Supplement

# Inhaled Ciclesonide for the Treatment of COVID-19 in Nonhospitalized Adults (CONTAIN): A phase-2, randomized, double-blind, placebo-controlled trial

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Table of Contents:

Section A: Inclusion and Exclusion Criteria and Additional Details

Inclusion Criteria:

- >= 18 years of age
- Symptomatic COVID-19 disease (fever, cough, OR shortness of breath) AND confirmed diagnosis with PCR+ SARS-CoV-2 within <= 5 days of enrolment*
    - Fever is defined as >38C by self-report
    - Cough is defined as “dry cough” or “wet cough” by self-report
    - Shortness of breath is defined by self-report as “shortness of breath,” “chest tightness” or “chest congestion” of any severity.
- Mild to moderately 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

**Up to 6 days were permitted provided the patient lived in an area which could receive study drugs on the same day (added as an inclusion criterion in November 2020).*

Exclusion Criteria:

- Currently hospitalized
- Current use of oxygen at home or in hospital
- Allergy to ciclesonide or components (non-medicinal ingredients) of study medication
- Lactose Allergy (Type I)
- Known pregnancy
- Currently on inhaled and/or nasal corticosteroids
- Current use of systemic steroids (oral or intravenous or intramuscular such as Prednisone) or use of steroids 7 days prior to enrolment
- Patients with untreated fungal, bacterial, or tubercular infections of the respiratory tract
- One or more doses of any COVID-19 vaccine*

**Added as exclusion on April 7, 2021; prior to that time, however, vaccination was not widely available in Canada.*

Screening Form:

Participants enrolled online at contain-covid-19.com (website no longer active).

Screening form in RedCAP requested the following information:
Date of survey completion
Email
Province of Canada residing in
Tested positive for COVID-19 (yes/no)
Facility tested in
Date of first positive test
Occupation
Age
Biological sex at birth
Whether they had one of the following symptoms: fever, cough, or shortness of breath

A checklist for all symptoms they were currently having which included:

- Dry or hacking cough / Toux sèche
- Wet or loose cough / Toux grasse ou sécrétoire
- Shortness of Breath / Essoufflement
- Chest congestion / congestion thoracique
- Fever/Fièvre
- Chest tightness/ Oppression thoracique
- Body aches or pains/ douleurs ou raideurs corporelles
- Sore or painful throat / Gorge irritée ou mal de gorge
- Weak or Tired / Faiblesse ou Fatigue
- Chills or shivering /Frissons ou tremblements
- Nasal, sinus congestion / Congestion nasale, sinusienne
- Runny or dripping nose/ Écoulement nasal
- Loss of smell / Perte d'odorat
- Loss of taste/ Perte de goût
- Diarrhea/Diarrhées
- Other/Autre
- None/Aucun

Date of first symptoms
An overall visual analogue score of severity of all symptoms (0-10)
A checklist of any exclusion criteria (see above)
A full medication list

***Eligible patients based on the screening form were emailed an Enrolment Form***

Enrolment Form:

The Enrolment Form informed the participant that they appeared to be eligible for the study.

A link containing an attachment (PDF) with the consent form was embedded in the enrolment form.

The participant read and provided an electronic signature if they consented to a part of the study.

Other information collected in the Enrolment Form:

Details:
Name
Telephone contact
Email contact
Emergency contact name, email and telephone
Address, including city and province
Study comprehension questions (5) that were true or false questions related to comprehension of the study (e.g. which days are surveys sent on, whether you are guaranteed to receive the study medication, can you share your study medication etc…)
Participants were asked to upload a copy of their provincial health insurance card as proof of identity.

