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Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064374
Article Type:	Original research
Date Submitted by the Author:	05-May-2022
Complete List of Authors:	<p>Brodin, Daniel; Capio Sankt Görans Sjukhus Tornhammar, Per; Karolinska Institute, Functional Area of Emergency Medicine Ueda, Peter; Karolinska Institutet Krifors, Anders; Karolinska Institutet, Department of Physiology and Pharmacology; Västmanlands sjukhus Västerås Westerlund, Eli; Danderyd University Hospital, Department of Clinical Sciences Athlin, Simon; Örebro University Wojt, Sandra; Danderyd University Hospital, Department of Internal Medicine Elvstam, Olof; Central Hospital Växjö, Department of Infectious Diseases Neumann, Anca; Capio Sankt Görans Sjukhus Elshani, Arsim; Karlskoga Hospital Giesecke, Julia; Karolinska Universitetssjukhuset Edvardsson-Källkvist, Jens; Karolinska University Hospital Bunpuckdee, Sayam; Karolinska Institutet Unge, Christian; Danderyd University Hospital, Department of Internal Medicine Larsson, Martin; Karolinska Institutet Department of Clinical Science and Education Sodersjukhuset Johansson, Björn; Halland County Ljungberg, Johan; Halland County Lindell, Jonas; Visby Hospital, Department of Infectious Diseases Hansson, Johan; Östersund Hospital, Department of Infectious Diseases Blennow, Ola; Karolinska University Hospital, Department of Infectious Diseases Andersson, Daniel Peter; Karolinska University Hospital, Department of Medicine Huddinge H7, Karolinska Institutet; Karolinska Institute, Medicine (H7)</p>
Keywords:	COVID-19, Clinical trials < THERAPEUTICS, Respiratory infections < THORACIC MEDICINE

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Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

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8 Word count: 3002
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11 Abstract word count: 244
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For peer review only

Abstract

Objective: To assess the efficacy of ciclesonide in reducing the duration of oxygen therapy (an indicator of time to clinical improvement) among adults hospitalized with Covid-19.

Design: Multicenter, randomized, controlled, open-label trial.

Setting: 9 hospitals (3 academic hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May 17, 2021.

Participants: Adults hospitalized with Covid-19 and receiving oxygen therapy.

Intervention: Ciclesonide 320 µg twice daily for 14 days versus standard care.

Main outcome measures: Primary outcome was duration of oxygen therapy, an indicator of time to clinical improvement. Key secondary outcome was a composite of invasive mechanical ventilation/death.

Results: Data from 98 participants were analyzed (48 receiving ciclesonide and 50 receiving standard care; median (IQR) age, 59.5 (49-67) years; 67 (68%) male). Median (IQR) duration of oxygen therapy was 5.5 (3-9) days in the ciclesonide group and 4 (2-7) days in the standard care group (hazard ratio (HR) for termination of oxygen therapy 0.73 (95% CI 0.47-1.11), with the upper 95% CI being compatible with a 10% relative reduction in oxygen therapy duration, corresponding to a <1-day absolute reduction). Three participants in each group died/received invasive mechanical ventilation (HR 0.90 (95% CI 0.15-5.32)). The trial was discontinued early due to slow enrollment.

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3 **Conclusions:** In hospitalized Covid-19 patients receiving oxygen therapy, this trial
4 ruled out, with 0.95 confidence, a treatment effect of ciclesonide corresponding to
5 more than a one-day reduction in duration of oxygen therapy. Ciclesonide is unlikely
6 to improve this outcome meaningfully.
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16 **Strengths and limitations of this study**

- 17 • This was a multicenter, randomized, controlled, open-label trial comparing
18 treatment with the inhaled corticosteroid ciclesonide 320 µg twice daily for 14
19 days versus standard care.
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- 21 • While inhaled corticosteroids have been assessed among non-hospitalized
22 patients with Covid-19, data from studies on hospitalized Covid-19 patients
23 with more severe disease are scarce.
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- 25 • The trial was terminated early due to slow recruitment. Healthcare providers
26 and participants were not blinded to treatment assignment.
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Introduction

Patients with Covid-19 can develop acute respiratory failure that may require invasive mechanical ventilation, associated with high mortality. The unregulated inflammation in the lungs, poor oxygenation and pulmonary infiltrates characterizing severe Covid-19 have been considered as a type of acute respiratory distress syndrome (ARDS).[1, 2]

Prior to the Covid-19 pandemic, studies have indicated that inhaled corticosteroids may reduce the risk of ARDS. In a randomized controlled trial including 61 patients at risk of ARDS, none of the patients assigned to aerosolized budesonide/formoterol vs 7 assigned to placebo developed ARDS,[3] and 6 (20%) and 16 (53%) of the patients, respectively, received mechanical ventilation. In another trial including 60 patients with acute lung injury or ARDS, nebulized budesonide improved oxygenation and peak and plateau airway pressures, and reduced inflammatory markers.[4] Moreover, potentially protective and preventive effects of inhaled corticosteroids for ARDS is supported by animals models of lung injury,[5-8] and *in vitro* studies.[9]

Therefore, it could be hypothesized that inhaled corticosteroids may be beneficial for patients with severe Covid-19. The hypothesis is further supported by reports that inhaled corticosteroids reduce the epithelial expression of genes linked to SARS-CoV-2 entry into host cells.[10, 11] Among the inhaled corticosteroids, ciclesonide has been identified as a particularly promising treatment as it can suppress replication of SARS-CoV-2 *in vitro*. [12, 13]

While previous randomized controlled trials have assessed the effects of inhaled budesonide[14, 15] or ciclesonide[16, 17] in non-hospitalized Covid-19 patients, no study has been performed in hospitalized patients with more severe Covid-19.

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3 This open-label randomized controlled trial investigated the effects of inhaled
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5 ciclesonide, compared to standard care, in adult patients hospitalized with Covid-19
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7 and requiring oxygen therapy.
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10 11 12 13 **Methods**

14 15 16 *Study design*

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21 The HALT Covid-19 (inHALation of ciclesonide for Treatment of Covid-19) trial was a
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23 multicenter, open-label randomized controlled trial to assess the efficacy and safety
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25 of inhaled ciclesonide for the treatment of hospitalized patients with Covid-19
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27 receiving oxygen therapy. The trial was conducted at 9 hospitals (3 academic
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29 hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May
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31 17, 2021.
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37 All participants provided written informed consent. The study was approved by the
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39 Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the
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41 Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and
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43 registered at clinicaltrials.gov (NCT04381364).
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46 47 48 *Protocol changes and rationale*

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53 The trial was designed in the beginning of the Covid-19 pandemic. After trial initiation,
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55 treatments for, and hospitalization rates of, patients with Covid-19 changed rapidly.
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57 Therefore, we made protocol changes (described in detail in the Online Appendix)
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59 and the trial was stopped early.
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5 In brief, we increased the number of study centers, removed the upper age limit (≤ 85
6 years) for patient inclusion, changed the inclusion criteria from ≤ 48 hours since
7 hospital admission to ≤ 48 hours from initiation of oxygen therapy and allowed for
8 patients to be included on the basis of a positive antigen test for SARS-Cov-2. All
9 changes were approved by the Data Monitoring Committee, Ethical Review Authority
10 and the Swedish Medical Products Agency and implemented from December 2020.
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21 In June 2021, 99 patients had been included in the study, a large and increasing
22 proportion of the adult Swedish population had received Covid-19 vaccination and
23 hospitalizations for Covid-19 had dropped substantially. We determined that it was
24 unlikely that the intended sample size would be reached and asked the Data
25 Monitoring Committee to convene for a meeting. Following the recommendation of
26 the Data Monitoring Committee, the study was terminated for futility to meet the
27 targeted enrolment.
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41 *Participants*

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44 Based on observations from Covid-19 patients treated at the study centers, we
45 expected that 85% of the standard care group would survive and terminate oxygen
46 therapy within 30 days (median 8 days). We considered a 25% (2 days) reduction in
47 the duration of oxygen therapy to be a clinically meaningful effect. We estimated that
48 such an effect could be detected with α of 0.05, and 80% power if 446 participants
49 (223 in each group) were enrolled.
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3 Participants were eligible for inclusion if, they (1) were aged ≥ 18 years, (2) had a
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5 polymerase chain reaction confirmed SARS-CoV-2 infection or a positive SARS-CoV-
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7 2 antigen test from the upper respiratory tract, (3) were hospitalized at any of the
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9 study hospitals and (4) were receiving oxygen therapy, initiated within 48 hours
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11 before inclusion. Key exclusion criteria were ongoing treatment with inhaled or oral
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13 corticosteroids, oxygen therapy with >8 L oxygen/min or >50 % oxygen on nasal
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15 high-flow cannula, and ongoing or expected intensive care or palliative care (Online
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17 Appendix).

21 22 23 *Randomization*

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25 Patients were randomized 1:1 in blocks of 8, stratified by sex and hospital to receive
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27 ciclesonide or standard care. The randomization sequence was prepared by a
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29 statistician not involved in the trial. Treatment allocation was provided through a web-
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31 based interface. The participants and the physicians treating them were unblinded to
32
33 the treatment assignment.

34 35 36 37 38 39 *Intervention*

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42 The treatment was 320 μg of inhaled ciclesonide (80 μg per actuation, for a total of 4
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44 actuations, or 160 μg per actuation, for a total of 2 actuations) twice daily (total daily
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46 dose 640 μg) for 14 days. Ciclesonide was administered using a spacer (L'espace,
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48 Nordic Infucare, Stockholm Sweden). Participants randomized to ciclesonide
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50 received written instructions, including pictures, and practical instructions on how to
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52 use the inhalator and spacer; the first dose was taken under supervision. Ciclesonide
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54 was then prescribed in the participant's electronic medical record and each given
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56 dose during the hospitalization was recorded. Participants discharged before day 14
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3 were instructed to continue the treatment at home for a total treatment duration of 14
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5 days. Participants randomized to standard care did not receive any intervention
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7 related to the study. Physicians treating the participants were not given any
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9 restrictions concerning treatments during the study period. Participants who had been
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11 discharged were contacted by telephone after day 30 for a follow-up interview.
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17 *Outcomes*

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21 The primary outcome was duration of oxygen therapy (time to termination of oxygen
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23 therapy in days) up to 30 days from randomization. Oxygen therapy was defined as
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25 terminated on the day after which the patient did not receive oxygen therapy during
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27 at least 48 hours, while being alive. This outcome corresponded to clinical
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29 improvement for patients receiving oxygen therapy according to the World Health
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31 Organization clinical progression scale.[18]
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37 The key secondary outcome was a composite of invasive mechanical ventilation and
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39 death up to 30 days after randomization. Other secondary outcomes were each
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41 component of the key secondary outcome, admission to an intensive care unit,
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43 discharge from the hospital and dyspnea in daily living at 30-35 days after
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45 randomization as evaluated by the mMRC (Modified Medical Research Council)
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47 dyspnea scale. The scale ranges from 0 to 4 with a higher score indicating more
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49 severe dyspnea.[19, 20]
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55 Data on serious adverse events[21] were collected by review of electronic medical
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57 records. Information about non-serious adverse events associated with ciclesonide
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59 use (dryness of mouth, nausea and oral candidiasis) was reported using a paper-
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3 based reporting form which was filled in by the treating physician. Information about
4 non-serious adverse events occurring after hospital discharge was collected during
5 the follow-up interview.
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10 11 12 *Data collection* 13

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16 Patient characteristics at baseline (comorbidities, comedications, clinical parameters)
17 and study outcomes were obtained from electronic medical records. Investigators
18 contacted participants after day 30 after randomization to ask them about non-
19 serious adverse events and dyspnea in daily living (study outcome) at day 30-35 after
20 randomization.
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30 31 *Statistical analysis* 32

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34 According to the pre-specified analysis plan in the study protocol, the analyses were
35 performed by an investigator who had not been involved in the enrolment of
36 participants and was blinded to treatment assignment. An intention-to-treat
37 population was used. In the analysis of the duration of oxygen therapy, participants
38 were followed from randomization to termination of oxygen therapy, death, or 30 days
39 after randomization. Kaplan Meier cumulative incidence curves were generated to
40 illustrate the cumulative incidence of termination of oxygen therapy in the ciclesonide
41 and standard care groups. A Cox proportional hazard regression model, adjusted for
42 study hospital (Appendix Table 1), age (continuous variable) and sex was used to
43 estimate hazard ratios (HR) with 95% CI for time-to-event outcomes. Proportions and
44 the absolute risk difference with 95% CI were presented for binary outcomes.
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60 Subgroup analyses were performed for the primary outcome by sex, age (<70 years

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3 and ≥ 70 years) and duration of Covid-19 symptoms (< 10 days and ≥ 10 days). In a
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5 per-protocol analysis of the primary outcome, participants assigned to ciclesonide
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7 were censored at the time of discontinuing treatment. The median mMRC score was
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9 compared using the Kruskal-Wallis test. A logistic regression model adjusted for
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11 study hospital, age and sex was used to compare the likelihood of reporting a mMRC
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13 score of 0 (dyspnea only with strenuous exercise).
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20 95% CIs of ratios not including 1 and 95% CIs for absolute risk differences not
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22 including 0 were considered statistically significant. Secondary outcome analyses
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24 and subgroup analyses were considered hypothesis-generating and no adjustment
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26 for multiple testing was made. Analyses were performed using Stata version 16.1
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28 (StataCorp).
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36 *Patient and Public involvement*

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38 No patients were involved in setting the research question, nor in the design,
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40 conduct, or interpretation of the study.
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50 **Results**

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52 Of the 99 participants who underwent randomization 48 were assigned to receive
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54 ciclesonide and 51 to standard care (Figure 1). One participant in the standard care
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56 group withdrew consent and was excluded from the analysis. Ninety-eight patients
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58 (48 in the ciclesonide group and 50 in the standard care group) were included in the
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60

final analysis. All participants assigned to ciclesonide received the treatment at least once. None of the participants were lost to follow-up. The median age of participants was 59.5 (IQR 49, 67) years, 68% were men and the median duration of symptoms was 9 (IQR 8, 11) days. There were no relevant between-group differences in demographic characteristics, laboratory test results or comorbidities at enrollment (Table 1).

