James Martin, MD; Todd Lee, MD; Emily McDonald, MD; Andrea Benedetti, PhD Statistician; Ben Smith, MD, PhD; Susan Barlett, PhD, Sara Belga, MD; Shay Daniels, MD; Nick Daneman, MD; Adrienne Chan, MD
Study Population	>=18 years of age Laboratory confirmed COVID-19 as determined by PCR within 5 days of enrolment Early mild symptomatic patients: Non-hospitalized adults or health care workers with COVID-19 (n= 159 per arm)
Objective	Evaluate whether early treatment with inhaled and nasal ciclesonide improves symptoms at day 7 in early mild to moderate symptomatic patients
Study Design	Adaptive, Double-blind, randomized placebo-controlled clinical trial Pragmatic trial with internet based self-referral, electronic consent, virtual online follow-up and self-reported outcomes. Study medicine delivered by courier to consented participants. Follow up through 7 days and 14 days and 30 days after randomization.

Intervention Arm:	Ciclesonide (600mcg BID inhaled with aerochamber) *plus* nasal ciclesonide (200 mcg DIE) for 14 days
Control Arm:	Placebo (delivered by metered dose inhaler BID with aerochamber) *plus* intranasal saline DIE for 14 days.
Primary Endpoint	Proportion of participants with no symptoms of cough, fever or dyspnea at day 7.
Secondary Endpoints	• Hospitalization for SARS-CoV-2 related illness at day 14 • Primary outcome (proportion of patients with no cough fever or dyspnea) measured at day 14 • Mortality at day 14 and 29 • Ordinal Scale for Evaluating subject Clinical Status • PROMIS dyspnea, anxiety and sleep at day 7 and 14. • Visual Analog scale from 0-10 indicating improvement in symptoms at day 7 and 14. • Time to symptom resolution (post-hoc)
Duration of Participation	• Recruitment and follow up will be internet-based. • Clinical Assessment: 14 days post ciclesonide initiation to assess final outcome • Clinical assessment at Day 29: Clinical assessment, Follow up vital status, self reported hospitalization
Inclusion Criteria	Symptomatic adult patients positive by PCR for COVID-19 within 5 days of enrollment with fever, cough or shortness of breath (day 6 if shipped same day). Provision of Informed Consent At Day 0, patients should be at home

Exclusion Criteria	● Already on inhaled corticosteroid medication ● Currently using systemic steroids (oral or intravenous or intramuscular such as Prednisone) or use of steroids 7 days prior to enrolment ● Severely ill patients at enrollment (i.e., admitted to ICU at admission) ● Unable to self-administer the inhaler ● Known or suspected pregnancy and breastfeeding ● Known allergy to study medication or its components (non-medicinal ingredients; including lactose allergy (type I)) ● Patients with untreated fungal, bacterial or tubercular infections of the respiratory tract ● Current hospitalization ● Current use of oxygen at home or in hospital ● Vaccinated for COVID-19
Stratification	Randomization will be stratified by sex
Statistical Assumptions	With 159 subjects per arm we will be able to detect an absolute increase of 15% in the number of patients with resolved symptoms at day 7.
Safety	Safety of the intervention will be assessed by the cumulative incidence of Grade 3 and 4 AE and SAEs using the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events version 2.1

Schematic of Study Design:



1 KEY ROLES – MCGILL UNIVERSITY HEALTH CENTRE

Individuals:

Principal Investigator: Nicole Ezer MDCM, MPH, FRCPC

Co-Investigator: Emily G. McDonald MDCM MSc

Co-Investigator: Todd C. Lee MD MPH FIDSA

Co-Investigator: James Martin MDCM

Co-Investigator: Ben Smith MD

Co-Investigator: Sara Belga MD

Co-Investigator: Shay Daniels, MD

Co-Investigator: Nick Daneman, MD

Co-Investigator: Adrienne Chan, MD

Medical Monitor: Richard Menzies MD

Research Pharmacist: Kathleen Normandin B. Pharm MSc

Database Management: Alek Lefebvre

Institutions:

Division of Respiratory Medicine, Department of Medicine, McGill University Health Centre (Research Institute), Montreal, QC

University of British Columbia, Vancouver General Hospital, Vancouver, BC

Sunnybrooke Hospital, Toronto, Ontario

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Significance of Research Question/Purpose:
Coronaviruses are a large family of viruses that usually cause mild to moderate respiratory illness. However, three major coronaviruses capable of causing serious disease have been identified in the last two decades, namely SARS-CoV, MERS-CoV and most recently, the novel SARS-CoV-2. First identified in December 2019 in the province of Wuhan, China, SARS-CoV-2 has rapidly emerged as a highly transmissible and potentially fatal virus, causing COVID-19. It has shown to be capable of causing mild to severe disease, requiring oxygen therapy, hospitalization, intensive care, mechanical ventilation, and has led to widespread illness and death.

The number of global COVID-19 cases has rapidly progressed in the last few months. The outbreak was declared a Public Health Emergency of International Concern on January 30, 2020, and on March 11th, the World Health Organization declared COVID-19 a global pandemic.

As of April 20, 2020, there were 2.36 million confirmed COVID-19 cases worldwide, and 164 656 deaths related to COVID-19. In Canada, there were 34 777 cases and 1580 deaths(1). In an effort to prevent disease progression and overload of healthcare systems, provincially and internationally, authorities have held multiple public services and public spaces, postponed various in and out-hospital services and have imposed travel restrictions.

Only one antiviral therapy is currently approved in Canada for patients with mild to moderate symptoms of COVID-19 (Bamlanivimab) (2) however it is not widely available due to costs and the need for IV infusion. The standard of care remains supportive measures and quarantine of infected persons for a minimum of 14 days.

Global efforts to evaluate novel antivirals and therapeutic strategies to treat COVID-19 have intensified and there is an urgent public health need for rapid development of novel interventions.

Preliminary Data:
Like MERS-CoV and SARS-CoV (3), SARS-CoV-2 virus is a betacoronavirus. It has 79.5% sequence identity with that of human SARS-CoV (4).

Ciclesonide has shown *in vitro* activity against MERS-CoV, SARS-CoV and SARS-CoV-2. In vitro, the viral replication of SARS-COV-2 showed 2-fold reduction at 27 hours post infection. (5) In Vero cells, the half maximal inhibitory concentration (IC50) of ciclesonide against SARS-CoV-2 was 4.33 mcM (5). The NSP15 homo-hexamer was possibly the target of ciclesonide. Other steroids tested (cortisone, prednisolone, fluticasone, dexamethasone) showed no significant effect on viral replication suggesting the ciclesonide effect is drug specific and not a steroid class effect (6). Subsequently, reduced viral load of SARS-CoV-2 has been shown to be associated with reduced clinical disease severity (7).

Existing Literature:

In February 2020, 5406 compounds (including 2069 FDA approved drugs) were tested for anti-MERS-CoV activity by determining viral spike protein expression in infected Vero cells and 12 compounds were selected for having demonstrated a greater than 70% anti MERS-CoV activity. Ciclesonide was identified as one of the drugs that inhibit MERS-CoV replication, similar to chloroquine (8).