Other information:
Smoking status
How they rate their overall health prior to COVID-19 diagnosis (very good, good, moderate, bad, very bad)
Date of birth

Ethnicity:

White or Caucasian / Blanc ou Caucasien
Black or African Canadian / Noir ou Afro-Canadien
Asian / Asiatique
Hispanic or Latino / Hispanique ou Latino
Middle Eastern / Moyen-Orient
South Asian / Asiatique du Sud
Other / Autre

Any chronic health conditions:

None / Aucune
High blood pressure / Hypertension artérielle
Diabetes / Diabète
Cardiovascular disease / Maladie cardiovasculaire
Cancer or malignancy / Cancer ou malignité
Chronic kidney disease / Maladie rénale chronique
Asthma / Asthme
Other chronic lung disease /Autres maladies pulmonaires chroniques
Chronic liver disease / Maladie chronique du foie
HIV / VIH
Transplant recipient / Receveur de greffe
Chronic steroids, chemotherapy, or other immunosuppressants / Stéroïdes chroniques, chimiothérapie ou autres immunosuppresseurs
Chronic hepatitis B or C / Hépatite chronique B ou C
Other / Autre

If the patient consented, they were enrolled in the study and randomized to receive either ciclesonide or placebo metered dose inhaler and nasal spray.

Depending on the time of day, the drug was shipped the same day or the following day.
Upon receipt of the study medication (either the same day or the day following enrolment) they participant completed the Day 0 questionnaire prior to initiating the study drug.

Day 0 Questionnaire:

The Day 0 Questionnaire asks the participant: (completed prior to starting the study medication)

- Do you have any symptoms today?
- When was the last day you had symptoms?
- If yes, to rate the overall severity on a visual analogue scale (0-10)
- A checklist of all symptoms they were having that day
- A measure of dyspnea severity if present (visual analogue scale 0-10)
- A measure of cough severity if present (visual analogue scale 0-10)
- The PROMIS sleep disturbance questionnaire
- The PROMIS emotional distress-anxiety questionnaire

Days 1, 3, 7, 10 and 14 and 29 Questionnaires: (completed after starting the study medication)

- Asks the participant to compare how they are feeling compared to when they started the study:

Very much improved/Énormément mieux
Much improved/Beaucoup mieux
Minimally improved/Un peu mieux
No change/Pas de changemnet
Minimally worse/Un peu plus mal
Much worse/Beaucoup plus mal
Very much worse/Énormément plus mal

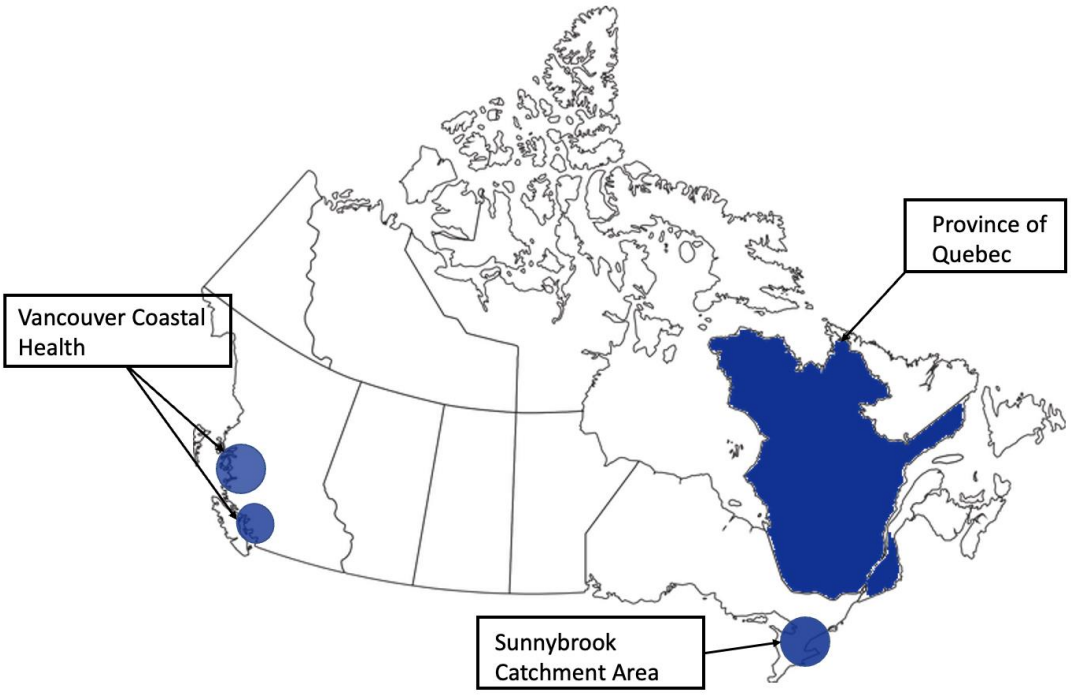
- Confirms they received the study medication
- Confirms that they started taking the study inhaler and the study nasal spray and subsequently that they are taking them on the day of the other questionnaires
- Confirms the medication start date