Table 1 Demographic and clinical characteristics of participants at study enrolment.

	Total (n=98)	Ciclesonide (n=48)	Standard care (n=50)
Age, median (IQR)	59.5 (49, 67)	61 (49, 67)	59 (49, 67)
Men, n (%)	67 (68)	34 (71)	33 (66)
Days since symptom onset, median (IQR)	9 (8, 11)	9 (7.5, 11.5)	10 (8, 11)
Body mass index in kg/m ² , median (IQR)	29.7 (25.6, 34.0)	28.7 (25.4, 34.0)	30.6 (26.8, 34.3)
Oxygen flow of oxygen therapy in L/min, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 2)
Respiratory rate per minute, median (IQR)	20 (18, 24)	20 (19, 25)	20 (18, 23)
C-reactive protein in mg/L, median (IQR)	100 (56, 142)	103 (62, 164)	91.5 (45.5, 124.5)
White cell count in x 10 ⁹ /L, median IQR	5.7 (4.5, 7.0)	5.3 (4.3, 6.9)	6.1 (4.9, 7.0)
eGFR in mL/min/1.73m ² , median (IQR)	83 (70.5, 90)	81.5 (70, 90)	87 (73, 90)
Coexisting conditions, n (%)			
Diabetes mellitus	18 (18)	8 (17)	10 (20)
Hypertension ^a	45 (46)	22 (46)	23 (46)
Hyperlipidemia ^b	27 (28)	12 (25)	15 (30)
Chronic obstructive lung disease	3 (3)	1 (2)	2 (4)
Asthma	8 (8)	6 (13)	2 (4)
Current smoker	12 (12)	6 (13)	6 (12)
Ischemic heart disease	8 (8)	2 (4)	6 (12)
Heart failure	3 (3)	2 (4)	1 (2)
Atrial fibrillation	5 (5)	3 (6)	2 (4)

Cancer	10 (10)	5 (10)	5 (10)
Chronic kidney disease	9 (9)	5 (10)	4 (8)

^a Diagnosis of hypertension or use of antihypertensive drugs

^b Diagnosis of hyperlipidemia or use of lipid lowering therapy

Missing values were: n=1 for days since symptom onset, n=20 for body mass index, n=1 for oxygen flow of oxygen therapy, n=1 for body temperature, n=1 for heart rate, n=3 for respiratory rate, n=3 for C-reactive protein, n=7 for white cell count and n=22 for eGFR.

eGFR: estimated glomerular filtration rate

The results of primary and secondary outcome analyses are presented in Table 2.

Kaplan-Meier estimates of the median duration of oxygen therapy were 5.5 (IQR 3, 9) days in the ciclesonide group and 4 (2, 7) days in the standard care group. (Figure 2).

The HR for termination of oxygen therapy used to compare ciclesonide vs standard care showed that ciclesonide treatment was not statistically significantly associated with the duration of oxygen therapy (0.73 (95% CI 0.47 to 1.11)). The upper limit of the 95% CI was compatible with a maximum relative reduction^[22] in duration of oxygen therapy of 10% (1-1/1.11) with ciclesonide, corresponding to a <1 day absolute reduction. In the per-protocol analysis, the HR for termination of oxygen therapy was 0.79 (95% CI 0.51 to 1.23) (Table 2).

Table 2 Outcomes.

	Ciclesonide	Standard care	Difference ^a
Primary outcome			
Duration of oxygen therapy, median (IQR) days	5.5 (3, 9)	4 (2, 7)	0.73 (0.47 to 1.11)
Key secondary outcome			
Death or invasive mechanical ventilation, n (%)	3 (6)	3 (6)	0 (-9 to 10)

Time to death or invasive mechanical ventilation, median (IQR) days	2 (2, 10)	4 (2, 7)	0.90 (0.15 to 5.32)
Secondary outcomes			
Death, n (%)	2 (4)	1 (2)	-
Invasive mechanical ventilation, n (%)	1 (2)	3 (6)	-
Admission to an intensive care unit, n (%)	4 (8)	4 (8)	-
mMRC dyspnea scale score at day 30-35, median (IQR) ^b	3 (2, 4)	3 (2, 4)	0.97
mMRC dyspnea scale score 0 at day 30-35, n (%) ^b	4 (9)	7 (15)	0.48 (0.11 to 2.04)
Subgroup analyses^c			
<i>Sex: Men</i>			
Duration of oxygen therapy, median (IQR) days	5.5 (3, 9)	5 (2, 7)	0.61 (0.36 to 1.05)
<i>Sex: Women</i>			
Duration of oxygen therapy, median (IQR) days	5.5 (2, 7)	4 (2, 8)	0.91 (0.41 to 2.01)
<i>Age group: <70 years</i>			
Duration of oxygen therapy, median (IQR) days	5 (3, 7)	4 (2, 7)	0.77 (0.48 to 1.23)
<i>Age group: ≥70 years</i>			
Duration of oxygen therapy, median (IQR) days	9 (5, 10)	6 (5, 8)	0.37 (0.08 to 1.78)
<i>Days since symptom onset: <10 days</i>			
Duration of oxygen therapy, median (IQR) days	7 (3, 10)	4 (2, 5)	0.54 (0.28 to 1.03)
<i>Days since symptom onset: ≥10 days</i>			
Duration of oxygen therapy, median (IQR) days	5 (3, 6)	5 (3, 8)	0.97 (0.48 to 1.94)
Per protocol analysis^d			
Duration of oxygen therapy, median (IQR) days	5 (3, 9)	4 (2, 7)	0.79 (0.51 to 1.23)

^a. Differences are expressed as hazard ratios (95% CI) estimated using a Cox proportional hazards model for time to event outcomes and as absolute risk difference (95% CI) in percent for outcomes of absolute risk. The comparison of the mMRC dyspnea score was done using the Kruskal-Wallis test and the difference is expressed as a p-value. The comparison of the likelihood of reporting a mMRC score of 0 was done using a logistic regression model and the difference is expressed as an odds ratio (95% CI). Statistical testing for differences in proportions and time-to-event analyses were not performed for the secondary outcome events, including death, invasive mechanical ventilation, and admission to an intensive care unit due to few events.

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3 ^b. Not including 1 participant in the standard care group and 2 participants in the ciclesonide group who died within
4 30 days of randomization and 1 participant in the standard care group and 1 participant in the ciclesonide group with
5 missing data on this outcome.
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9 ^c. The subgroup analyses included n=33 in the standard care group and n=34 in the ciclesonide group for men, n=17 in
10 the standard care group and n=14 in the ciclesonide group for women, n=41 in the standard care group and n=37 in
11 the ciclesonide group for those aged <70 years, n=9 in the standard care group and n=11 in the ciclesonide group for
12 those aged ≥70 years, n=24 in the standard care group and n=27 in the ciclesonide group for those with <10 days
13 since symptom onset, and n=25 in the standard care group and n=21 in the ciclesonide group for those with ≥10 days
14 since symptom onset. 1 participant had missing data on days since symptom onset and was not included in the
15 subgroup analysis.
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22 ^d. In the per-protocol analysis for duration of oxygen therapy, patients assigned to ciclesonide were censored at the
23 time of discontinuing treatment.
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29 In total, 3 (6%) participants assigned to ciclesonide and 3 (6%) participants assigned
30 to standard care experienced the key secondary outcome of mechanical invasive
31 ventilation or death (absolute difference 0% (95% CI -10 to 9%; HR 0.90 (95% CI
32 0.15 to 5.32)). Median mMRC dyspnea score at 30-35 days after randomization was
33 3 (IQR 2, 4) in both groups (p-value for difference 0.97) (Table 2).
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43 There were no statistically significant differences between those assigned to
44 ciclesonide vs standard care in the primary outcome in any of the subgroup analyses
45 by sex, age (<70 years and ≥70 years) and days since symptom onset (<10 days and
46 ≥10 days) (Table 2).
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56 There were no apparent differences between the groups in treatments that
57 participants received after randomization (Table 3); 26 (54%) of the participants
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3 assigned to ciclesonide and 22 (44%) of the participants in the standard care group
4
5 received treatment with systemic corticosteroids after randomization.
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11 Few serious adverse clinical events occurred during the study. The most frequently
12 reported adverse event was dry mouth (7 (15%) participants in the ciclesonide group
13 and 11 (22%) participants in the standard care group). Two participants assigned to
14 ciclesonide and 0 in the placebo group reported that they experienced oral
15 candidiasis (Table 3).
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26 **Table 3** Participants' treatments and adverse clinical events through day 30 after
27 randomization.
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	Ciclesonide (n=48)	Standard care (n=50)
Received treatment, n (%)		
Systemic corticosteroids	26 (54)	22 (44)
Remdesivir	4 (8)	5 (10)
Low-molecular-weight heparin	45 (94)	45 (90)
Oral anticoagulants	32 (67)	30 (60)
Vasopressors	4 (8)	3 (6)
Non-invasive mechanical ventilation	8 (17)	7 (14)
Serious clinical events, n (%)		
Renal failure	2 (4)	3 (6)
Cardiac arrest	1 (2)	0 (0)
New onset atrial fibrillation	0 (0)	1 (2)
Pulmonary embolism	4 (8)	2 (4)
Other thromboembolic events	0 (0)	1 (2)

Sepsis	3 (6)	2 (4)
Other serious event	1 (2)	0 (0)
Non-serious adverse events, n (%)		
Nausea	6 (13)	8 (16)
Dry mouth	7 (15)	11 (22)
Oral candidiasis	2 (4)	0 (0)
Other non-serious adverse event	3 (6)	1 (2)

Some pre-specified analyses were not performed due to small sample size or low number of events. These included statistical testing of differences in proportions and time-to-event analyses for non-key secondary outcomes, including death, invasive mechanical ventilation, and admission to an intensive care unit; the secondary outcome analyses of discharge from hospital; subgroup analyses for the secondary outcomes, and the primary outcome analysis after exclusion of participants who received invasive mechanical ventilation or died.

Discussion

In this randomized open-label, controlled trial, including 98 hospitalized Covid-19 patients with ongoing oxygen therapy, treatment with inhaled ciclesonide did not result in a statistically significant reduction in the duration of oxygen therapy, used as a measure of time to clinical improvement. The trial ruled out, with 0.95 confidence, treatments effects of ciclesonide corresponding to more than a one-day reduction in duration of oxygen therapy.