The in vitro effect of different steroids on MERS-COV, SARS-CoV and SARS-CoV-2 showed that ciclesonide was suppressing the viral replication of those 3 coronaviruses with low cytotoxicity. For SARS-CoV-2, the viral replication was reduced 2-fold at 27 hours post infection (Figure 1). The NSP15 homo-hexamer was possibly the target of ciclesonide. Other steroids tested against MERS-CoV (cortisone, prednisolone, fluticasone, dexamethasone, mometasone) showed no significant effect on viral replication (except for mometasone) suggesting the ciclesonide effect is drug specific and not a steroid class effect, so these steroids were not tested against SARS-CoV-2 (Figure 2) (6).

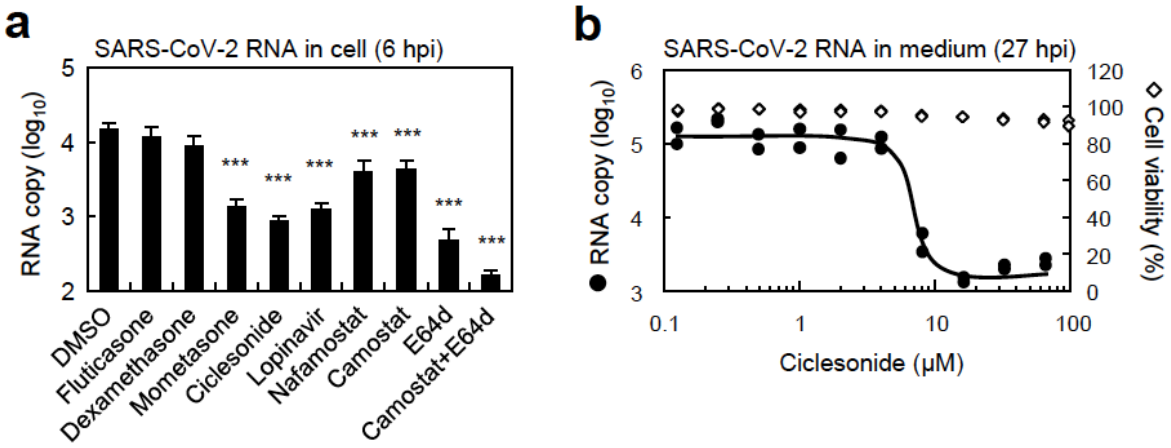


Figure 1. - Antiviral effects of steroids on SARS-CoV-2. (a) Intracellular SARS-CoV-2 RNA (6 hpi). VeroE6/TMPRSS2 cells were infected with SARS-CoV-2 at MOI = 1 in the presence of 10μM compounds for 6 h. Cellular viral RNA was quantified by real-time PCR using the E gene primer/probe set. (b) Culture Medium SARS-CoV-2 RNA (27 hpi). VeroE6/TMPRSS2 cells were infected with SARS-CoV-2 at MOI = 0.01 in the presence of ciclesonide for 27 h. Viral RNA in culture medium was quantified by real-time PCR using the E gene primer/probe set. Cell viability in the presence of ciclesonide was quantified at 27 hpi by WST assay (1).

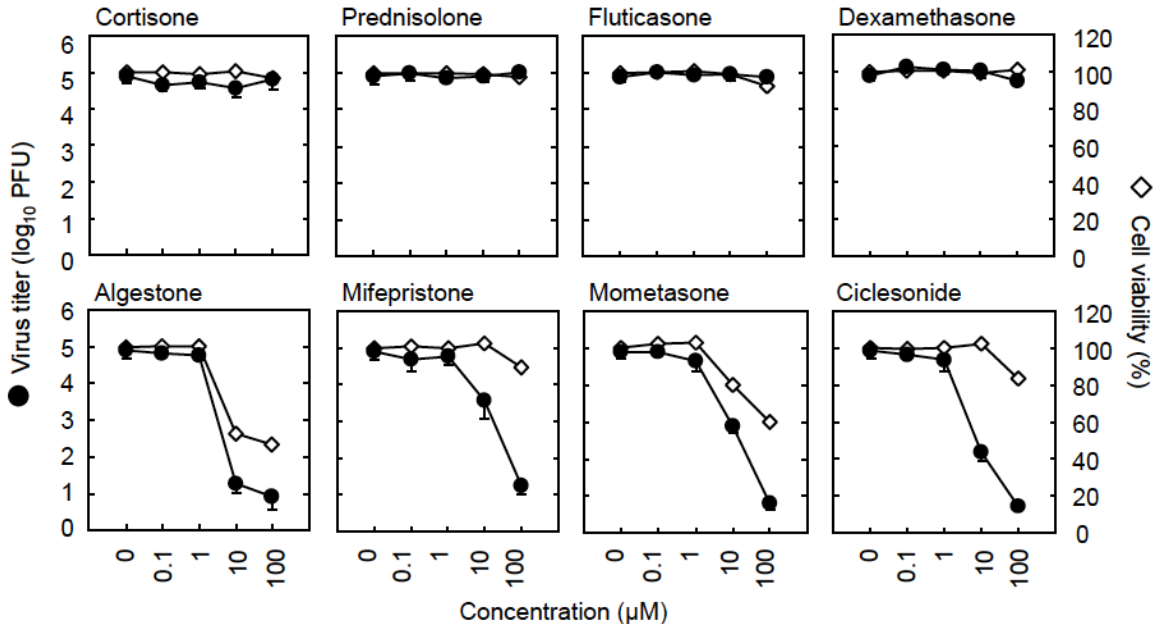


Figure 2- Antiviral effects of steroids on SARS-CoV-2. (a) Intracellular SARS-CoV-2 RNA (6 hpi). VeroE6/TMPRSS2 cells were infected with SARS-CoV-2 at MOI = 1 in the presence of 10μM compounds for 6 h. Cellular viral RNA was quantified by real-time PCR using the E gene primer/probe set.

In order to determine drug antiviral activity specific to SARS-CoV-2, 3000 FDA and IND-approved drugs were screened and ciclesonide showed a potent antiviral effect (IC50=4.33 mcM; Figure 3) in addition to its intrinsic anti-inflammatory function (5).