- Asks for an overall symptom visual analogue scale (0-10)


- A checklist of all symptoms that day
- A visual analogue scale for cough
- PROMIS sleep and anxiety questionnaires
- Whether there are any side effects from the medication (and to list these)
- Whether they were hospitalized or whether there were any adverse events

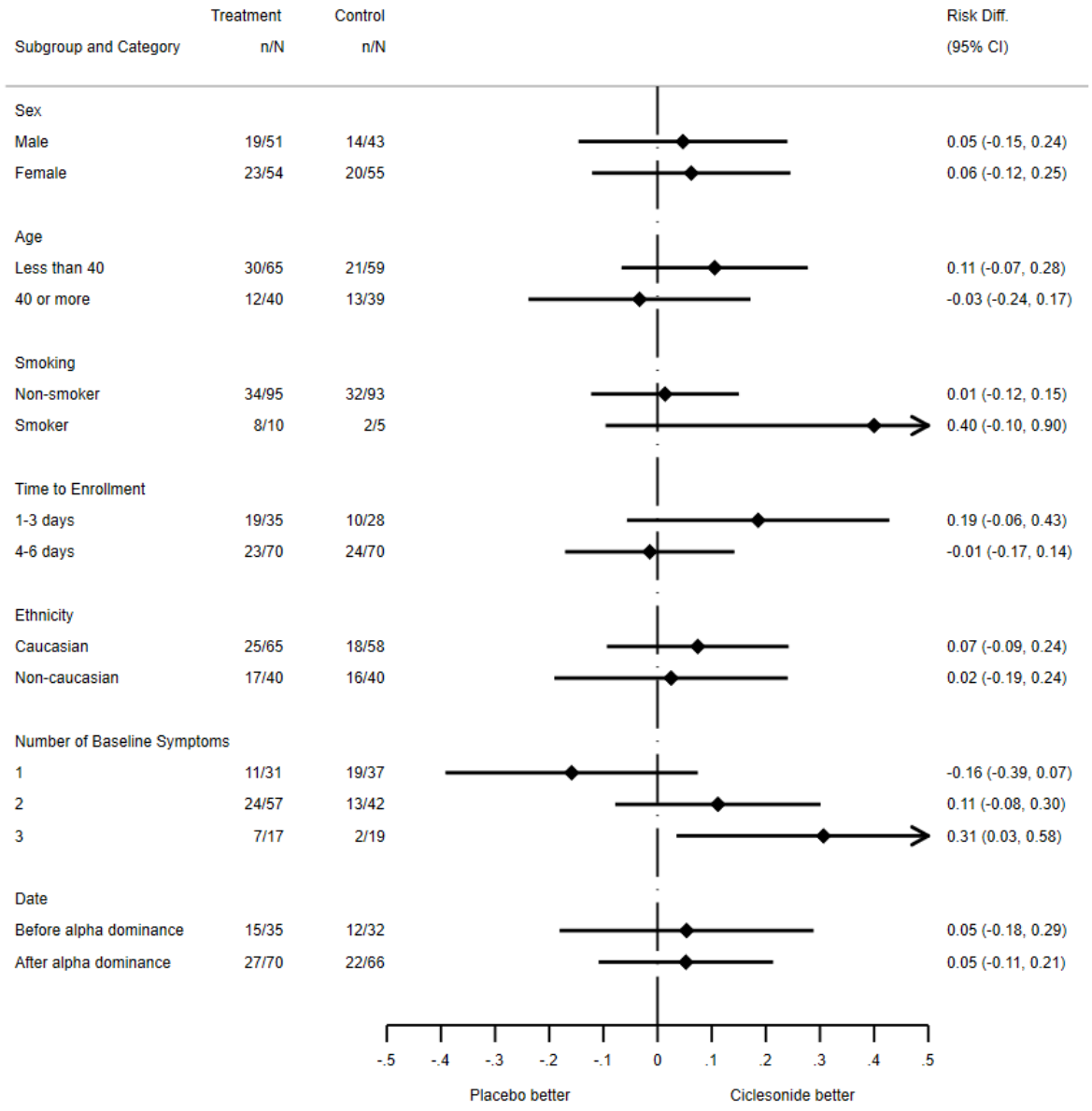
Section B: Geographic sites/regions included in the study