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3 While previous randomized controlled trials have assessed effects of inhaled
4 corticosteroids, including budesonide[14, 15] and ciclesonide[16, 17], in non-
5 hospitalized patients with Covid-19, this is the first trial that includes hospitalized
6 patients with more severe forms of the disease. In contrast to our hypothesis, the
7 median duration of oxygen therapy was nominally longer among patients assigned to
8 ciclesonide vs standard care (5.5 vs 4 days; HR for termination of oxygen therapy
9 0.73 (95% CI 0.47 to 1.11)). As such, the 95% CI indicates that,[22] even in the best
10 case, ciclesonide may reduce the duration of oxygen therapy with only 10% (1-
11 1/1.11; less than 1 day in our study) while it may in the worst case result in an over 2-
12 fold increase. Thus, the results of this trial indicate that ciclesonide is unlikely to
13 provide a clinically meaningful beneficial effect on the duration of oxygen therapy in
14 hospitalized Covid-19 patients receiving oxygen therapy.

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33 To date, 2 randomized controlled trials of ciclesonide in non-hospitalized patients with
34 Covid-19 have been presented. In the CONTAIN study,[16] which was terminated
35 early due to slow recruitment, 215 non-hospitalized patients with a median of 3 days
36 symptom duration were randomized to combination treatment with intranasal and
37 inhaled ciclesonide or placebo. No statistically significant difference between the
38 groups was observed for the primary endpoint, resolution of respiratory symptoms at
39 day 7 after randomization, which was reached by 40% of the patients in the treatment
40 group vs 35% in the placebo group (adjusted risk difference of 5.5% (95% CI -7.8%
41 to 18.8%).[16] Six (6%) patients assigned to ciclesonide vs 3 (3%) in the placebo
42 group were hospitalized within 14 days; none died. In another clinical trial of
43 ciclesonide, including 400 non-hospitalized patients with Covid-19,[17] randomization
44 to ciclesonid vs placebo did not result in a reduced time to alleviation of all Covid-19
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3 related symptoms. However, in secondary outcome analyses, patients assigned to
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5 ciclesonide had fewer emergency department visits or hospital admissions for
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7 reasons related to COVID-19 (odds ratio, 0.18, 95% CI, 0.04 to 0.85).
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12 In addition, 2 randomized clinical trials of the inhaled corticosteroid budesonide in
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14 non-hospitalized patients with Covid-19 have been presented. The STOIC trial was
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16 an open-label trial comparing inhaled budesonide vs standard care in 146 Covid-19
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18 patients with mild symptoms.[14] Compared to standard care, budesonide treatment
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20 led to a statistically significant reduction in Covid-19-related emergency department
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22 assessment and hospitalization (difference in proportions 0.123 (95% CI 0.043 to
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24 0.218).[14] Furthermore, budesonide treatment was associated with 1 day shorter
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26 time to clinical recovery. The PRINCIPLE trial was another open-label trial that
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28 included 4700 primary care patients at high risk of developing severe Covid-19 (1073
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30 randomized to budesonide treatment; 1988 to standard care; 1639 to other
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32 treatments).[15] Compared to standard care, randomization to budesonide led to a
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34 shorter time to self-reported recovery (difference 2.94 days (95% Bayesian credible
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36 interval 1.19 to 5.12) and a reduced likelihood of hospital admission or death,
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38 although the results for the latter outcomes did not meet the superiority threshold.
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47 Taken together, the previous studies indicate that inhaled corticosteroids might be
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49 useful for preventing deterioration of Covid-19 in non-hospitalized patients with mild
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51 symptoms. It is possible that the low likelihood of benefit associated with ciclesonide
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53 treatment observed in our study reflects the more severe pulmonary inflammation in
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55 our study population, as indicated by the need for hospitalization with oxygen therapy
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57 and a median symptom duration of 9 days: at such stages of disease progression, it
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3 could be speculated that pulmonary administration of corticosteroids may not suffice
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5 to confer benefit and that systemic treatment is needed. Accordingly, in the Recovery
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7 trial of hospitalized Covid-19 patients,[23] dexamethasone treatment reduced risk of
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9 death and the time to discharge from hospital, with these benefits primarily being
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11 observed among patients receiving oxygen therapy or invasive mechanical ventilation
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13 at baseline.
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19 Similar to other clinical trials including patients with Covid-19,[15, 23, 24] we used a
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21 pragmatic, open-label design. With this design, we intended to assess the effect of
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23 adding ciclesonide to standard care, rather than to examine the effect of ciclesonide
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25 compared to placebo. The research question that our study aimed to answer was
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27 “what is the effect of using ciclesonide as an addition to standard care as compared
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29 with standard care alone?” While this is a research question of relevance to clinical
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31 decision-making, the open-label design and the possible expectations of effect
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33 among both patients[25] and physicians might have affected the outcomes in our
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35 study, including when to terminate oxygen therapy. Another limitation of our study is
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37 that we were unable to recruit the intended number of patients due to the substantial
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39 decrease in hospitalized Covid-19 patients in Sweden during 2021. Importantly, the
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41 study could not provide much information regarding the key secondary outcome of
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43 death or invasive mechanical intervention. Further research in hospitalized Covid-19
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45 patients is needed to determine the potential effect of ciclesonide treatment on these
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47 outcomes. Moreover, it is a possibility that effects of ciclesonide differ as compared to
48
49 other inhaled corticosteroids (e.g., budesonide). Finally, results from the Recovery
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51 Trial were released 5 weeks after the initiation of our study and around half of the
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53 patients in both the ciclesonide group and the control group received systemic
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3 corticosteroids after randomization. Further studies would be needed to assess the
4
5 comparative effectiveness and safety of ciclesonide vs systemic corticosteroids.
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10 **Conclusions**

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13 In this open-label randomized controlled trial in patients hospitalized with Covid-19
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15 and receiving oxygen therapy, the findings indicated that treatment with ciclesonide
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17 vs standard care is unlikely to result in a clinically meaningful reduction in the
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19 duration of oxygen therapy.
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26 **Acknowledgements**

27
28
29 We would like to thank the following individuals that did not qualify for authorship but
30
31 contributed to the study: Dr Oscar Bakhouch (Skaraborg Hospital), Dr Eva-Marie
32
33 Boman and Dr Anders Lundqvist (Southern Älvsborg Hospital).
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40 **Contributorship statement**

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42
43 DB, PU, PT, OB and DPA conceived the study and were responsible for the
44
45 methods. OB and DPA were responsible for the study conduct. DB, PU, OB and DPA
46
47 were responsible for the financing. PT validated the data. PU performed the main
48
49 analysis. DPA, PU and PT wrote the original draft of the manuscript. All authors
50
51 wrote, reviewed, and edited the manuscript. OB and DPA supervised the study. DB,
52
53 DPA, PU, PT and OB were responsible for administration of the project. DPA and OB
54
55 are the guarantors. DB, PT, AK, EW, SA, SW, OE, AN, AE, JG, JEK, BJ, JL, JLI, JH,
56
57 OB and DPA enrolled participants in the study. The corresponding author attests that
58
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2
3 all listed authors meet authorship criteria and that no others meeting the criteria have
4
5 been omitted.
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10 **Competing interests**

11
12 This study received non-financial support from COVIS Pharma (study drug donation).
13
14 The authors have no conflict of interest to disclose.
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19 **Funding/Support**

20
21
22 This study was funded by the Swedish Heart and Lung Foundation (Number
23
24 20200421), The Axel and Margaret Ax:son Johnson Foundation (N/A), CIMED (N/A),
25
26 and Strategic Research Program at Karolinska Institutet (Number 961507), the
27
28 Stockholm County Council (Number: 954970, 963296, 962029), and the
29
30 Västmanland County Council (Grant nr LTV-938409). PU was supported by grants
31
32 from the Strategic Research Program in Epidemiology at Karolinska Institutet (N/A),
33
34 and a Faculty Funded Career Position at Karolinska Institutet (N/A).
35
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39 The funders had no role in the study design, conduct, collection, management,
40
41 analysis, interpretation of data, writing or reviewing the manuscript or decision to
42
43 submit the manuscript for publication. The study drug was donated by COVIS
44
45 Pharma but COVIS pharma did not participate in any other part of the study.
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49

50 **Data sharing statement**

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52 No additional data available.
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57 **Ethics Approval**

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2
3 All participants provided written informed consent. The study was approved by the
4
5 Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the
6
7 Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and
8
9 registered at clinicaltrials.gov (NCT04381364).
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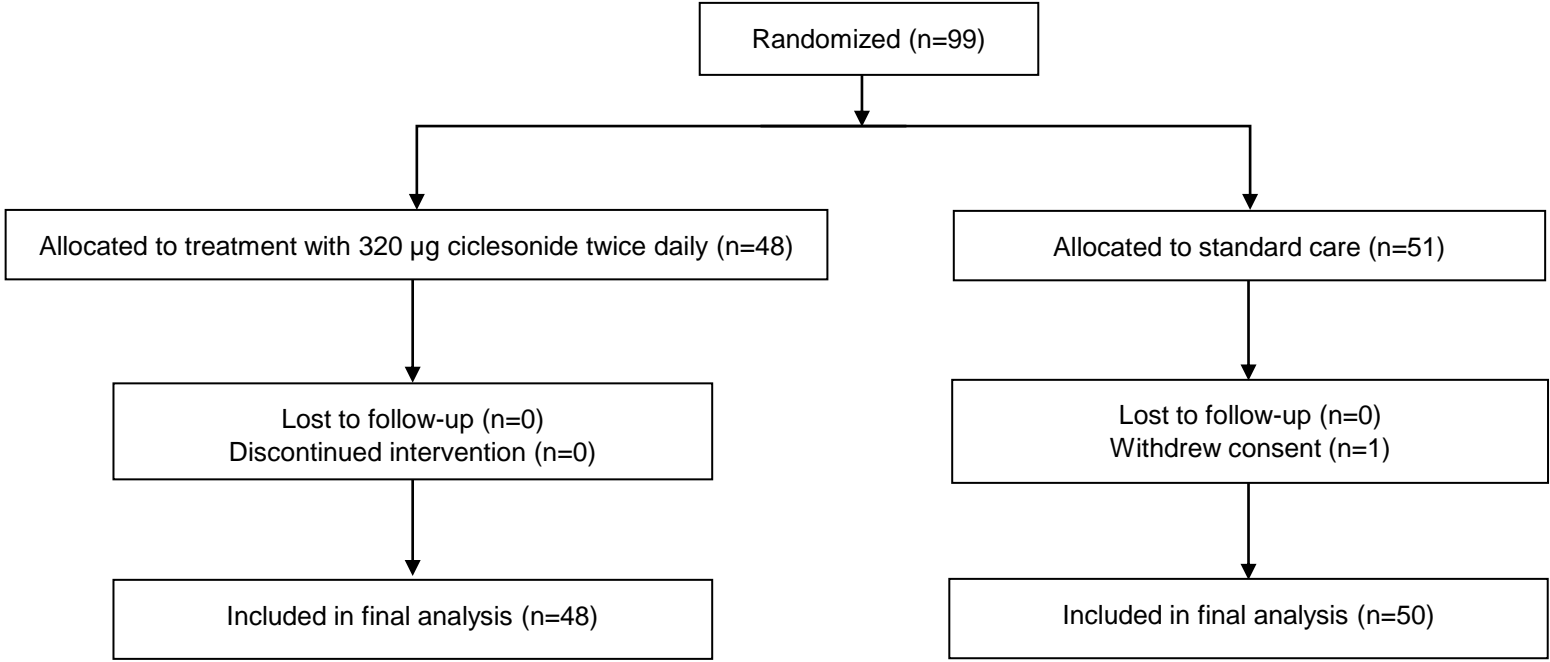
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3 **Figure 1** Flow diagram for study participants.
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5 **Figure 2** Time to termination of oxygen therapy.
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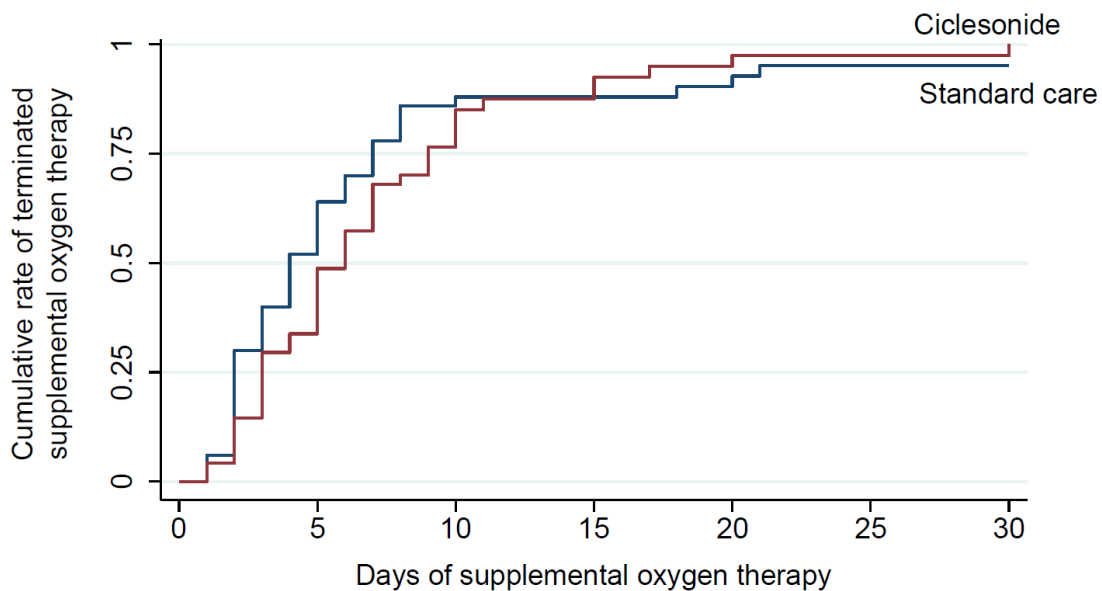
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1 **Figure 1**
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Figure 2 Time to termination of oxygen therapy.