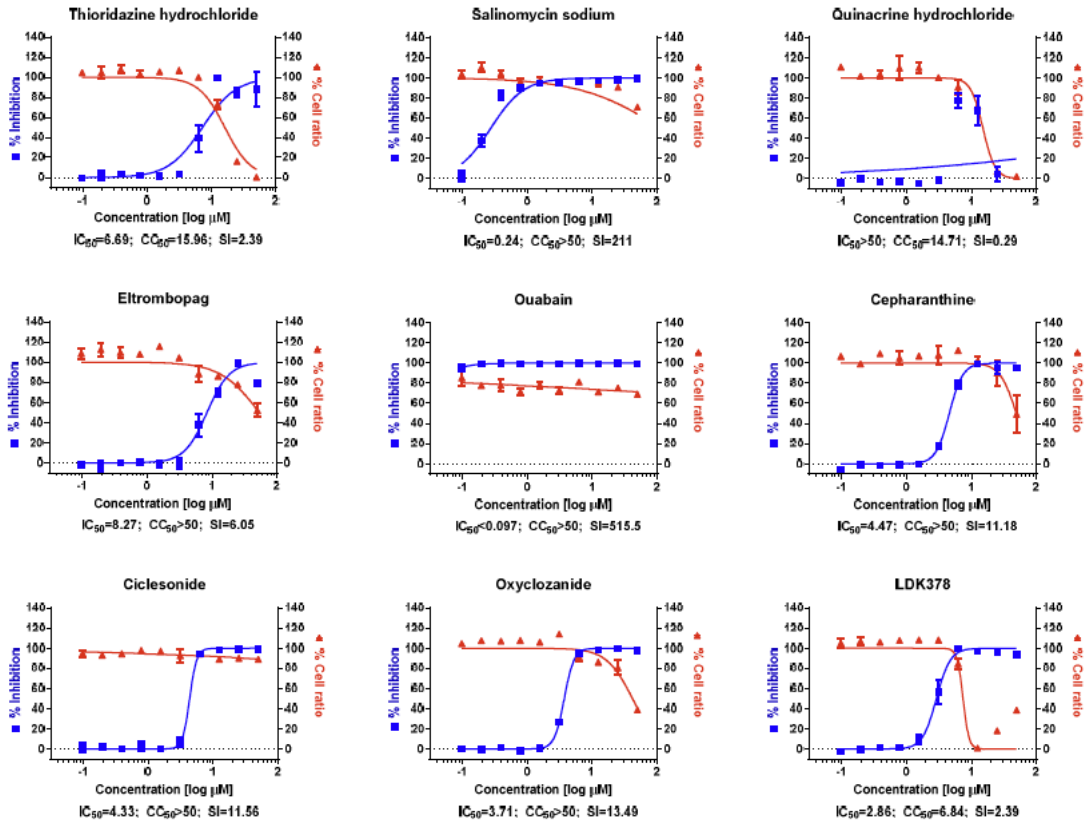


Figure 3 - (part of Figure 1B from reference 5) Dose response curve analysis by immunofluorescence for 45 drugs that were tested in this study. The blue squares represent inhibition of virus infection (%) and the red triangles represent cell viability (%). Means ± SD were calculated from duplicate experiments

Subsequently, reduced viral load of SARS-CoV-2 has been shown to be associated with reduced clinical disease severity (7).

2.2 Rationale

Current standard of care is supportive care after the diagnosis of COVID-19.

Ciclesonide is a corticosteroid currently used for asthma (in its inhaled form) and nasal rhinitis (in its spray form). It has a very good safety profile. Much higher doses of ciclesonide (up to a single inhalation of 3200 mcg) have been administered to healthy volunteers and were well tolerated (9). As such, inhaled and nasal ciclesonide at the doses of 600mcg BID for 2 weeks will have few adverse events. The usual doses for ciclesonide are:

Standard asthma treatment (ciclesonide, *Alvesco*):

- The recommended dose range for ciclesonide in inhalation is 100 to 800 mcg daily (9).
- The recommended starting dose for most asthmatic patients is 200 mcg daily in Canada (10).
- The maximum dose of 800 mcg daily should be administered as 400 mcg twice daily (9).

Standard allergic rhinitis treatment (ciclesonide, *Omnaris*) (11):

- The recommended dose of OMNARIS is 200 mcg per day administered as 2 sprays (50 mcg/spray) in each nostril once daily.
- The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day)

As the specific dose of ciclesonide to decrease SARS-CoV-2 is unknown, we planned to give a higher dose than the maximum approved dose for asthma of inhaled ciclesonide (1200 mcg daily administered as 600 mcg twice daily) plus the usual dose of intranasal ciclesonide (200 mcg/day) for 14 days. Given viral replication begins in the nasal cavity and then progress to the lungs, we have chosen to administer ciclesonide both intranasally and inhaled. This dose has been chosen in order to maximize deposition of the study drug in the lower airways. Although the usual dose of ciclesonide for asthma is 400 mcg twice daily (for a total of 800 mcg/day), single doses (up to 3200 mcg) have been administered to healthy subjects without significant side effects (9).

The in vitro replication of SARS-CoV-2 was reduced by twice in 27h, so we expect the effect of ciclesonide to be rapid. Moreover, as we hypothesize its antiviral effects will affect the nasal/upper airways replication of the virus, it should be more effective at the beginning of the disease compared to when the virus has spread to the lung. Therefore, we aim to recruit patients at the beginning of their disease (within 5 days of positive SARS-CoV-2 PCR) and to have a rapid benefit on symptom severity (at 7 days of enrollment). However, multiple complications of COVID-19 appear after the first 7 days (Zhou and al., 2020) so we will continue our treatment for a total of 14 days (4).

The proposed treatment will allow faster symptom resolution of COVID-19 symptoms in mildly symptomatic outpatients and return to work for healthcare workers and essential workers.
In Canada we will be using DIN 02285614 / Alvesco) and intranasal Ciclesonide (DIN 02303671/ Omnaris) as the active drug and a placebo inhaler (NDC 70515-710-01) as the placebo.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Ciclesonide is a drug currently used for asthma maintenance treatment (in its inhaled form) and nasal rhinitis. It has been approved by Health Canada in 2008 in this setting. It has a very good safety profile with mainly local possible side effects. The principal sides effects as listed on the monograph are:

Common Clinical Trial Adverse Drug Reactions (≥1% - <10%)
Respiratory: Paradoxical bronchospasm (1.6%), Dysphonia (1.0%).

Uncommon Clinical Trial Adverse Drug Reactions (≥0.1% to <1%)
Cardiovascular: Palpitations (0.1%).
Eye: Cataract subcapsular (0.1%).
Gastrointestinal: Nausea (0.2%), Dry mouth (0.1%), Dyspepsia (0.1%)
Infections: Oral candidiasis (0.6%), Candidiasis (0.1%), Oral fungal infection (0.1%), Pharyngitis (0.1%).
Injury: Contusion (0.1%).
Investigations: ALT increased (0.1%), Gamma-glutamyltransferase increased (0.1%)
Weight increased (0.1%)
Nervous System: Headache (0.4%), Dysgeusia (0.3%), Dizziness (0.1%).
Respiratory, thoracic and mediastinal disorders: Pharyngolaryngeal pain (0.4 %), Throat irritation (0.3%), Dry throat (0.1%).
Skin: Rash (0.1%).
The incidence of local oropharyngeal adverse reactions in ALVESCO-treated patients was low and comparable to placebo.

The risk of thrush (appearance of Candida albicans in the mouth and throat) is rare but can be further reduced by the use of an aerochamber and a proper mouth rinsing after using Ciclesonide.

The contraindications to Ciclesonide, as listed on the monograph:

CONTRAINDICATIONS ALVESCO (ciclesonide) is contraindicated in patients with known hypersensitivity to any of the ingredients.

ALVESCO is not to be used in the primary treatment of status asthmaticus or other acute episodes of asthma, or in patients with moderate to severe bronchiectasis.

OMNARIS (ciclesonide) is contraindicated in patients with hypersensitivity to any of the ingredients.

OMNARIS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract.

2.3.2 Known Potential Benefits

- There are no proven benefits in humans for treatment of COVID-19
- At the Kanagawa Prefectural Ashigarakami Hospital, in Japan, three patients with COVID-19 were treated with inhaled Alvesco and clinically improved (12).
- *In vitro* antiviral activity against SARS-CoV and SARS-CoV-2 viruses
- Ciclesonide both in inhalation and spray have a long history of safe, effective use is asthma and allergic rhinitis, both acutely and long-term.
- 2 randomized clinical trials on Ciclesonide for COVID-19 are about to start, one in mild patients taking place in Korea (13) and one pre-symptomatic patients, taking place in Japan (14).
- Recent studies have shown potential direct-acting antiviral activity in addition to its intrinsic anti-inflammatory function (5).