Supplemental Figure S1: Map of Recruitment Regions Across Canada



Section C: Supplemental Analysis- Subgroups

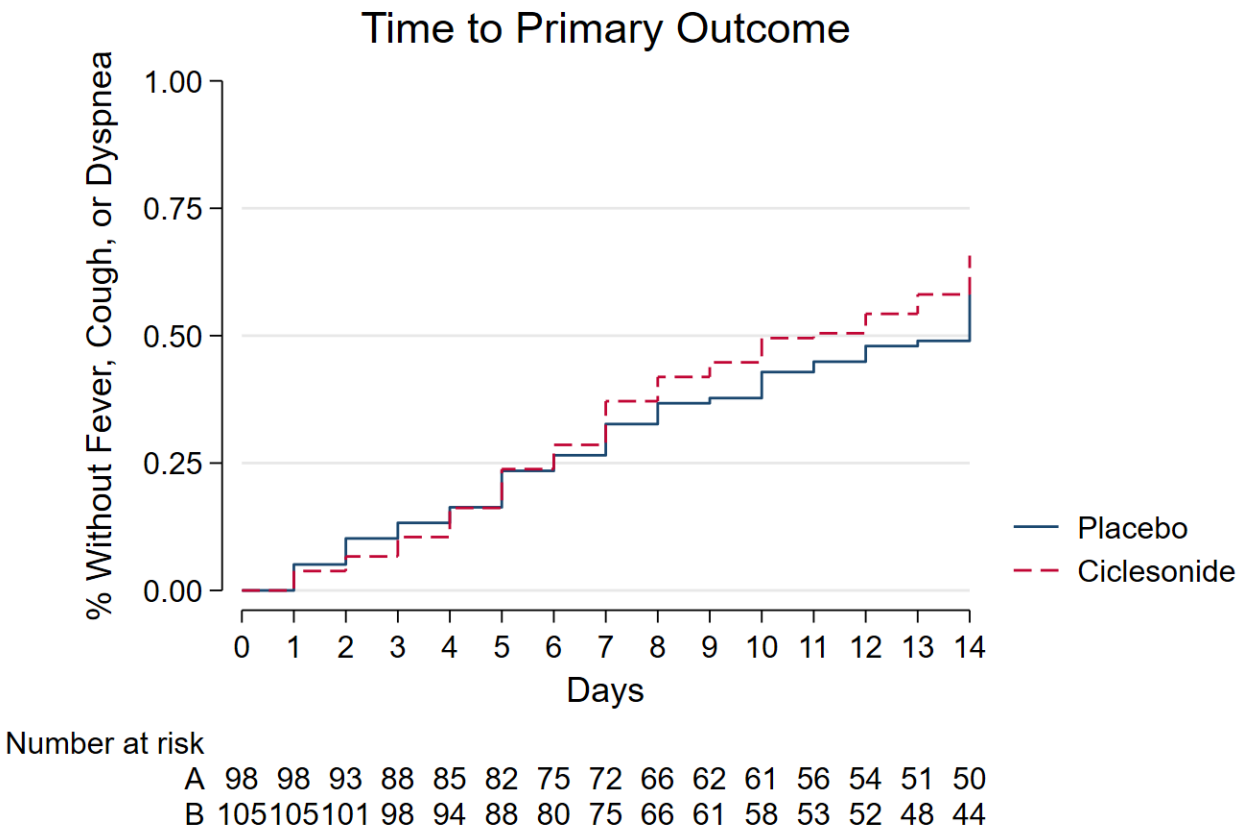
Supplemental Figure S2: Analysis of the Primary Outcome of Respiratory Symptom Resolution by Treatment Assignment and by Subgroup