No at risk							
Standard care	50	24	7	6	4	2	2
Ciclesonide	48	31	11	5	2	1	1

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ONLINE APPENDIX

Brodin D, Tornhammar P, Ueda P, Krifors A, Westerlund E, Athlin S, Wojt S, Elvstam O, Neumann A, Elshani A, Giesecke J, Edvardsson J, Bunpuckdee S, Unge C, Larsson M, Johansson B, Ljungberg J, Lindell J, Hansson J, Blennow O, Andersson DP. Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19).

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Protocol changes and rationale

The trial was designed in the beginning of the covid-19 pandemic when data from randomized clinical trials of Covid-19 treatment were scarce. After trial initiation, treatments for patients with Covid-19 and hospitalization rates of such patients changed rapidly. Therefore, we made changes to the protocol and the trial was stopped early.

5 weeks after the start of patient inclusion in our study, in July 2020, the Recovery Collaborative group presented preliminary data¹ showing protective effects of dexamethasone treatment in patients hospitalized for covid-19; a subgroup analysis of this study indicated that the effect was driven by patients receiving invasive mechanical ventilation or oxygen therapy. These data, in combination with local experience from treating patients with Covid-19,² led to most patients receiving oxygen therapy with ≥ 4 L oxygen/min at the study hospitals being treated with systemic corticosteroids. As use of systemic corticosteroids was an exclusion criterion, the change in practice made a large proportion of the Covid-19 patients ineligible for participation.

Initially the trial was conducted at 4 hospitals. To increase the inclusion rate, 9 additional hospitals were included as study sites, although only 5 of them ended up recruiting patients to the study. We also removed the previous upper age limit of 85 years for inclusion and allowed for inclusion of patients based on a positive antigen test for SARS-CoV-2. Moreover, because some patients may start receiving oxygen therapy before hospital admission (e.g., at nursing homes before being transported

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2
3 to the hospital) or a period after hospital admission (e.g., if the patient's condition
4 deteriorated) and we aimed to include patients shortly after initiation of such therapy,
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6 we changed the inclusion criteria from hospitalization within 48 hours prior to
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8 enrollment to initiation of oxygen therapy no longer than 48 hours prior to enrollment.
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14 All changes were approved by the Data Monitoring Committee, Ethical Review
15 Authority and the Swedish Medical Products Agency and implemented from
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17 December 2020.
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24 In June 2021, when 99 patients had been included in the study, a large and
25 increasing proportion of the adult Swedish population had received vaccination for
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27 Covid-19. The number of patients hospitalized with Covid-19 had dropped
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29 substantially and there were none to only a few Covid-19 patients admitted to the
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31 study hospitals per week. We determined that it was unlikely that we would reach the
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33 intended sample size and asked the Data Monitoring Committee to convene for a
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35 meeting. Following the recommendation of the Data Monitoring Committee, the study
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37 was terminated early due to expected futility to meet total enrolment.
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Inclusion and exclusion criteria^a

Participants were eligible for inclusion if, at the time of study inclusion, they (1) were aged ≥ 18 years, (2) had a polymerase chain reaction confirmed SARS-CoV-2 infection or a positive antigen test for SARS-CoV-2, (3) were hospitalized at any of the study hospitals and (4) were receiving oxygen therapy with not more than 48 hours having passed since initiation of this treatment.

Patients were not eligible for inclusion if they (1) had a history of hypersensitivity to ciclesonide or other substances included in the treatment, (2) received ongoing treatment with inhaled or oral corticosteroids, ketokonazol, itrakonazol, ritonavir or nelfinavir, (3) received >8 L oxygen/min or >50 % oxygen with nasal high-flow therapy, (4) were receiving or under consideration for palliative care or had an expected survival of less than 72 h, (5) were expected to be admitted to an intensive care unit within 48 h, (6) had active or inactive pulmonary tuberculosis, severe liver failure (Child-Pugh C), pulmonary arterial hypertension or fibrosis, cognitive or physical impairment, (7) had insufficient language skills to understand information given about the study, (8) had been included in a clinical trial within 30 days, or (9) were women and pregnant, breastfeeding or did not agree to take highly effective contraceptive measures while receiving treatment plus an additional 7 days.

^a The presentation of these inclusion and exclusion criteria have been modified for readability as compared with the version presented in the study protocol.

Appendix table 1 Number of participants included in the final study population by study center.

<i>Study center</i>	<i>n participants</i>
Danderyd Hospital	26
Capio S:t Göran Hospital	24
Karolinska University Hospital	21
Västmanland County Hospital	13
Örebro University Hospital ^a	6
Växjö Central Hospital ^a	3
Halland County Hospital ^a	2
Östersund Hospital ^a	2
Visby Hospital ^a	1

^a In the analyses adjusted for study center, these hospitals were categorized into one group.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	5-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,7,9
Participants	4a	Eligibility criteria for participants	7,8
	4b	Settings and locations where the data were collected	6,7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6,7
Sample size	7a	How sample size was determined	6-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6,7
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8,11

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10,11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10,11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11-13
	13b	For each group, losses and exclusions after randomisation, together with reasons	11-13
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6,7
	14b	Why the trial ended or was stopped	7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Yes
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10,11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-17
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18,19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064374.R1
Article Type:	Original research
Date Submitted by the Author:	08-Nov-2022
Complete List of Authors:	<p>Brodin, Daniel; Capio Sankt Görans Sjukhus Tornhammar, Per; Karolinska Institute, Functional Area of Emergency Medicine Ueda, Peter; Karolinska Institutet Krifors, Anders; Karolinska Institutet, Department of Physiology and Pharmacology; Västmanlands sjukhus Västerås Westerlund, Eli; Danderyd University Hospital, Department of Clinical Sciences Athlin, Simon; Örebro University Wojt, Sandra; Danderyd University Hospital, Department of Internal Medicine Elvstam, Olof; Central Hospital Växjö, Department of Infectious Diseases Neumann, Anca; Capio Sankt Görans Sjukhus Elshani, Arsim; Karlskoga Hospital Giesecke, Julia; Karolinska Universitetssjukhuset Edvardsson-Källkvist, Jens; Karolinska University Hospital Bunpuckdee, Sayam; Karolinska Institutet Unge, Christian; Danderyd University Hospital, Department of Internal Medicine Larsson, Martin; Karolinska Institutet Department of Clinical Science and Education Sodersjukhuset Johansson, Björn; Halland County Ljungberg, Johan; Halland County Lindell, Jonas; Visby Hospital, Department of Infectious Diseases Hansson, Johan; Östersund Hospital, Department of Infectious Diseases Blennow, Ola; Karolinska University Hospital, Department of Infectious Diseases Andersson, Daniel Peter; Karolinska University Hospital, Department of Medicine Huddinge H7, Karolinska Institutet; Karolinska Institute, Medicine (H7)</p>
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Respiratory medicine
Keywords:	COVID-19, Clinical trials < THERAPEUTICS, Respiratory infections < THORACIC MEDICINE

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Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

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6
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8 Word count: 3076
9

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11 Abstract word count: 250
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For peer review only

Abstract

Objective: To assess the efficacy of inhaled ciclesonide in reducing the duration of oxygen therapy (an indicator of time to clinical improvement) among adults hospitalized with Covid-19.

Design: Multicenter, randomized, controlled, open-label trial.

Setting: 9 hospitals (3 academic hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May 17, 2021.

Participants: Adults hospitalized with Covid-19 and receiving oxygen therapy.

Intervention: Inhaled ciclesonide 320 µg twice daily for 14 days versus standard care.

Main outcome measures: Primary outcome was duration of oxygen therapy, an indicator of time to clinical improvement. Key secondary outcome was a composite of invasive mechanical ventilation/death.

Results: Data from 98 participants were analyzed (48 receiving ciclesonide and 50 receiving standard care; median (IQR) age, 59.5 (49-67) years; 67 (68%) male). Median (IQR) duration of oxygen therapy was 5.5 (3-9) days in the ciclesonide group and 4 (2-7) days in the standard care group (hazard ratio (HR) for termination of oxygen therapy 0.73 (95% CI 0.47-1.11), with the upper 95% CI being compatible with a 10% relative reduction in oxygen therapy duration, corresponding to a <1-day absolute reduction in a post-hoc calculation). Three participants in each group died/received invasive mechanical ventilation (HR 0.90 (95% CI 0.15-5.32)). The trial was discontinued early due to slow enrollment.

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3 **Conclusions:** In hospitalized Covid-19 patients receiving oxygen therapy, this trial
4 ruled out, with 0.95 confidence, a treatment effect of ciclesonide corresponding to
5 more than a one-day reduction in duration of oxygen therapy. Ciclesonide is unlikely
6 to improve this outcome meaningfully.
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16 **Strengths and limitations of this study**

- 17 • This was a multicenter, randomized, controlled, open-label trial comparing
18 treatment with the inhaled corticosteroid ciclesonide 320 µg twice daily for 14
19 days versus standard care.
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- 21 • Healthcare providers and participants were not blinded to treatment
22 assignment.
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- 24 • The trial was terminated early due to slow recruitment.
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Introduction

Patients with Covid-19 can develop acute respiratory failure that may require invasive mechanical ventilation, associated with high mortality. The unregulated inflammation in the lungs, poor oxygenation and pulmonary infiltrates characterizing severe Covid-19 have been considered as a type of acute respiratory distress syndrome (ARDS).[1, 2]

Prior to the Covid-19 pandemic, studies have indicated that inhaled corticosteroids may reduce the risk of ARDS. In a randomized controlled trial including 61 patients at risk of ARDS, none of the patients assigned to aerosolized budesonide/formoterol vs 7 assigned to placebo developed ARDS,[3] and 6 (20%) and 16 (53%) of the patients, respectively, received mechanical ventilation. In another trial including 60 patients with acute lung injury or ARDS, nebulized budesonide improved oxygenation and peak and plateau airway pressures, and reduced inflammatory markers.[4] Moreover, potentially protective and preventive effects of inhaled corticosteroids for ARDS is supported by animals models of lung injury,[5-8] and *in vitro* studies,[9] and it has been speculated that local administration of the drug in the lung may maximize therapeutic benefits with fewer systemic side effects, as compared with systemic steroids.[3]

Therefore, it could be hypothesized that inhaled corticosteroids may be beneficial for patients with severe Covid-19. The hypothesis is further supported by reports that inhaled corticosteroids reduce the epithelial expression of genes linked to SARS-CoV-2 entry into host cells.[10, 11] Among the inhaled corticosteroids, ciclesonide has been identified as a particularly promising treatment as it can suppress replication of SARS-CoV-2 *in vitro*.[12, 13]

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3 While previous randomized controlled trials have assessed the effects of inhaled
4 budesonide[14, 15] or ciclesonide[16, 17] in non-hospitalized Covid-19 patients, no
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7 study has been performed in hospitalized patients with more severe Covid-19.
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10 This open-label randomized controlled trial investigated the effects of inhaled
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13 ciclesonide, compared to standard care, in adult patients hospitalized with Covid-19
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16 and requiring oxygen therapy.
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21 **Methods**

22 *Study design*

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28 The HALT Covid-19 (inHALation of ciclesonide for Treatment of Covid-19) trial was a
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31 multicenter, open-label randomized controlled trial to assess the efficacy and safety
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34 of inhaled ciclesonide for the treatment of hospitalized patients with Covid-19
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37 receiving oxygen therapy. The trial was conducted at 9 hospitals (3 academic
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40 hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May
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17, 2021.