3 OBJECTIVES

3.1 Study Objectives

To evaluate whether early treatment with inhaled and nasal ciclesonide results in symptom resolution at day 7 in early mild symptomatic patients (particularly dyspnea)

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Primary outcome is defined as the proportion of patients with resolved respiratory symptoms (fever, cough, shortness of breath, chest congestion or chest tightness) at day 7.

3.2.2 Secondary Outcome Measures

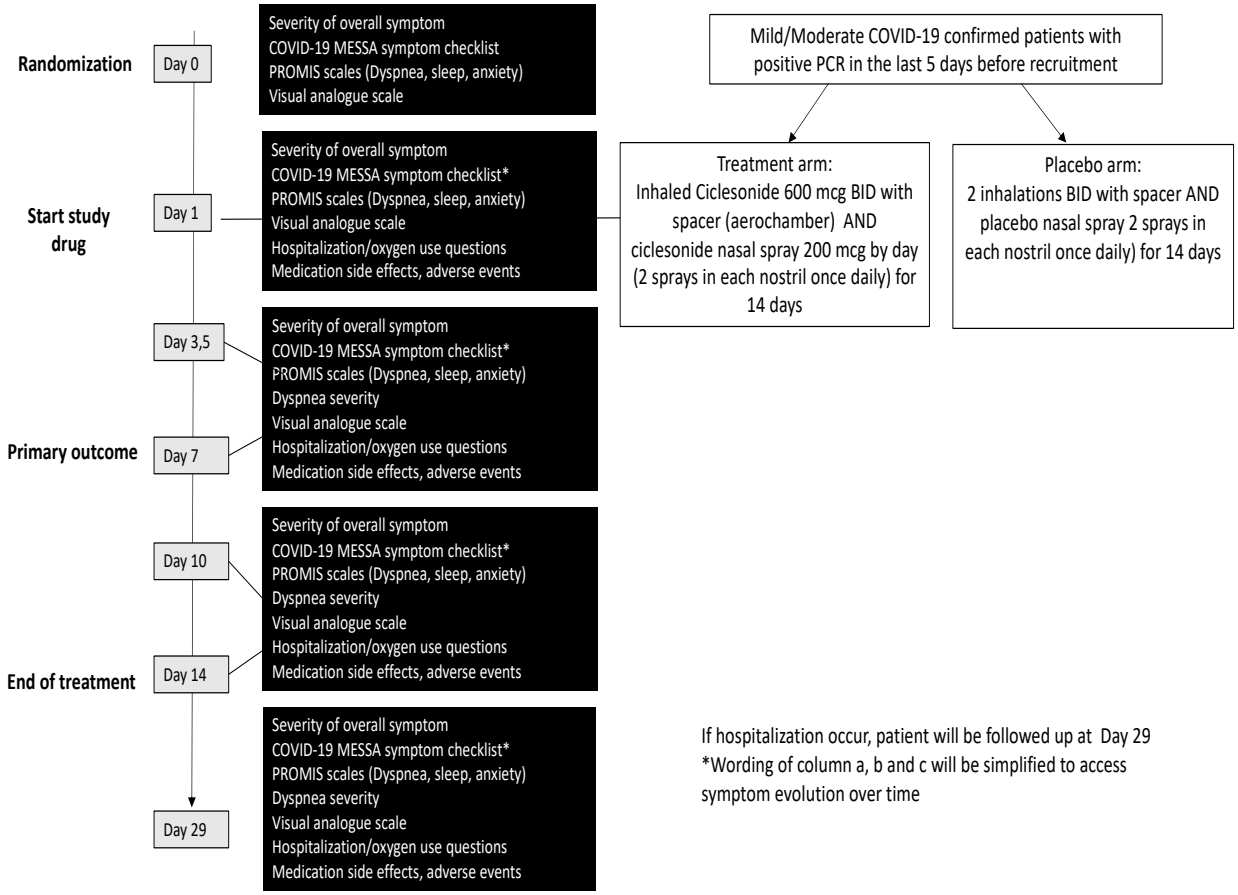
a) Hospitalization for SARS-CoV-2 related illness at day 14
b) Primary outcome (proportion of patients with no cough, fever or dyspnea) measured at day 14
c) Mortality at day 14 and 29
d) Ordinal Scale for Evaluating subject Clinical Status (overall feeling) (see Appendix 2) measured on day 0, 1, 3, 5, 7, 14 and 29: We will evaluate the proportion who are reporting that they are “very much improved” or “much improved” by day 7 and day 14 (vs. not).
e) PROMIS dyspnea, anxiety and sleep (respectively). We will look at the questionnaires at day 7 and at day 14 and compare the proportions between groups with a 3 point or higher change (compared to day 0 and using the t-score adjusted for population). We will also report the mean T scores. Raw scores are converted to standardized T scores using

calibrated algorithms for the general population. They are standardized scores with a mean of 50 and SD of 10; 45 to 55 on a PROMIS T score is considered the normal range. 55-60 is mild levels of symptoms (anxiety, sleep, dyspnea), 60-70 is moderate, and 70+ is severe. A meaningful change will be considered a 3 point change on the T score.

f) Visual Analog scale from 0-10 indicating improvement in symptoms measured at day 0, 1, 3, 5, 7, 10, 14 and 29; analysis will look at resolution of symptoms at day 7 and day 14, and resolution of cough at day 7 and 14.
g) Time to symptom resolution (post-hoc)

Assessment of outcome measures will be primarily by self-report. As necessary, COVID-19 disease will be verified from public health records, medical records, or death certificates. The primary analysis will use PCR+ confirmed disease.

4 STUDY DESIGN



4.1 DESIGN

Randomized, double-blind, placebo-controlled clinical trial, parallel design

- Intervention Arm: Ciclesonide 600mcg BID inhaled with aero chamber *plus* intranasal ciclesonide 200 mcg DIE for 14 days. The aerochamber is Respichamber from the hospital which will be discarded after the 14 days. For information on how to use the aerochamber please refer to: https://www.youtube.com/watch?time_continue=1&v=O92_Ftf6Wnk&feature=emb_title

- Control Arm: Placebo inhaled BID with respichamber (same as above) *plus* intranasal saline DIE for 14 days.

In Canada we will be using inhaled Ciclesonide (DIN 02285614 / Alvesco) and intranasal Ciclesonide (DIN 02303671/ Omnaris) as the active drug and a placebo inhaler (NDC 70515-710-01) as the placebo.

At present, all these products are sourced from Canadian wholesale distributors.

4.2 Study participant duration

- 14 days consisting of internet-based virtual visits
- Observational follow up at day 29 to assess final outcome status of hospitalization and SAE.

4.3 Study procedures

- All procedures will consist of internet-based questionnaires completed by self-report.
- Informed consent is provided to access medical records to verify information, as necessary and in accordance with individual provincial laws.