*Respiratory symptoms were defined as shortness of breath, chest congestion, or chest tightness and were analyzed at Day 7 (the primary outcome)*

Section D: Supplemental analysis- Time to symptom resolution

Supplemental Figure S3: Time to Resolution of Respiratory Symptoms to Day 14




*Respiratory symptoms were defined as shortness of breath, chest congestion, or chest tightness and were analyzed to Day 14 (a secondary outcome). This was a post-hoc analysis.*

Supplementary analyses perfomed at the request of the Reviewers and the Journal Statistician:

Supplemental Table S1

Sensitivity Analysis: Adjustment for Sex and Province of Enrolment:

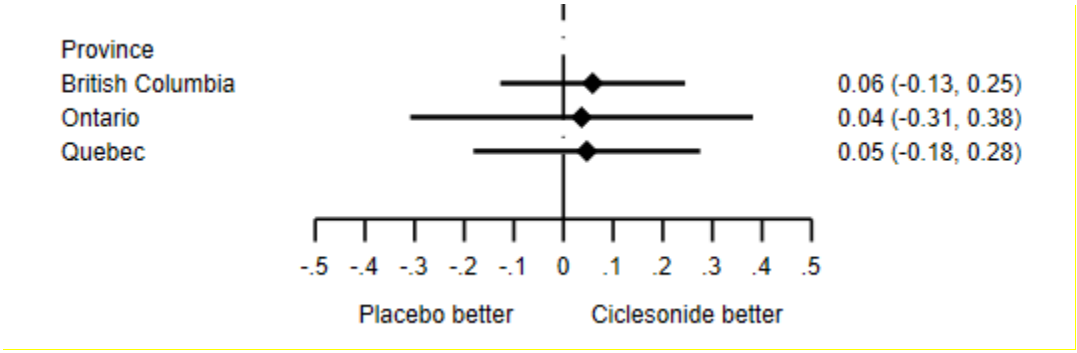
| Factor Adjusted For | Risk Difference | 95% Confidence Interval |
|---|---|---|
| Sex (male) | -0.04 | -0.08 to 0.19 |
| Province | | |
| Quebec (reference) | ------ | ------ |
| British Columbia | -0.01 | -0.16 to 0.14 |
| Ontario | -0.3 | -0.18 to 0.23 |

Supplemental Table S2

Sensitivity Analysis: Adjustment for Sex, Province of Enrolment, Age and Baseline Number of Symptoms

| Factor Adjusted For | Risk Difference | 95% Confidence Interval |
|---|---|---|
| Sex (male) | -0.03 | -0.05 to 0.21 |
| Province | | |
| Quebec (reference) | ----- | ----- |
| British Columbia | -0.03 | -0.18 to 0.12 |
| Ontario | -0.05 | -0.15 to 0.25 |
| Age | -0.004 | -0.01 to 0.001 |
| Baseline number of symptoms (cough, fever and dyspnea) | | |
| 1 symptom (reference) | ----- | ----- |
| 2 symptoms | -0.09 | -0.24 to 0.06 |
| 3 symptoms | -0.2 | -0.39 to -0.01 |
| Overall | -0.08 | -0.05 to 0.21 |