All participants provided written informed consent. The study was approved by the
Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the
Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and
registered at clinicaltrials.gov (NCT04381364).

Protocol changes and rationale

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5 The trial was designed in the beginning of the Covid-19 pandemic. After trial initiation,
6 treatments for, and hospitalization rates of, patients with Covid-19 changed rapidly.
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8 Therefore, we made protocol changes (described in detail in the Online Appendix)
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10 and the trial was stopped early.
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17 In brief, we increased the number of study centers, removed the upper age limit (≤ 85
18 years) for patient inclusion, changed the inclusion criteria from ≤ 48 hours since
19 hospital admission to ≤ 48 hours from initiation of oxygen therapy and allowed for
20 patients to be included on the basis of a positive antigen test for SARS-Cov-2. All
21 changes were approved by the Data Monitoring Committee, Ethical Review Authority
22 and the Swedish Medical Products Agency and implemented from December 2020.
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33 In June 2021, 99 patients had been included in the study, a large and increasing
34 proportion of the adult Swedish population had received Covid-19 vaccination and
35 hospitalizations for Covid-19 had dropped substantially. We determined that it was
36 unlikely that the intended sample size would be reached and asked the Data
37 Monitoring Committee to convene for a meeting. Following the recommendation of
38 the Data Monitoring Committee, the study was terminated for futility to meet the
39 targeted enrolment.
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53 *Participants*

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56 Based on observations from Covid-19 patients treated at the study centers, we
57 expected that 85% of the standard care group would survive and terminate oxygen
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3 therapy within 30 days (median 8 days). We considered a 25% (2 days) reduction in
4 the duration of oxygen therapy to be a clinically meaningful effect. We estimated that
5 such an effect could be detected with α of 0.05, and 80% power if 446 participants
6 (223 in each group) were enrolled.
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15 Participants were eligible for inclusion if, they (1) were aged ≥ 18 years, (2) had a
16 polymerase chain reaction confirmed SARS-CoV-2 infection or a positive SARS-CoV-
17 2 antigen test from the upper respiratory tract, (3) were hospitalized at any of the
18 study hospitals and (4) were receiving oxygen therapy, initiated within 48 hours
19 before inclusion. Key exclusion criteria were ongoing treatment with inhaled or oral
20 corticosteroids (previous use was accepted), oxygen therapy with >8 L oxygen/min or
21 >50 % oxygen on nasal high-flow cannula, and ongoing or expected intensive care or
22 palliative care (Online Appendix).
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36 *Randomization*

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38 Patients were randomized 1:1 in blocks of 8, stratified by sex and hospital to receive
39 ciclesonide or standard care. The randomization sequence was prepared by a
40 statistician not involved in the trial. Treatment allocation was provided through a web-
41 based interface. The participants and the physicians treating them were unblinded to
42 the treatment assignment.
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52 *Intervention*

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55 The treatment was 320 μg of inhaled ciclesonide (80 μg per actuation, for a total of 4
56 actuations, or 160 μg per actuation, for a total of 2 actuations) twice daily (total daily
57 dose 640 μg) for 14 days. Ciclesonide was administered using a spacer (L'espace,
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3 Nordic Infucare, Stockholm Sweden). Participants randomized to ciclesonide
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5 received written instructions, including pictures, and practical instructions on how to
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7 use the inhalator and spacer; the first dose was taken under supervision. Ciclesonide
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9 was then prescribed in the participant's electronic medical record and each given
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11 dose during the hospitalization was recorded. Participants discharged before day 14
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13 were instructed to continue the treatment at home for a total treatment duration of 14
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15 days. Participants randomized to standard care did not receive any intervention
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17 related to the study. Physicians treating the participants were not given any
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19 restrictions concerning treatments during the study period. Participants who had been
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21 discharged were contacted by telephone after day 30 for a follow-up interview.
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29 *Outcomes*

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32 The primary outcome was duration of oxygen therapy (time to termination of oxygen
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34 therapy in days) up to 30 days from randomization. Oxygen therapy was defined as
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36 terminated on the day after which the patient did not receive oxygen therapy during
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38 at least 48 hours, while being alive. This outcome corresponded to clinical
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40 improvement for patients receiving oxygen therapy according to the World Health
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42 Organization clinical progression scale.[18]
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49 The key secondary outcome was a composite of invasive mechanical ventilation and
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51 death up to 30 days after randomization. Other secondary outcomes were each
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53 component of the key secondary outcome, admission to an intensive care unit,
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55 discharge from the hospital and dyspnea in daily living at 30-35 days after
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57 randomization as evaluated by the mMRC (Modified Medical Research Council)
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3 dyspnea scale. The scale ranges from 0 to 4 with a higher score indicating more
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5 severe dyspnea.[19, 20]
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10 Data on serious adverse events[21] were collected by review of electronic medical
11 records. Information about non-serious adverse events associated with ciclesonide
12 use (dryness of mouth, nausea and oral candidiasis) was reported using a paper-
13 based reporting form which was filled in by the treating physician. Information about
14 non-serious adverse events occurring after hospital discharge was collected during
15 the follow-up interview.
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26 *Data collection*

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30 Patient characteristics at baseline (comorbidities, comedications, clinical parameters)
31 and study outcomes were obtained from electronic medical records. Investigators
32 contacted participants after day 30 after randomization to ask them about non-
33 serious adverse events and dyspnea in daily living (study outcome) at day 30-35 after
34 randomization.
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45 *Statistical analysis*

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48 According to the pre-specified analysis plan in the study protocol, the analyses were
49 performed by an investigator who had not been involved in the enrolment of
50 participants and was blinded to treatment assignment. An intention-to-treat
51 population was used. In the analysis of the duration of oxygen therapy, participants
52 were followed from randomization to termination of oxygen therapy, death, or 30 days
53 after randomization. Kaplan Meier cumulative incidence curves were generated to
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3 illustrate the cumulative incidence of termination of oxygen therapy in the ciclesonide
4 and standard care groups. A Cox proportional hazard regression model, adjusted for
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6 study hospital (Appendix Table 1), age (continuous variable) and sex was used to
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8 estimate hazard ratios (HR) with 95% CI for time-to-event outcomes. Proportions and
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10 the absolute risk difference with 95% CI were presented for binary outcomes.
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14 Subgroup analyses were performed for the primary outcome by sex, age (<70 years
15 and ≥70 years) and duration of Covid-19 symptoms (<10 days and ≥10 days). In a
16
17 per-protocol analysis of the primary outcome, participants assigned to ciclesonide
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19 were censored at the time of discontinuing treatment. The median mMRC score was
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21 compared using the Kruskal-Wallis test. A logistic regression model adjusted for
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23 study hospital, age and sex was used to compare the likelihood of reporting a mMRC
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25 score of 0 (dyspnea only with strenuous exercise).
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34 95% CIs of ratios not including 1 and 95% CIs for absolute risk differences not
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36 including 0 were considered statistically significant. Secondary outcome analyses
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38 and subgroup analyses were considered hypothesis-generating and no adjustment
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40 for multiple testing was made. Analyses were performed using Stata version 16.1
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42 (StataCorp).
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50 *Patient and Public involvement*

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52 No patients were involved in setting the research question, nor in the design,
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54 conduct, or interpretation of the study.
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Results

Of the 99 participants who underwent randomization 48 were assigned to receive ciclesonide and 51 to standard care (Figure 1). One participant in the standard care group withdrew consent and was excluded from the analysis. Ninety-eight patients (48 in the ciclesonide group and 50 in the standard care group) were included in the final analysis. All participants assigned to ciclesonide received the treatment at least once. None of the participants were lost to follow-up. The median age of participants was 59.5 (IQR 49, 67) years, 68% were men and the median duration of symptoms was 9 (IQR 8, 11) days. There were no relevant between-group differences in demographic characteristics, laboratory test results or comorbidities at enrollment (Table 1).

Table 1 Demographic and clinical characteristics of participants at study enrolment.

	Total (n=98)	Ciclesonide (n=48)	Standard care (n=50)
Age, median (IQR)	59.5 (49, 67)	61 (49, 67)	59 (49, 67)
Age ≥70 years, n (%)	78 (80)	37 (77)	41 (82)
Men, n (%)	67 (68)	34 (71)	33 (66)
Days since symptom onset, median (IQR)	9 (8, 11)	9 (7.5, 11.5)	10 (8, 11)
Days since symptom onset: <10 days, n (%)	51 (52)	27 (56)	24 (48)
Body mass index in kg/m ² , median (IQR)	29.7 (25.6, 34.0)	28.7 (25.4, 34.0)	30.6 (26.8, 34.3)
Oxygen flow of oxygen therapy in L/min, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 2)
Respiratory rate per minute, median (IQR)	20 (18, 24)	20 (19, 25)	20 (18, 23)
C-reactive protein in mg/L, median (IQR)	100 (56, 142)	103 (62, 164)	91.5 (45.5, 124.5)
White cell count in x 10 ⁹ /L, median IQR	5.7 (4.5, 7.0)	5.3 (4.3, 6.9)	6.1 (4.9, 7.0)

eGFR in mL/min/1.73m ² , median (IQR)	83 (70.5, 90)	81.5 (70, 90)	87 (73, 90)
Coexisting conditions, n (%)			
Diabetes mellitus	18 (18)	8 (17)	10 (20)
Hypertension ^a	45 (46)	22 (46)	23 (46)
Hyperlipidemia ^b	27 (28)	12 (25)	15 (30)
Chronic obstructive lung disease	3 (3)	1 (2)	2 (4)
Asthma	8 (8)	6 (13)	2 (4)
Current smoker	12 (12)	6 (13)	6 (12)
Ischemic heart disease	8 (8)	2 (4)	6 (12)
Heart failure	3 (3)	2 (4)	1 (2)
Atrial fibrillation	5 (5)	3 (6)	2 (4)
Cancer	10 (10)	5 (10)	5 (10)
Chronic kidney disease	9 (9)	5 (10)	4 (8)

^a Diagnosis of hypertension or use of antihypertensive drugs

^b Diagnosis of hyperlipidemia or use of lipid lowering therapy

Missing values were: n=1 for days since symptom onset, n=20 for body mass index, n=1 for oxygen flow of oxygen therapy, n=1 for body temperature, n=1 for heart rate, n=3 for respiratory rate, n=3 for C-reactive protein, n=7 for white cell count and n=22 for eGFR.

eGFR: estimated glomerular filtration rate

The results of primary and secondary outcome analyses are presented in Table 2.

Kaplan-Meier estimates of the median duration of oxygen therapy were 5.5 (IQR 3, 9) days in the ciclesonide group and 4 (2, 7) days in the standard care group. (Figure 2).

The HR for termination of oxygen therapy during 30 days following randomization, used to compare ciclesonide vs standard care, showed that ciclesonide treatment was not statistically significantly associated with the duration of oxygen therapy (0.73 (95% CI 0.47 to 1.11)). The upper limit of the 95% CI was compatible with a maximum relative reduction[22] in duration of oxygen therapy of 10% (1-1/1.11) with

ciclesonide, which in a post-hoc calculation described in the Online Appendix, corresponded to a <1 day absolute reduction. In the per-protocol analysis, the HR for termination of oxygen therapy during 30 days following randomization was 0.79 (95% CI 0.51 to 1.23) (Table 2).

Table 2 Outcomes. All outcomes are recorded during 30 days following randomization unless otherwise indicated.