4.4 Individually identifiable health information:

Name, date of birth, phone number and address will be collected centrally at the RI-MUHC to prescribe study medication. These names and addresses will be communicated to approved study sites in other provinces to facilitate timely prescription and local shipping in each participating province. Email addresses will be collected for communication. If participants are hospitalized, the hospitalization date will be collected. **NO IDENTIFIABLE HEALTH INFORMATION WILL BE TRANSMITTED OUTSIDE OF CANADA.**

4.5 Substudies (if applicable)

Additional sub-studies will undergo separate IRB approval, and these studies will involve separate informed consent. Consented participants will be queried as to if they wish to participate in future research.

4.6 Participation in concomitant clinical trials

Because of unknown potential drug-drug interactions between ciclesonide and other investigational products we will ask participants not to enroll in other clinical trials for the study duration.

5 STUDY ENROLLMENT AND WITHDRAWAL

Participants will undergo screening via REDCap.. The screening and inclusion criteria will be based on self-report.

5.1 Subject Inclusion Criteria

- Symptomatic COVID-19 disease (fever, cough OR shortness of breath) AND confirmed diagnosis with PCR+ SARS-CoV-2 within <= 6 days of enrolment (day 6 if same day shipping geographically permits)
- Shortness of breath is defined by self report as " shortness of breath", "chest tightness" or "chest congestion"
- Cough is defined as "dry cough" or "wet cough" by self report
- >= 18 years of age
- Provision of informed consent
- Mild symptomatic SARS-CoV-2 disease is defined as individuals who are SARS-CoV-2 PCR positive AND present with more than one symptom listed on the symptom checklist developed by the National Institute of Health MESA COVID-19 questionnaire (Version dated 04/10/2020; symptom checklist page 8) at study entry (see Appendix 2).

5.2 Subject Exclusion Criteria

- Already on inhaled corticosteroid medication
- Currently using systemic steroids (oral or intravenous or intramuscular such as Prednisone) or use of steroids 7 days prior to enrolment
- Severely ill patients at enrollment (i.e., admitted to ICU at admission)
- Unable to self-administer the inhaler
- Anticipated transfer to another hospital within 72 hours which is not a study site
- Known or suspected pregnancy and breastfeeding
- Known allergy to study medication or its components (non-medicinal ingredients; including lactose allergy (type I))
- Patients with untreated fungal, bacterial or tubercular infections of the respiratory tract
- Current hospitalization
- Current use of oxygen at home or in hospital
- Vaccinated for COVID-19

Rationale for inclusion / exclusion criteria:
Mean Incubation period is ~5.2 days, thus we wish to limit enrollment such that delivery of the study medicine occurs in the time period in which it can ameliorate disease (i.e. start

of study medicine by <=6 days after positive PCR). Day 6 only if able to ship the drug and commence it the same day as receiving it.

In clinical practice, oral and nasal ciclesonide is prescribed without any baseline laboratory testing or monitoring.

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Participants will be randomized via permuted block randomization. Randomization will be created and recorded on an electronic log. Study investigators and subjects will be blinded.

5.3.2 Masking Procedures

Participants will be provided masked study medicine, shipped by courier (e.g. FedEx). The intervention vs. placebo will not be identical; however, participants and outcome assessors will be masked to their assignment.

5.3.3 Subject withdrawal criteria

Participants may withdraw at any time point at their discretion. Subject withdrawal is defined as decision to terminate trial treatment. Subject will be replaced until the targeted 318 patients required for our power calculation. Study recruitment will be on a rolling basis. Our accrual ceiling is 2 times the required number of participants for the study. Based an alpha of 0.05 and a 15% subject dropout rate, we require 159 participants per arm. Our current power calculations account for a 25% subject dropout rate. As such, should individuals drop out (ie. be lost to follow up), it is unlikely to affect the study error.

5.3.4 Handling of Withdrawals

Patients who discontinue the study drug will be encouraged to stay on study and will continue to be followed for safety and efficacy endpoints, unless they have withdrawn consent.

5.3.5 Termination of Study

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Unexpected, significant, or unacceptable risk to subjects
- Regulatory authorities decide that study should be terminated
- Insufficient compliance with protocol requirements
- Data are not sufficiently complete and/or not evaluable

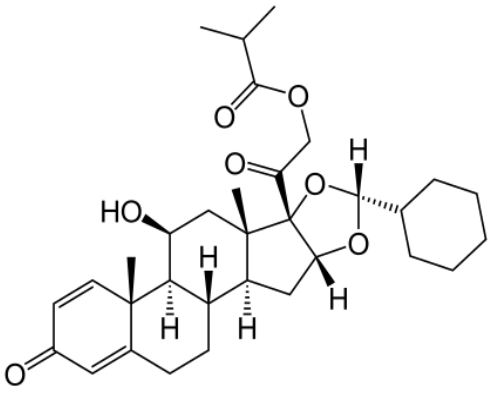
6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

Omnaris (aqueous nasal ciclesonide) and Alvesco (aerosol oral ciclesonide) will be supplied free of charge by Covis Pharma

6.1.2 Formulation, Packaging, and Labeling



The study medicines will be packaged in GCP appropriate packaging/labelling by the Research Pharmacies at each of the approved provincial centers. RI-MUHC will do this for the province of Quebec. Dispensed medications will be delivered by courier (e.g. Fedex) to study participants directly from the research pharmacies in packaging which obscures the content. At the end of the treatment period, patients will be asked to safely dispose of their unused medication by going to the nearest pharmacy or ecocenter. Due to the COVID-19 pandemic, pateints will not be allowed to send back their unsed medication to the study site due to risk of fomites.

6.1.3 Drug Description:

Drug name: [11 beta, 16 alpha (R)]-16, 17-[(Cyclohexylmethylene)-bis(oxy)]-11- hydroxy-21-(2-methyl-1-oxopropoxy) pregna-1,4-diene-3,20-dione

6.1.4 Formulation:

Oral: 100 or 200mcg/actuation (ex-valve)

Nasal: 50mcg/metered spray

6.1.5 Product Storage and Stability

Omnaris: Store at room temperature up to 30°C

Alvesco: Cannister contains pressurized liquid. Store at room temperature 15-25°C and protect from temperatures above 50°C. Do not freeze.

6.2 Dosage, Preparation, and Administration of Investigational Product

6.2.1 Drug/Device Handling: Omnaris (aqueous nasal ciclesonide) and Alvesco (aerosol oral ciclesonide) or placebo will be dispensed by the Research Pharmacy in each approved center. The RI-MUHC will do this for the province of Quebec. To do so, the study investigators will send a prescription to the Pharmacy, the pharmacy will dispense the appropriate study medicine. The medicine will then be provided to research volunteers via FedEx / courier delivery in the province of approval (e.g. within Quebec for RI-MUHC).

6.3 Modification of Investigational Product for a Participant

In the event of substantial side effects, participants may discontinue the study medication and stay in the study to complete follow up.

6.4 Accountability Procedures for the Investigational Product:

Accountability will be via self-report at the day 14 virtual questionnaire.