Supplemental Figure S4: Subroup Analysis by Province Presented as a Forest Plot



Section E: Adverse Events and Safety Analysis

Supplemental Table S3: Adverse Event and Safety Analysis of Placebo vs. Ciclesonide for the Safety Analysis Population

| Adverse Event (N=209)* | Placebo (N=103) N (%) | Ciclesonide (N=106) N (%) |
|---|---|---|
| Any adverse event (N=22) | 10 (9.7) | 12 (11.3) |
| Serious adverse events (N=12)** | 5 (4.9) | 7 (6.6) |
| Hospitalization | 3 (2.9) | 6 (5.7) |
| Emergency department or urgent care visit | 2 (1.9) | 1 (0.9) |
| Side effect leading to study drug discontinuation (N=10)*** | 5 (4.9) | 5 (4.7) |
| Throat/nose dryness | 0 (0) | 1 (0.9) |
| Severe headache | 1(1) | 1 (0.9) |
| Loss of smell | 1 (1) | 1 (0.9) |
| Severe nausea | 1 (1) | 1 (0.9) |
| Voice change | 1 (1) | 0 (0) |
| Persistent cough | 0 (0) | 1 (0.9) |
| Worsening shortness of breath | 1 (1) | 0 (0) |

**The safety population was N=209 (includes 6 more participants than the mITT as some participants contacted the study team directly to report a side effect after one dose of the study drug that led to study drug discontinuation, but never completed any surveys related to primary outcome of symptom resolution).*

***All 12 serious adverse events were related to seeking care for COVID-19; none were related to the study drug.*

****Of the 10 people who stopped the study medication due to severe side effects, in the placebo group, 3 of 5 were probably related to the study drug (headache, nausea, voice change) and 2 of 5 were unlikely related to the placebo (loss of smell and worsening shortness of breath). For ciclesonide, 3 of 5 were possibly related to the study drug (nausea, headache, throat dryness) and 2 of 5 were unlikely related to the study medication (persistent cough and loss of smell).*

Section F: PROMIS Anxiety and Sleep questionnaires

Supplemental Table S4: PROMIS Anxiety and Sleep Questionnaires Comparing Placebo vs. Ciclesonide

| **Anxiety 7a - Anxiety/Fear** | **Placebo** | **Ciclesonide** | **Adjusted Risk Difference** |
|---|---|---|---|
| | **(n=95)** | **(n=101)** | **% (95% CI)** |
| Baseline T-Score (Median, IQR) | 58.9 (53-63.9) | 57.6 (50.5-62.7) | -- |
| Completed Day 7 Assessment | **(n=92)** | **(n=96)** | |
| Day 7 T-Score (Median, IQR) | 47.4 (36.3-53.3) | 47.1 (36.3-53) | -- |
| Improved by at least 3 from baseline | 68 (73.9) | 69 (71.9) | -0.6% (-13.2% to 12.0%) |
| Completed Day 14 Assessment | **(n=91)** | **(n=95)** | |
| Day 14 T-Score (Median, IQR) | 45.4 (36.3-53.6) | 36.3 (36.3-50.3) | -- |
| Improved by at least 3 from baseline | 72 (79.1) | 79 (83.2) | 3.9% (-7.2% to 15.2%) |
| **Sleep Disturbance 4a** | **(n=95)** | **(n=101)** | |
| Baseline T-Score (Median, IQR) | 53 (43.8-57.5) | 52.7 (44.7-58.6) | -- |
| Completed Day 7 Assessment | **(n=92)** | **(n=96)** | |
| Day 7 T-Score (Median, IQR) | 47.1 (41.2-52.75) | 46.4 (41.2-53.9) | -- |
| Improved by at least 3 from baseline | 53 (57.6) | 52 (54.2) | -2.3% (-16.6% to 11.9%) |
| Completed Day 14 Assessment | **(n=94)** | **(n=94)** | |
| Day 14 T-Score (Median, IQR) | 44.5 (38.4-51.3) | 43.5 (37.1-51.1) | -- |
| Improved by at least 3 from baseline | 53 (56.4) | 60 (63.8) | 7.3% (-6.6% to 21.2%) |