	Ciclesonide	Standard care	Difference^a
Primary outcome			
Duration of oxygen therapy, median (IQR) days	5.5 (3, 9)	4 (2, 7)	0.73 (0.47 to 1.11)
Key secondary outcome			
Death or invasive mechanical ventilation, n (%)	3 (6)	3 (6)	0 (-9 to 10)
Time to death or invasive mechanical ventilation, median (IQR) days	2 (2, 10)	4 (2, 7)	0.90 (0.15 to 5.32)
Secondary outcomes			
Death, n (%)	2 (4)	1 (2)	-
Invasive mechanical ventilation, n (%)	1 (2)	3 (6)	-
Admission to an intensive care unit, n (%)	4 (8)	4 (8)	-
mMRC dyspnea scale score at day 30-35, median (IQR) ^b	3 (2, 4)	3 (2, 4)	0.97
mMRC dyspnea scale score 0 at day 30-35, n (%) ^b	4 (9)	7 (15)	0.48 (0.11 to 2.04)
Subgroup analyses^c			
<i>Sex: Men</i>			
Duration of oxygen therapy, median (IQR) days	5.5 (3, 9)	5 (2, 7)	0.61 (0.36 to 1.05)
<i>Sex: Women</i>			
Duration of oxygen therapy, median (IQR) days	5.5 (2, 7)	4 (2, 8)	0.91 (0.41 to 2.01)
<i>Age group: <70 years</i>			
Duration of oxygen therapy, median (IQR) days	5 (3, 7)	4 (2, 7)	0.77 (0.48 to 1.23)
<i>Age group: ≥70 years</i>			
Duration of oxygen therapy, median (IQR) days	9 (5, 10)	6 (5, 8)	0.37 (p=0.266 ^d)
<i>Days since symptom onset: <10 days</i>			

Duration of oxygen therapy, median (IQR) days	7 (3, 10)	4 (2, 5)	0.54 (0.28 to 1.03)
<i>Days since symptom onset: ≥10 days</i>			
Duration of oxygen therapy, median (IQR) days	5 (3, 6)	5 (3, 8)	0.97 (0.48 to 1.94)
Per protocol analysis^e			
Duration of oxygen therapy, median (IQR) days	5 (3, 9)	4 (2, 7)	0.79 (0.51 to 1.23)

^a. Differences are expressed as hazard ratios (95% CI) estimated using a Cox proportional hazards model for time to event outcomes and as absolute risk difference (95% CI) in percent for outcomes of absolute risk. The comparison of the mMRC dyspnea score was done using the Kruskal-Wallis test and the difference is expressed as a p-value. The comparison of the likelihood of reporting a mMRC score of 0 was done using a logistic regression model and the difference is expressed as an odds ratio (95% CI). Statistical testing for differences in proportions and time-to-event analyses were not performed for the secondary outcome events, including death, invasive mechanical ventilation, and admission to an intensive care unit due to few events.

^b. Not including 1 participant in the standard care group and 2 participants in the ciclesonide group who died within 30 days of randomization and 1 participant in the standard care group and 1 participant in the ciclesonide group with missing data on this outcome.

^c. The subgroup analyses included n=33 in the standard care group and n=34 in the ciclesonide group for men, n=17 in the standard care group and n=14 in the ciclesonide group for women, n=41 in the standard care group and n=37 in the ciclesonide group for those aged <70 years, n=9 in the standard care group and n=11 in the ciclesonide group for those aged ≥70 years, n=24 in the standard care group and n=27 in the ciclesonide group for those with <10 days since symptom onset, and n=25 in the standard care group and n=21 in the ciclesonide group for those with ≥10 days since symptom onset. 1 participant had missing data on days since symptom onset and was not included in the subgroup analysis.

^d. 95% CI were not calculated due to low sample size. The p-value is calculated using the Mann-Whitney U Test for duration of oxygen therapy after exclusion 1 patients in the standard care group and 2 patient in the ciclesonide group who died or received invasive mechanical intervention during 30 days after randomization. The use of the Mann-Whitney U Test was a post-hoc decision and the analysis could not be adjusted for age, sex and study hospital.

^e. In the per-protocol analysis for duration of oxygen therapy, patients assigned to ciclesonide were censored at the time of discontinuing treatment.

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3 In total, 3 (6%) participants assigned to ciclesonide and 3 (6%) participants assigned
4 to standard care experienced the key secondary outcome of mechanical invasive
5 ventilation or death (absolute difference 0% (95% CI -10 to 9%; HR 0.90 (95% CI
6 0.15 to 5.32)). Median mMRC dyspnea score at 30-35 days after randomization was
7 3 (IQR 2, 4) in both groups (p-value for difference 0.97) (Table 2).
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17 There were no statistically significant differences between those assigned to
18 ciclesonide vs standard care in the primary outcome in any of the subgroup analyses
19 by sex, age (<70 years and ≥70 years) and days since symptom onset (<10 days and
20 ≥10 days) (Table 2).
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30 There were no apparent differences between the groups in treatments that
31 participants received after randomization (Table 3); 26 (54%) of the participants
32 assigned to ciclesonide and 22 (44%) of the participants in the standard care group
33 received treatment with systemic corticosteroids after randomization.
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43 Few serious adverse clinical events occurred during the study. The most frequently
44 reported adverse event was dry mouth (7 (15%) participants in the ciclesonide group
45 and 11 (22%) participants in the standard care group). Two participants assigned to
46 ciclesonide and 0 in the placebo group reported that they experienced oral
47 candidiasis (Table 3).
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57 **Table 3** Participants' treatments and adverse clinical events through day 30 after
58 randomization.
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	Ciclesonide (n=48)	Standard care (n=50)
Received treatment, n (%)		
Systemic corticosteroids	26 (54)	22 (44)
Remdesivir	4 (8)	5 (10)
Low-molecular-weight heparin	45 (94)	45 (90)
Oral anticoagulants	32 (67)	30 (60)
Vasopressors	4 (8)	3 (6)
Non-invasive mechanical ventilation	8 (17)	7 (14)
Serious clinical events, n (%)		
Renal failure	2 (4)	3 (6)
Cardiac arrest	1 (2)	0 (0)
New onset atrial fibrillation	0 (0)	1 (2)
Pulmonary embolism	4 (8)	2 (4)
Other thromboembolic events	0 (0)	1 (2)
Sepsis	3 (6)	2 (4)
Other serious event	1 (2)	0 (0)
Non-serious adverse events, n (%)		
Nausea	6 (13)	8 (16)
Dry mouth	7 (15)	11 (22)
Oral candidiasis	2 (4)	0 (0)
Other non-serious adverse event	3 (6)	1 (2)

Some pre-

specified analyses were not performed due to small sample size or low number of events. These included statistical testing of differences in proportions and time-to-event analyses for non-key secondary outcomes, including death, invasive mechanical ventilation, and admission to an intensive care unit; the secondary outcome analyses of discharge from hospital; subgroup analyses for the secondary

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3 outcomes, and the primary outcome analysis after exclusion of participants who
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5 received invasive mechanical ventilation or died.
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10 **Discussion**

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15 In this randomized open-label, controlled trial, including 98 hospitalized Covid-19
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17 patients with ongoing oxygen therapy, treatment with inhaled ciclesonide did not
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19 result in a statistically significant reduction in the duration of oxygen therapy, used as
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21 a measure of time to clinical improvement. The trial ruled out, with 0.95 confidence,
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23 treatments effects of ciclesonide corresponding to more than a one-day reduction in
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25 duration of oxygen therapy.
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32 While previous randomized controlled trials have assessed effects of inhaled
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34 corticosteroids, including budesonide[14, 15] and ciclesonide[16, 17], in non-
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36 hospitalized patients with Covid-19, this is the first trial that includes hospitalized
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38 patients with more severe forms of the disease. In contrast to our hypothesis, the
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40 median duration of oxygen therapy was nominally longer among patients assigned to
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42 ciclesonide vs standard care (5.5 vs 4 days; HR for termination of oxygen therapy
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44 0.73 (95% CI 0.47 to 1.11)). As such, the 95% CI indicates that,[22] even in the best
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46 case, ciclesonide may reduce the duration of oxygen therapy with only 10% (1-
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48 1/1.11; less than 1 day in our study) while it may in the worst case result in an over 2-
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50 fold increase. Thus, the results of this trial indicate that ciclesonide is unlikely to
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52 provide a clinically meaningful beneficial effect on the duration of oxygen therapy in
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54 hospitalized Covid-19 patients receiving oxygen therapy.
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3 To date, 2 randomized controlled trials of ciclesonide in non-hospitalized patients with
4 Covid-19 have been presented. In the CONTAIN study,[16] which was terminated
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8 early due to slow recruitment, 215 non-hospitalized patients with a median of 3 days
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12 symptom duration were randomized to combination treatment with intranasal and
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15 inhaled ciclesonide or placebo. No statistically significant difference between the
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18 groups was observed for the primary endpoint, resolution of respiratory symptoms at
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21 day 7 after randomization, which was reached by 40% of the patients in the treatment
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24 group vs 35% in the placebo group (adjusted risk difference of 5.5% (95% CI -7.8%
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27 to 18.8%).[16] Six (6%) patients assigned to ciclesonide vs 3 (3%) in the placebo
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30 group were hospitalized within 14 days; none died. In another clinical trial of
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33 ciclesonide, including 400 non-hospitalized patients with Covid-19,[17] randomization
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36 to ciclesonid vs placebo did not result in a reduced time to alleviation of all Covid-19
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39 related symptoms. However, in secondary outcome analyses, patients assigned to
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42 ciclesonide had fewer emergency department visits or hospital admissions for
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45 reasons related to COVID-19 (odds ratio, 0.18, 95% CI, 0.04 to 0.85).

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48 In addition, 2 randomized clinical trials of the inhaled corticosteroid budesonide in
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51 non-hospitalized patients with Covid-19 have been presented. The STOIC trial was
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54 an open-label trial comparing inhaled budesonide vs standard care in 146 Covid-19
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57 patients with mild symptoms.[14] Compared to standard care, budesonide treatment
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60 led to a statistically significant reduction in Covid-19-related emergency department
assessment and hospitalization (difference in proportions 0.123 (95% CI 0.043 to
0.218).[14] Furthermore, budesonide treatment was associated with 1 day shorter
time to clinical recovery. The PRINCIPLE trial was another open-label trial that
included 4700 primary care patients at high risk of developing severe Covid-19 (1073

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3 randomized to budesonide treatment; 1988 to standard care; 1639 to other
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5 treatments).[15] Compared to standard care, randomization to budesonide led to a
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7 shorter time to self-reported recovery (difference 2.94 days (95% Bayesian credible
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9 interval 1.19 to 5.12) and a reduced likelihood of hospital admission or death,
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11 although the results for the latter outcomes did not meet the superiority threshold.
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17 Taken together, the previous studies indicate that inhaled corticosteroids might be
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19 useful for preventing deterioration of Covid-19 in non-hospitalized patients with mild
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21 symptoms. It is possible that the low likelihood of benefit associated with ciclesonide
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23 treatment observed in our study reflects the more severe pulmonary inflammation in
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25 our study population, as indicated by the need for hospitalization with oxygen therapy
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27 and a median symptom duration of 9 days: at such stages of disease progression, it
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29 could be speculated that pulmonary administration of corticosteroids may not suffice
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31 to confer benefit and that systemic treatment is needed. Accordingly, in the Recovery
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33 trial of hospitalized Covid-19 patients,[23] dexamethasone treatment reduced risk of
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35 death and the time to discharge from hospital, with these benefits primarily being
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37 observed among patients receiving oxygen therapy or invasive mechanical ventilation
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39 at baseline.
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47 Similar to other clinical trials including patients with Covid-19,[15, 23, 24] we used a
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49 pragmatic, open-label design. With this design, we intended to assess the effect of
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51 adding ciclesonide to standard care, rather than to examine the effect of ciclesonide
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53 compared to placebo. The research question that our study aimed to answer was
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55 “what is the effect of using ciclesonide as an addition to standard care as compared
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57 with standard care alone?” While this is a research question of relevance to clinical
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3 decision-making, the open-label design and the possible expectations of effect
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5 among both patients[25] and physicians might have affected the outcomes in our
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7 study, including when to terminate oxygen therapy. Another limitation of our study is
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9 that we were unable to recruit the intended number of patients due to the substantial
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11 decrease in hospitalized Covid-19 patients in Sweden during 2021. Importantly, the
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13 study could not provide much information regarding the key secondary outcome of
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15 death or invasive mechanical intervention. Further research in hospitalized Covid-19
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17 patients is needed to determine the potential effect of ciclesonide treatment on these
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19 outcomes. Moreover, it is a possibility that effects of ciclesonide differ as compared to
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21 other inhaled corticosteroids (e.g., budesonide). Patients were instructed to use
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23 ciclesonide without a spacer after discharge from the hospital; this may have affected
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25 drug delivery. Finally, results from the Recovery Trial were released 5 weeks after the
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27 initiation of our study and around half of the patients in both the ciclesonide group
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29 and the control group received systemic corticosteroids after randomization. Further
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31 studies would be needed to assess the comparative effectiveness and safety of
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33 ciclesonide vs systemic corticosteroids.
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42 **Conclusions**

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45 In this open-label randomized controlled trial in patients hospitalized with Covid-19
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47 and receiving oxygen therapy, the findings indicated that treatment with ciclesonide
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49 vs standard care is unlikely to result in a clinically meaningful reduction in the
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51 duration of oxygen therapy.
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58 **Acknowledgements**