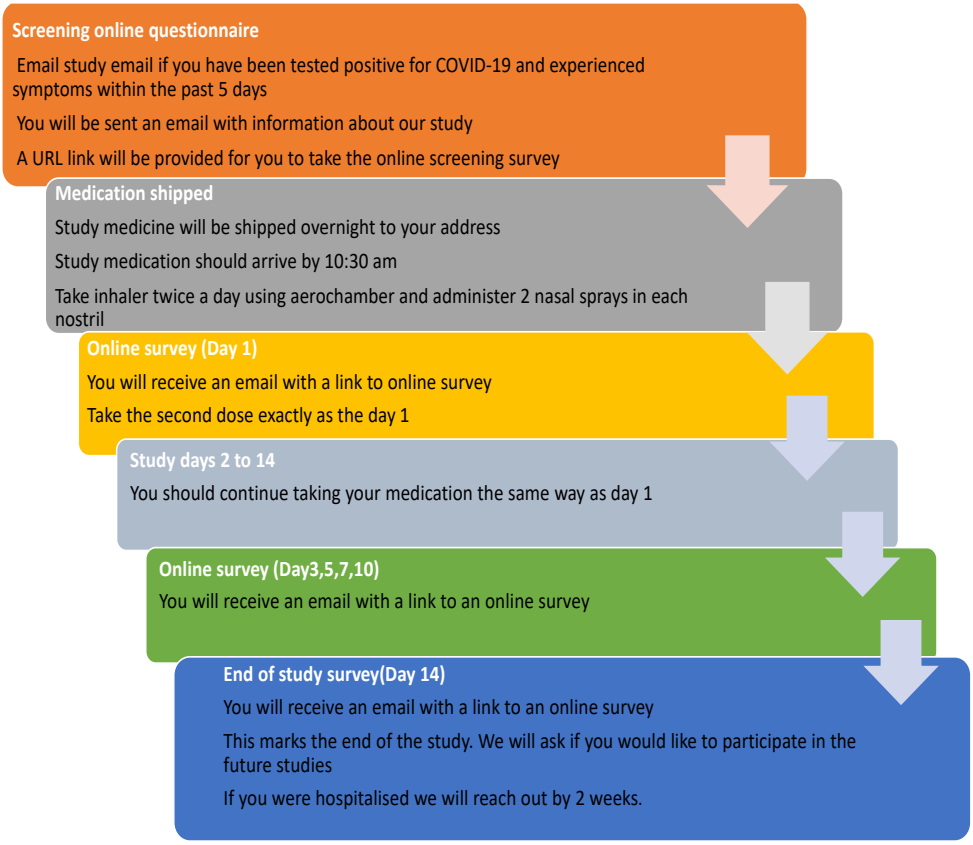
6.5 Assessment of Subject Compliance

Adherence will be via self-report at day 14 virtual questionnaire.

6.6 Concomitant Medications/Treatments

Participants may receive other concomitant medications or therapies and will be asked to report these in regard to other therapies received on day 1, 3, 5, 7, 10, 14 and in the event of hospitalization. Participants will be recommended not to continue the study drug if hospitalized.

7 STUDY SCHEDULE



1) Information includes consent document. The patient signs electronically in the application after answering questions which confirm comprehension.
2) If eligible, drug is prescribed, they are randomized, and shipping is arranged for study drug or placebo

Questionnaire	Day 0	Day1	Day 3	Day 5	Day 7	Day 10	Day 14	Day 29
Eligibility (screening form)	x							
Enrolment form (for eligible patients)	x							
Follow up questionnaire (MESA COVID 19)	x	x	x	x	x	x	x	x
Severity of overall symptoms	x	x	x	x	x	x	x	x
Dyspnea characteristics	x	x	x	x	x	x	x	x
Dyspnea severity	x	x	x	x	x	x	x	x
Visual analog scale for individual symptoms	x	x	x	x	x	x	x	x
Sleep PROMIS scale	x	x	x	x	x	x	x	x
Anxiety PROMIS scale	x	x	x	x	x	x	x	x

WHO ordinal scale	x	x	x	x	x	x	x	x
Hospitalization/Oxygen use query		x	x	x	x	x	x	x
Side effects query		x	x	x	x	x	x	x
Mortality							x	x
Subject orientation of the type of the study drug (placebo or active drug)							x	

7.1 Screening

- Baseline screening for eligibility through online questionnaire
- Informed consent by electronic consent form in REDCap
- Participant answers comprehension questions to ensure understands study protocol
- This will be performed via a web-based form. Eligibility criteria will be by self-report.

7.2 Enrollment/Baseline

7.2.1 Randomization (Day 0)

- Medication list and screening form will be reviewed by central physician using the doctor review function in REDCap.
    - If there are any doubts about the subject's appropriateness, the patient will be called by telephone to obtain more details. The medication list provided by the patient will be specifically reviewed by an expert physician in Internal Medicine who is aware of issues surrounding polypharmacy. Patients who have an unacceptable medical review will be excluded prior to randomization and the reason noted.
- Participants will be randomized by a computer-generated algorithm using a permuted block randomization sequence
- Randomization will be stratified by study site and sex
- Investigational pharmacy will dispense the masked study medicine
- Study personnel will then courier study medicine to the participant
- Participant will be sent an email about when to expect medication to arrive

7.3 Follow-up

Day 0 Virtual questionnaire

- Query for symptom status

Day 1 Virtual questionnaire

- Verify receipt of study medicine
- Clinical status check-in
- Participant starts study medicine Ciclesonide 600mcg BID inhaled with aero chamber plus intranasal ciclesonide 200 mcg DIE

- Confirm the positive SARS-CoV-2 test result
- Query for symptom status
- Assess other medicines used during study period
- self reported hospitalization and oxygen use

Day 3, 5, 7, 10 Virtual questionnaires

- Clinical status check-in
- Query for symptom status
- Query for medication-related side effects / AEs
- Assess other medicines used during study period
- self reported hospitalization and oxygen use

7.4 Final Study Visit

- Day 14 Visit
    - Clinical status check-in
        - Query for study medicine side effects since enrollment
        - Query for hospitalization or SAEs
    - Final outcome assessment
    - Completion of study medicine, which has a ~6-hour half-life
    - Assessment of adherence by self-report
    - Assess whether or not the patient believes they received study drug or placebo
    - Assess other medicines used during study period

- Day 29: Vital Status, clinical status, self reported hospitalization and oxygen use

7.5 Early Termination Visit

If patients feel they are worsening they will need to see their healthcare providers to be medically assessed. They are to notify us via email or phone and case report forms will be generated. If patients are admitted to hospital, study drug will be stopped.

7.6 Unscheduled/Sick Visit

Subjects will be provided a central email contact (info@contain-covid19.com). This is their central electronic point of contact and will be regularly responded to 7 days a week in a timely fashion. The person monitoring that account will either be a physician or will be someone who can contact a physician.

Patients will also receive phone numbers which will be manned but also have voicemail and will be responded to in a timely fashion.

All such interactions which may be due to coronavirus or a SAE will trigger a new daily CRF to be sent manually to log the patient's issue in the core dataset.

As this is a distance study, patients who are significantly unwell and who need urgent or emergent care will need to access regular channels for healthcare (e.g. doctors office, emergency room, etc.)

Additionally, those who have symptoms at baseline, or those who have developed NEW symptoms will be sent a follow-up eCRF on Day 10.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

Clinical evaluations are by self-report

8.2 Laboratory Evaluations

There are no laboratory evaluations in the protocol.

SARS-CoV2 positivity is laboratory-confirmed and self-reported. Informed consent asks for access to medical records in case this needs to be verified.

Informed consent will request permission to contact local public health authorities or their medical provider in the event of loss to follow up or COVID-19 disease.