Section G: PROMIS Dyspnea scores

The PROMIS dyspnea (severity and characteristic) scores didn't contain sufficient usable data for analysis. Summarized below is a qualitative description of the results.

- Only a subset of participants reported shortness of breath at baseline (57/203 or 28.1%).
- The PROMIS dyspnea scores were only offered to people who self-reported "shortness of breath" at baseline (and not to those who reported chest congestion or chest tightness, which we also included in a composite symptom we called "dyspnea".)
- Among those who reported shortness of breath at enrolment, the symptom resolved in many participants early on (~50% of those who reported shortness of breath on enrolment resolved by day 3).
- In total there were only 102 dyspnea scores collected across all participants and all surveyed days.
- The PROMIS dyspnea severity questionnaire (which asks about 10 different circumstances under which someone may have experienced shortness of breath) was not incomplete on many surveyed days.
- There were only 40 instances where the measure was complete (all 10 items).
- From these responses, many people omitted responses to higher order questions (e.g., sweeping, making the bed, or carrying groceries). This may have been because they did not feel well enough to participate in these tasks, or related to isolation/confinement, whereby many of these tasks were possibly not accessible (e.g., walking faster than their usual speed for half a mile without stopping).
- The PROMIS Dyspnea characteristic scores also didn't contain enough data to analyze, as again, there were only 102 total scores collected across the entire study. For those with resolved shortness of breath, we did not offer the option to complete the survey to force a response that dyspnea was resolved.
- This lack of response likely reflects scores that were not filled out by participants' whose shortness of breath had resolved, leaving a very small denominator for analysis that the study investigators did not consider stable enough for analysis.

Section H: Treatment Guess

Supplemental Table S5: Treatment Guess by Treatment Assignment of Placebo vs. Ciclesonide

| **Treatment Guess** | **Placebo** | **Ciclesonide** |
|---|---|---|
| | **(n=90)** | **(n=97)** |
| Not sure | 40 (44.4) | 42 (43.3) |
| Placebo | 24 (26.7) | 24 (24.7) |
| Ciclesonide | 26 (28.9) | 31 (32.0) |

*On Day 14 participants were asked to guess whether they had been receiving ciclesonide or placebo.*

Section I: Last Survey Carried Forward, the mITT Population and Adherence

Last survey carried forward:

- 9 patients had survey results inferred on day 7.
    - 2/9 of these patients were hospitalized and were still symptomatic on day 14 so we believe this inference is legitimate;
    - 6/9 were already symptomatically resolved when they stopped the medication and filled out their last surveys prior to day 7 indicating that their symptoms had completely resolved.
    - 1/9 participants didn't complete the entire day 7 survey, but did report they were still coughing (still symptomatic on day 7).
- Each of these participants were included in the mITT.

Regarding the PRISMA diagram:

- 2 participants had no outcome data (1 who took 1 dose and 1 who took no doses) in the ciclesonide group.
- 6 participants had no outcome data (3 who took 1 dose and 3 who took no doses) in the placebo group.
- As there was no outcome data for these participants they could not be included in the mITT
- 3 participants withdrew and so we are not permitted to use their data (all in the placebo group).

Adherence:

- We defined adherence as taking the study medication on at least 3 of the 4 days surveyed. Adherence was high and similar between groups as we defined it (92-94%).