1
2
3 We would like to thank the following individuals that did not qualify for authorship but
4 contributed to the study: Dr Oscar Bakhouch (Skaraborg Hospital), Dr Eva-Marie
5 Boman and Dr Anders Lundqvist (Southern Älvsborg Hospital).
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13 **Contributorship statement**

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17 DB, PU, PT, OB and DPA conceived the study and were responsible for the
18 methods. OB and DPA were responsible for the study conduct. DB, PU, OB and DPA
19 were responsible for the financing. PT validated the data. PU performed the main
20 analysis. DPA, PU and PT wrote the original draft of the manuscript. All authors
21 wrote, reviewed, and edited the manuscript. OB and DPA supervised the study. DB,
22 DPA, PU, PT and OB were responsible for administration of the project. DPA and OB
23 are the guarantors. DB, PT, AK, EW, SA, SW, OE, AN, AE, JG, JEK, BJ, JL, JLI, JH,
24 OB and DPA enrolled participants in the study. The corresponding author attests that
25 all listed authors meet authorship criteria and that no others meeting the criteria have
26 been omitted.
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43 **Competing interests**

44
45 This study received non-financial support from COVIS Pharma (study drug donation).
46
47 The authors have no conflict of interest to disclose.
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52 **Funding/Support**

53
54
55 This study was funded by the Swedish Heart and Lung Foundation (Number
56 20200421), The Axel and Margaret Ax:son Johnson Foundation (N/A), CIMED (N/A),
57 and Strategic Research Program at Karolinska Institutet (Number 961507), the
58
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1
2
3 Stockholm County Council (Number: 954970, 963296, 962029), and the
4
5 Västmanland County Council (Grant nr LTV-938409). PU was supported by grants
6
7 from the Strategic Research Program in Epidemiology at Karolinska Institutet (N/A),
8
9 and a Faculty Funded Career Position at Karolinska Institutet (N/A).
10
11
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13 The funders had no role in the study design, conduct, collection, management,
14
15 analysis, interpretation of data, writing or reviewing the manuscript or decision to
16
17 submit the manuscript for publication. The study drug was donated by COVIS
18
19 Pharma but COVIS pharma did not participate in any other part of the study.
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23 24 **Data sharing statement**

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26 Data are available upon reasonable request
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31 32 **Ethics Approval**

33 All participants provided written informed consent. The study was approved by the
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35 Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the
36
37 Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and
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39 registered at clinicaltrials.gov (NCT04381364).
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3 **Figure 1** Flow diagram for study participants.
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5 **Figure 2** Time to termination of oxygen therapy during 30 days after randomization.
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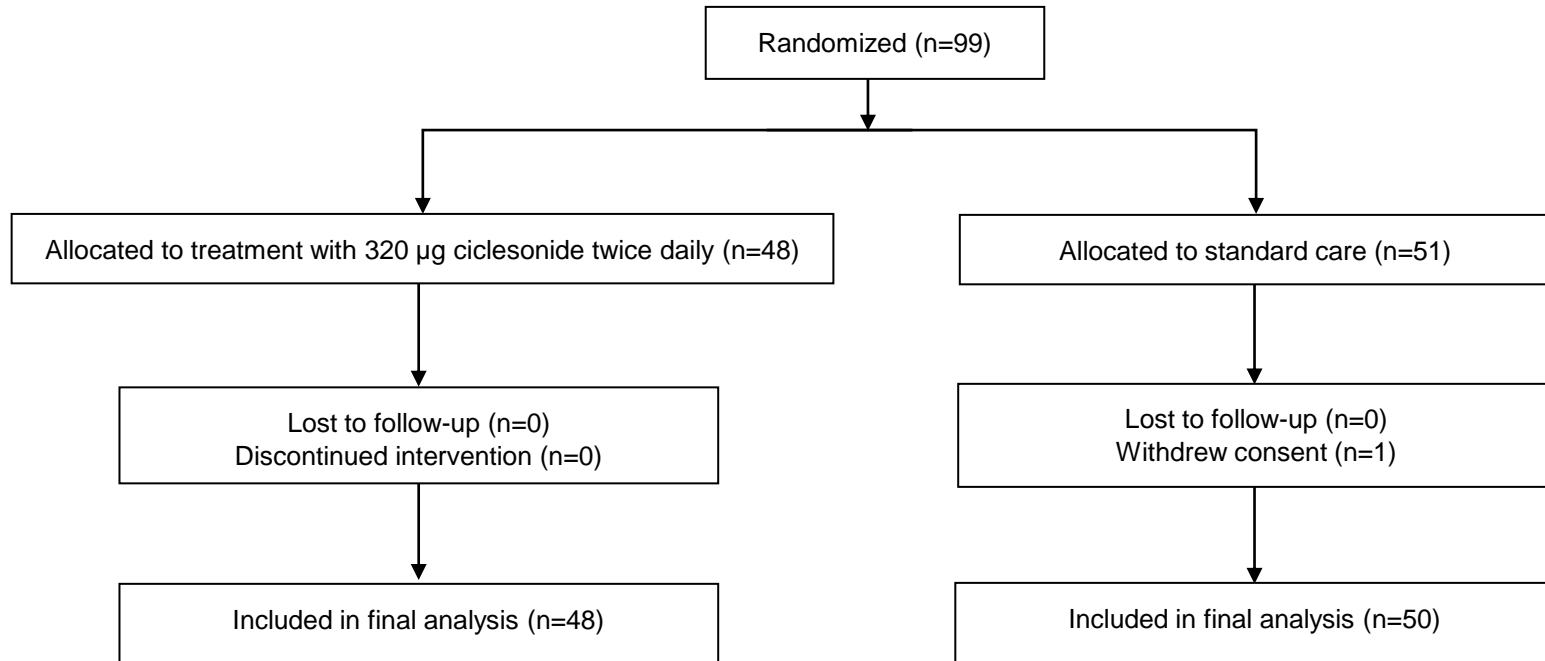
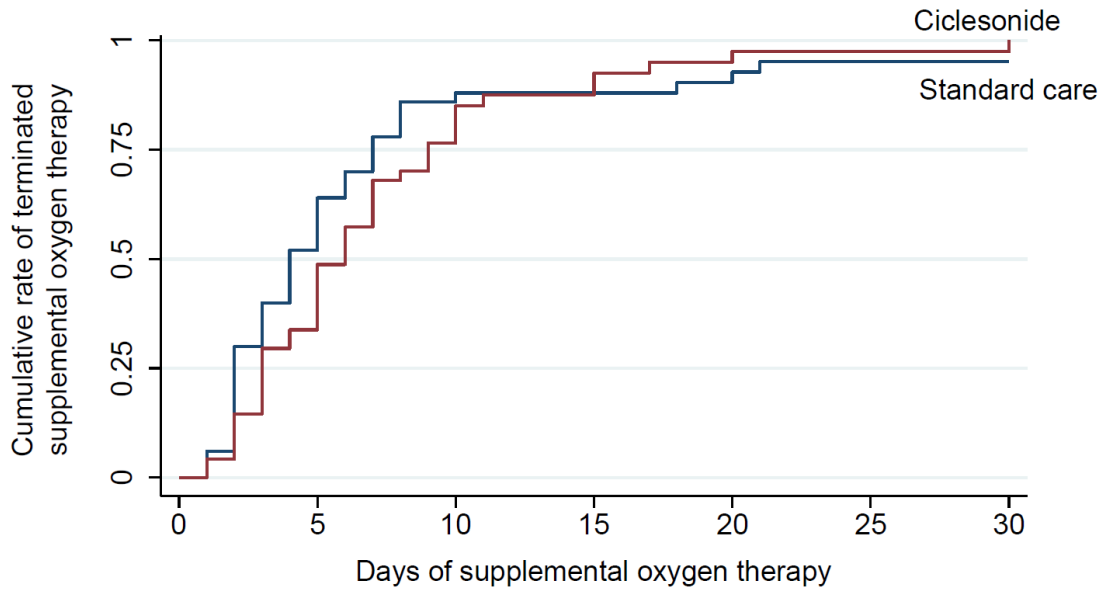
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Figure 1

Figure 2 Time to termination of oxygen therapy.



No at risk								
Standard care	50	24	7	6	4	2	2	
Ciclesonide	48	31	11	5	2	1	1	

ew only

ONLINE APPENDIX

Brodin D, Tornhammar P, Ueda P, Krifors A, Westerlund E, Athlin S, Wojt S, Elvstam O, Neumann A, Elshani A, Giesecke J, Edvardsson J, Bunpuckdee S, Unge C, Larsson M, Johansson B, Ljungberg J, Lindell J, Hansson J, Blennow O, Andersson DP. Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19).

For peer review only

Protocol changes and rationale

The trial was designed in the beginning of the covid-19 pandemic when data from randomized clinical trials of Covid-19 treatment were scarce. After trial initiation, treatments for patients with Covid-19 and hospitalization rates of such patients changed rapidly. Therefore, we made changes to the protocol and the trial was stopped early.

5 weeks after the start of patient inclusion in our study, in July 2020, the Recovery Collaborative group presented preliminary data¹ showing protective effects of dexamethasone treatment in patients hospitalized for covid-19; a subgroup analysis of this study indicated that the effect was driven by patients receiving invasive mechanical ventilation or oxygen therapy. These data, in combination with local experience from treating patients with Covid-19,² led to most patients receiving oxygen therapy with ≥ 4 L oxygen/min at the study hospitals being treated with systemic corticosteroids. As use of systemic corticosteroids was an exclusion criterion, the change in practice made a large proportion of the Covid-19 patients ineligible for participation.

Initially the trial was conducted at 4 hospitals. To increase the inclusion rate, 9 additional hospitals were included as study sites, although only 5 of them ended up recruiting patients to the study. We also removed the previous upper age limit of 85 years for inclusion and allowed for inclusion of patients based on a positive antigen test for SARS-CoV-2. Moreover, because some patients may start receiving oxygen therapy before hospital admission (e.g., at nursing homes before being transported

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3 to the hospital) or a period after hospital admission (e.g., if the patient's condition
4 deteriorated) and we aimed to include patients shortly after initiation of such therapy,
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6 we changed the inclusion criteria from hospitalization within 48 hours prior to
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8 enrollment to initiation of oxygen therapy no longer than 48 hours prior to enrollment.
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14 All changes were approved by the Data Monitoring Committee, Ethical Review
15 Authority and the Swedish Medical Products Agency and implemented from
16
17 December 2020.
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24 In June 2021, when 99 patients had been included in the study, a large and
25 increasing proportion of the adult Swedish population had received vaccination for
26
27 Covid-19. The number of patients hospitalized with Covid-19 had dropped
28
29 substantially and there were none to only a few Covid-19 patients admitted to the
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31 study hospitals per week. We determined that it was unlikely that we would reach the
32
33 intended sample size and asked the Data Monitoring Committee to convene for a
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35 meeting. Following the recommendation of the Data Monitoring Committee, the study
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37 was terminated early due to expected futility to meet total enrolment.
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Inclusion and exclusion criteria^a

Participants were eligible for inclusion if, at the time of study inclusion, they (1) were aged ≥ 18 years, (2) had a polymerase chain reaction confirmed SARS-CoV-2 infection or a positive antigen test for SARS-CoV-2, (3) were hospitalized at any of the study hospitals and (4) were receiving oxygen therapy with not more than 48 hours having passed since initiation of this treatment.

Patients were not eligible for inclusion if they (1) had a history of hypersensitivity to ciclesonide or other substances included in the treatment, (2) received ongoing treatment with inhaled or oral corticosteroids, ketokonazol, itrakonazol, ritonavir or nelfinavir, (3) received >8 L oxygen/min or >50 % oxygen with nasal high-flow therapy, (4) were receiving or under consideration for palliative care or had an expected survival of less than 72 h, (5) were expected to be admitted to an intensive care unit within 48 h, (6) had active or inactive pulmonary tuberculosis, severe liver failure (Child-Pugh C), pulmonary arterial hypertension or fibrosis, cognitive or physical impairment, (7) had insufficient language skills to understand information given about the study, (8) had been included in a clinical trial within 30 days, or (9) were women and pregnant, breastfeeding or did not agree to take highly effective contraceptive measures while receiving treatment plus an additional 7 days.

^a The presentation of these inclusion and exclusion criteria have been modified for readability as compared with the version presented in the study protocol.