8.3 Subject Recruitment

- List of outpatients with COVID positive test will be contacted by research assistants by phone using script in appendix 3. They will ask patients for their email. If patients demonstrate interest in participation, research assistants will send them a link to study website. Study website has a link to REDCap portal for enrollment (www.contain-covid19.com). Participants will only have data saved in REDCap. Research assistants will not enter any data from COVID list into REDCap.
- Flyers will be left at the testing center for interested participants to visit the study website. See appendix 4 for flyers

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Ciclesonide has a years-long track record of safety in Canada and the USA. As an already, Health Canada-approved medicine, this trial is designed as a pragmatic trial in the setting of a public health emergency.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Minor Adverse events will not be captured, unless they result in hospitalization. See Serious Adverse Events below.

Expected adverse events would include normal events within the general population as well COVID-19-related disease events which may include need for hospitalization, pneumonia, respiratory failure, sepsis, and death.

9.2.2 Reactogenicity (for Vaccine Studies and Some Therapeutic Trials)

Not applicable

9.2.3 Serious Adverse Events (SAEs)

SAEs (e.g. hospitalization) will be followed for up to 29 days to assess final outcome.

A patient who reports hospitalization and/or an adverse effect of the study drug on a CRF who has not reached out to the team by phone or email will be contacted in a timely fashion and the site doctor made aware. We will review the "positive" CRFs to detect these. We also collect details about the hospitalization.

Patients who do not complete their day 14 CRF will receive reminder emails and, if they do not respond to that, they will be telephoned. Patients must provide an alternate contact at enrollment. If they do not respond to the above means, we will call that contact to find out what has happened. If that person does not know or is not available, we will send registered mail to the address of the patient before concluding loss to follow-up. A sensitivity analysis of the mortality outcome will be performed assuming patients lost to follow-up despite these means have died.

9.2.4 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Not applicable

9.3 Reporting Procedures

9.3.1 Serious Adverse Events

An AE or suspected adverse reaction is considered a serious adverse event (SAE) if it results in any of the following outcomes:

- Death,
- life-threatening adverse event (as below),
- Hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Important medical events that may not result in death, but are life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

  Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening adverse events: An AE is considered "life-threatening" if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death. For life threatening AEs, subjects would be recommended /expected to be hospitalized.

Based on the known safety track record of ciclesonide, this pragmatic protocol will focus on death, life-threatening AEs, and hospitalizations. Incapacity / permanent disability is a possibility with COVID-19, but this is not associated with ciclesonide. In the event of incapacity, the subject would be expected to be hospitalized.

Ciclesonide can be used in asthmatic pregnant women. However, as per product monograph; ''There are no adequate and well controlled studies in pregnant women. However, serum concentrations of ciclesonide are generally very low following inhaled administration; thus, fetal exposure is expected to be negligible and the potential for reproductive toxicity low. As with other inhaled corticosteroids, ciclesonide should only be used during pregnancy when the potential benefit to the mother justifies the potential risk to the mother, fetus or infant. Infants born to mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.'' As we don't know the potential benefit of ciclesonide in COVID-19 patients, we will exclude pregnant women for our trial.

Thus, the hospitalization or death secondary endpoint will capture relevant SAEs for those with ongoing hospitalization at the day 14 study visit, participants will be queried in 14-days with the hospital eCRF to assess their final outcome.

9.3.2 Regulatory Reporting

As ciclesonide is a Health Canada-approved medicine being used at standard dosing, reporting to regulatory authorities will occur as standard and at a frequency of at least annually.

Serious unexpected suspected adverse reactions (SUSARs) which are not expected with COVID-19 nor listed in the Health Canada package insert will be reported to the IRB.

Those SUSARS which are deemed by an independent medical monitor to be related to the study medicine will be reported to Health Canada and the IRB.

9.3.3 Reporting of Pregnancy

We are excluding women who are pregnant, and we will ask child-bearing age women participants to use a contraceptive measure during the trial. Methods of contraception include hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS), and/or barrier methods of contraception while on the study drug.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

Participants who are hospitalized for COVID-19 or SAEs will have up to 29 day follow up conducted to assess their final outcome. As this is a distance study, management or complications of COVID-19 will need to be as per the participant's local healthcare provider.

9.5 Safety Oversight (DSMB)

A DSMB was formed and met at 50% enrolment and when trial enrolment dropped off. There were no early stopping criteria defined. Members included: Richard Menzies MD, Faiz Khan MD and Sandra Dial MD.

10 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected and that the reported trial data are accurate, complete, and verifiable. Clinical monitoring also ensures that conduct of the trial is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and Sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions. Monitoring in Canada will be the responsibility each Site PI under the overall responsibility of Nicole Ezer, RI-MUHC.

The automated logic of the REDCap database system will enable complete records. All data are by self-report.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

We hypothesize that ciclesonide is superior to placebo for reducing dyspnea due to COVID-19 disease among who are symptomatic.

11.2 Sample Size Considerations

Our primary outcome is the proportion of patients with resolved respiratory symptoms (fever, cough, shortness of breath, chest congestion or chest tightness) at day 7.

This study is powered based on determining if there is a 15% increase in our primary outcome, the proportion of participants with no symptoms of shortness of breath (including chest congestion and chest tightness), cough or fever at Day 7. Based on the assumption that, by Day 7, 65% of untreated subjects, and 80% of treated subjects, will have resolved their symptoms, we will need 159 subjects per group to detect this difference with 80% power (5% alpha). This analysis has been adjusted to include a 15% dropout rate. The total number of study participants required is 318. These assumptions were made based on another outpatient RCT evaluating symptoms in COVID-19(15).

% Resolved by Day 7- **Placebo arm**	% Resolved by Day 7- **Treatment arm**	Proportion difference	Nominal Power, p=0.05	Total participants	Total participants including 15% drop out
75%	85%	10%	0.8	250	
75%	90%	15%	0.8	200	
75%	95%	20%	0.8	98	
70%	80%	10%	0.8	586	
70%	85%	15%	0.8	240	
70%	90%	20%	0.8	124	
70%	95%	25%	0.8	70	
65%	75%	10%	0.8	656	
65%	**80%**	**15%**	**0.8**	**276**	**318 (159 per arm)**
65%	80%	15%	0.9	368	
65%	85%	20%	0.8	144	
65%	90%	25%	0.8	86	
60%	70%	10%	0.8	712	
60%	75%	15%	0.8	304	
60%	75%	15%	0.9	406	
60%	80%	20%	0.8	162	
60%	85%	25%	0.8	98	
60%	90%	30%	0.8	62	

11.3 Planned Interim Analyses

No interim analyses are planned.

11.4 Primary Analysis

Primary outcome analyses:

A modified intention to treat approach will be used where subjects will be analyzed according to the group they were randomized provided they have been shipped the drug, taken one dose and completed at least one follow-up assessment.

The proportion of patients who meet the primary outcome will be compared by binomial regression adjusting for stratification and the difference will be reported as an absolute risk difference and 95% CI.

Secondary Analyses:

Proportions meeting each secondary outcome will be analyzed by binomial regression adjusting for stratification and the differences will be reported as an absolute risk difference and 95% CI.

The post-hoc analysis of time to symptom resolution will use the Kaplan Meier plot.

Handling of withdrawn subjects.

If there is a large lost to follow up / study discontinue rate, then the primary endpoint would have a secondary analysis to assess incidence as a 3-category analysis of: i) increase in disease symptoms, ii) decrease in disease symptoms, iii) no change in disease symptoms or iiii) unknown.

Participants who stop taking the study medicine but who agree to be followed for the duration of the study will be assessed as intent-to-treat. On Day 1, 3, 5, 7, 14 and 29, we will ask for other medications or vitamins that were taken during the study period.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents will include internet forms self-completed by participants directly entered into a REDCap database.

This protocol is based on self-report.

This internet-based protocol is meant to enable a large number of participants to be recruited, quickly as well as maintain the safety of the research staff. In person visits, create a public health risk due to transmission of COVID-19 from unrecognized cases. Likewise, paper documents and consent forms also carry this risk (as fomites) and so all consent documentation will be recorded electronically with an online signature.

Participants will be asked to provide consent to obtain medical records from their healthcare provider or public health official, if there is the need to verify outcomes – for SARS-CoV-2 test results or hospitalizations.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Study medications will be Health Canada-approved following Good Manufacturing Practice.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

This study is to be conducted in the spirit of Canadian and international standards of Good Clinical Practice (International Conference on Harmonization guidelines), Declaration of Helsinki, and International Ethical Guidelines for Biomedical Research Involving Human Subjects, applicable provincial regulations and institutional research policies and procedures. All investigators must have received ethics and GCP training prior to human subject involvement.

14.2 Institutional Review Board

Prior to the initiation of the study, the protocol, all informed consent forms, and the participant Information materials will be submitted to and approved by the RI-MUHC. For outside of Quebec, other REBs will take responsibility for their provinces using this master protocol. Likewise, any future amendments to the study protocol will be submitted and approved by the IRB before implementation. This protocol and any amendments will undergo review and approval.

14.3 Informed Consent Process

- Written informed consent will be obtained via an English or French-language, internet-based web form. If potential participants have questions, they may contact a study staff

member in their province to answer their questions about the research, either via email or phone call. Participants will electronically sign the consent form.

- Participants will be asked to upload a photo ID (provincial health card) to confirm their identification.
- After completion of reading the form, participants will be assessed for comprehension, querying:
    - Concept of Randomization to ciclesonide or placebo
    - Whether ciclesonide is known to be effective in preventing disease
    - Duration of the study? (14 days)
    - Duration of taking the study medicine (14 days)
    - When follow up surveys will be sent (Days 1, 3, 5, 7, 10, and 14)
    - If ciclesonide can be shared? (No)

14.4 Exclusion of Women, Minorities, and Children

- Persons under 18 years of age are not eligible to participate.
- Women who are pregnant or breastfeeding are excluded because the safety data is inadequately known for this study.
- Non-English or French speaking adults are not eligible as the webpage and consents will only be available in English or French.

14.5 Subject Confidentiality

- Interaction will be via internet-based REDCap eCRFs conforming to required Canadian privacy and server security standards.
- Clinical data will be entered into a study specific database by designated staff on a regular basis from completed electronic Case Record Forms (eCRF). Access to database will be given to authorized personnel only (members of the immediate study team). eCRF and trial documents will be kept in a secure database.
- Documentation, data and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party, without prior written approval of the participant except as necessary for monitoring by the IRB or public health authorities
- No participant identifying information will be disclosed in any publication or at any conference activities arising from the study.
- Anonymized data on demographics, survey responses and outcomes will be pooled with international collaborators subject to inter-institutional agreements.

14.6 Future Use of Stored Specimens

- No specimens are to be collected.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities

15.2 Data Capture Methods

- Data will be obtained via internet-based REDCap forms.

15.3 Types of Data

- Participants will be asked to provide data regarding COVID-19 exposure timing and location. They will also be asked to provide ongoing symptom reports during the follow-up period.

15.4 Timing/Reports

- An enrollment progress report will be generated monthly
    - Participants Enrolled
    - Participants on study
    - Participants completed the study
    - Lost to Follow Up
    - Cumulative Hospitalizations (pooled, both arms)
    - Cumulative mortality

- De-identified data will be shared with the research team members for analysis.

15.5 Study Records Retention

- No paper documents will be retained or stored.
- Digital records will be kept in a secure server setting.

15.6 Protocol Deviations

Protocol violations will be reported to the IRB of record in each province and forwarded to the main Canadian PI.

16 PUBLICATION POLICY

Publication will be expeditiously made with a full, de-identified data made available.

17 LITERATURE REFERENCES

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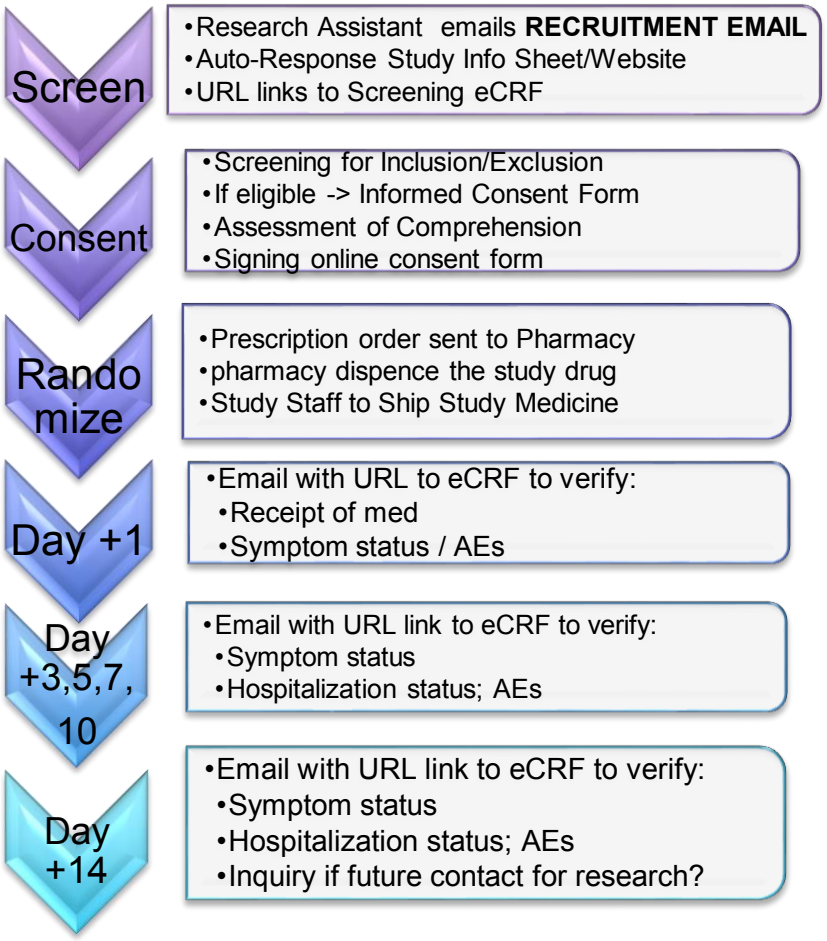
SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Overview of Study Procedures



Participants with ongoing hospitalization at day 14 will be followed with an additional eCRF after 14 days.

APPENDIX B: LOGIC

1) Must have all inclusion criteria as defined.

2) Must not have any exclusion criteria.

3) Patients who are not in the study provinces will receive a message saying the study is not available in their province (this is not counted as being formally ineligible).