Post-hoc calculation for interpretation of the 95% confidence interval in the primary outcome analysis

The research question that we aimed to assess was whether inhaled ciclesonide, as compared with standard care, could reduce the time to clinical improvement (as indicated by duration of oxygen therapy). While the interpretation of statistically non-significant findings is a recurring and well-known subject of debate in the medical literature, it is generally not recommended to use a binary interpretation based on an arbitrary cut-off for statistical significance³⁻⁶. This is particularly important in this trial as it was terminated early and thereby underpowered to assess its primary outcome. However, it has been suggested that in trials with statistically non-significant findings, the 95% CIs should be used to rule in or rule out potential effect sizes of the intervention. In this study, we therefore assessed the largest benefit of ciclesonide that was compatible with the confidence interval. Such a benefit was represented by the upper limit of the HR for time to termination of oxygen therapy (a higher HR indicates shorter duration of oxygen therapy for the ciclesonide group), i.e., 1.11. We took the inverse of this HR ($1/1.11 = 0.90$) to calculate the relative reduction in duration of oxygen therapy that the HR was compatible with (i.e., $1-0.90 = 10\%$ relative reduction). We then multiplied this 10% relative reduction with the absolute duration of oxygen therapy in the standard care group to calculate the corresponding absolute difference in duration of oxygen therapy ($10\% * 4 \text{ days} = 0.4 \text{ days}$, which is <1 day). Given the pre-specified minimally clinically important difference of 2 days (which was used for the power calculation of the study), we deemed this best-case difference to be clinically irrelevant.

Appendix table 1 Number of participants included in the final study population by study center.

<i>Study center</i>	<i>n participants</i>
Danderyd Hospital	26
Capio S:t Görän Hospital	24
Karolinska University Hospital	21
Västmanland County Hospital	13
Örebro University Hospital ^a	6
Växjö Central Hospital ^a	3
Halland County Hospital ^a	2
Östersund Hospital ^a	2
Visby Hospital ^a	1

^a In the analyses adjusted for study center, these hospitals were categorized into one group.

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2. Kan B, Ahl M, Blennow O, et al. *Lakartidningen* 2020;117 [published Online First: 2020/10/07]
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	5-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,7,9
Participants	4a	Eligibility criteria for participants	7,8
	4b	Settings and locations where the data were collected	6,7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6,7
Sample size	7a	How sample size was determined	6-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6,7
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8,11

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10,11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10,11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11-13
	13b	For each group, losses and exclusions after randomisation, together with reasons	11-13
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6,7
	14b	Why the trial ended or was stopped	7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Yes
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10,11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-17
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18,19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064374.R2
Article Type:	Original research
Date Submitted by the Author:	10-Jan-2023
Complete List of Authors:	<p>Brodin, Daniel; Capio Sankt Görans Sjukhus Tornhammar, Per; Karolinska Institute, Functional Area of Emergency Medicine Ueda, Peter; Karolinska Institutet Krifors, Anders; Karolinska Institutet, Department of Physiology and Pharmacology; Västmanlands sjukhus Västerås Westerlund, Eli; Danderyd University Hospital, Department of Clinical Sciences Athlin, Simon; Örebro University Wojt, Sandra; Danderyd University Hospital, Department of Internal Medicine Elvstam, Olof; Central Hospital Växjö, Department of Infectious Diseases Neumann, Anca; Capio Sankt Görans Sjukhus Elshani, Arsim; Karlskoga Hospital Giesecke, Julia; Karolinska Universitetssjukhuset Edvardsson-Källkvist, Jens; Karolinska University Hospital Bunpuckdee, Sayam; Karolinska Institutet Unge, Christian; Danderyd University Hospital, Department of Internal Medicine Larsson, Martin; Karolinska Institutet Department of Clinical Science and Education Sodersjukhuset Johansson, Björn; Halland County Ljungberg, Johan; Halland County Lindell, Jonas; Visby Hospital, Department of Infectious Diseases Hansson, Johan; Östersund Hospital, Department of Infectious Diseases Blennow, Ola; Karolinska University Hospital, Department of Infectious Diseases Andersson, Daniel Peter; Karolinska University Hospital, Department of Medicine Huddinge H7, Karolinska Institutet; Karolinska Institute, Medicine (H7)</p>
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Respiratory medicine
Keywords:	COVID-19, Clinical trials < THERAPEUTICS, Respiratory infections < THORACIC MEDICINE

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Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

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8 Word count: 3286
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11 Abstract word count: 250
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For peer review only

Abstract

Objective: To assess the efficacy of inhaled ciclesonide in reducing the duration of oxygen therapy (an indicator of time to clinical improvement) among adults hospitalized with Covid-19.

Design: Multicenter, randomized, controlled, open-label trial.

Setting: 9 hospitals (3 academic hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May 17, 2021.

Participants: Adults hospitalized with Covid-19 and receiving oxygen therapy.

Intervention: Inhaled ciclesonide 320 µg twice daily for 14 days versus standard care.

Main outcome measures: Primary outcome was duration of oxygen therapy, an indicator of time to clinical improvement. Key secondary outcome was a composite of invasive mechanical ventilation/death.

Results: Data from 98 participants were analyzed (48 receiving ciclesonide and 50 receiving standard care; median (IQR) age, 59.5 (49-67) years; 67 (68%) male). Median (IQR) duration of oxygen therapy was 5.5 (3-9) days in the ciclesonide group and 4 (2-7) days in the standard care group (hazard ratio (HR) for termination of oxygen therapy 0.73 (95% CI 0.47-1.11), with the upper 95% CI being compatible with a 10% relative reduction in oxygen therapy duration, corresponding to a <1-day absolute reduction in a post-hoc calculation). Three participants in each group died/received invasive mechanical ventilation (HR 0.90 (95% CI 0.15-5.32)). The trial was discontinued early due to slow enrollment.

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3 **Conclusions:** In hospitalized Covid-19 patients receiving oxygen therapy, this trial
4 ruled out, with 0.95 confidence, a treatment effect of ciclesonide corresponding to
5 more than a one-day reduction in duration of oxygen therapy. Ciclesonide is unlikely
6 to improve this outcome meaningfully.
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16 **Strengths and limitations of this study**

- 17 • This was a multicenter, randomized, controlled, open-label trial comparing
18 treatment with the inhaled corticosteroid ciclesonide 320 µg twice daily for 14
19 days versus standard care.
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- 21 • Healthcare providers and participants were not blinded to treatment
22 assignment.
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- 24 • The trial was terminated early due to slow recruitment.
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Introduction

Patients with Covid-19 can develop acute respiratory failure that may require invasive mechanical ventilation, associated with high mortality. The unregulated inflammation in the lungs, poor oxygenation and pulmonary infiltrates characterizing severe Covid-19 have been considered as a type of acute respiratory distress syndrome (ARDS).^{1 2}

Prior to the Covid-19 pandemic, studies have indicated that inhaled corticosteroids may reduce the risk of ARDS. In a randomized controlled trial including 61 patients at risk of ARDS, none of the patients assigned to aerosolized budesonide/formoterol vs 7 assigned to placebo developed ARDS,³ and 6 (20%) and 16 (53%) of the patients, respectively, received mechanical ventilation. In another trial including 60 patients with acute lung injury or ARDS, nebulized budesonide improved oxygenation and peak and plateau airway pressures, and reduced inflammatory markers.⁴ Moreover, potentially protective and preventive effects of inhaled corticosteroids for ARDS is supported by animals models of lung injury,⁵⁻⁸ and *in vitro* studies,⁹ and it has been speculated that local administration of the drug in the lung may maximize therapeutic benefits with fewer systemic side effects, as compared with systemic steroids.³

Therefore, it could be hypothesized that inhaled corticosteroids may be beneficial for patients with severe Covid-19. The hypothesis is further supported by reports that inhaled corticosteroids reduce the epithelial expression of genes linked to SARS-CoV-2 entry into host cells.^{10 11} Among the inhaled corticosteroids, ciclesonide has been identified as a particularly promising treatment as it can suppress replication of SARS-CoV-2 *in vitro*.^{12 13}

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3 While previous randomized controlled trials have assessed the effects of inhaled
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5 budesonide^{14 15} or ciclesonide^{16 17} in non-hospitalized Covid-19 patients, no study
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7 has been performed in hospitalized patients with more severe Covid-19.
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10 This open-label randomized controlled trial investigated the effects of inhaled
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12 ciclesonide, compared to standard care, in adult patients hospitalized with Covid-19
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14 and requiring oxygen therapy.
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21 **Methods**

24 *Study design*

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28 The HALT Covid-19 (inHALation of ciclesonide for Treatment of Covid-19) trial was a
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30 multicenter, open-label randomized controlled trial to assess the efficacy and safety
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32 of inhaled ciclesonide for the treatment of hospitalized patients with Covid-19
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34 receiving oxygen therapy. The trial was conducted at 9 hospitals (3 academic
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36 hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May
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38 17, 2021.
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44 All participants provided written informed consent. The study was approved by the
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46 Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the
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48 Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and
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50 registered at clinicaltrials.gov (NCT04381364).
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56 *Protocol changes and rationale*

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5 The trial was designed in the beginning of the Covid-19 pandemic. After trial initiation,
6 treatments for, and hospitalization rates of, patients with Covid-19 changed rapidly.
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8 Therefore, we made protocol changes (described in detail in the Online Appendix)
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10 and the trial was stopped early.
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17 In brief, we increased the number of study centers, removed the upper age limit (≤ 85
18 years) for patient inclusion, changed the inclusion criteria from ≤ 48 hours since
19 hospital admission to ≤ 48 hours from initiation of oxygen therapy and allowed for
20 patients to be included on the basis of a positive antigen test for SARS-Cov-2. All
21 changes were approved by the Data Monitoring Committee, Ethical Review Authority
22 and the Swedish Medical Products Agency and implemented from December 2020.
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33 In June 2021, 99 patients had been included in the study, a large and increasing
34 proportion of the adult Swedish population had received Covid-19 vaccination and
35 hospitalizations for Covid-19 had dropped substantially. We determined that it was
36 unlikely that the intended sample size would be reached and asked the Data
37 Monitoring Committee to convene for a meeting. Following the recommendation of
38 the Data Monitoring Committee, the study was terminated for futility to meet the
39 targeted enrolment.
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52 *Participants*

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56 Based on observations from Covid-19 patients treated at the study centers, we
57 expected that 85% of the standard care group would survive and terminate oxygen
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3 therapy within 30 days (median 8 days). We considered a 25% (2 days) reduction in
4 the duration of oxygen therapy to be a clinically meaningful effect. We estimated that
5 such an effect could be detected with α of 0.05, and 80% power if 446 participants
6 (223 in each group) were enrolled.
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15 Participants were eligible for inclusion if, they (1) were aged ≥ 18 years, (2) had a
16 polymerase chain reaction confirmed SARS-CoV-2 infection or a positive SARS-CoV-
17 2 antigen test from the upper respiratory tract, (3) were hospitalized at any of the
18 study hospitals and (4) were receiving oxygen therapy, initiated within 48 hours
19 before inclusion. Key exclusion criteria were ongoing treatment with inhaled or oral
20 corticosteroids (previous use was accepted), oxygen therapy with >8 L oxygen/min or
21 >50 % oxygen on nasal high-flow cannula, and ongoing or expected intensive care or
22 palliative care (Online Appendix).
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36 *Randomization*

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38 Patients were randomized 1:1 in blocks of 8, stratified by sex and hospital to receive
39 ciclesonide or standard care. The randomization sequence was prepared by a
40 statistician not involved in the trial. Treatment allocation was provided through a web-
41 based interface. The participants and the physicians treating them were unblinded to
42 the treatment assignment.
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52 *Intervention*

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55 The treatment was 320 μg of inhaled ciclesonide (80 μg per actuation, for a total of 4
56 actuations, or 160 μg per actuation, for a total of 2 actuations) twice daily (total daily
57 dose 640 μg) for 14 days. Ciclesonide was administered using a spacer (L'espace,
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3 Nordic Infucare, Stockholm Sweden). Participants randomized to ciclesonide
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5 received written instructions, including pictures, and practical instructions on how to
6
7 use the inhalator and spacer; the first dose was taken under supervision. Ciclesonide
8
9 was then prescribed in the participant's electronic medical record and each given
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11 dose during the hospitalization was recorded. Participants discharged before day 14
12
13 were instructed to continue the treatment at home for a total treatment duration of 14
14
15 days. Participants randomized to standard care did not receive any intervention
16
17 related to the study. Physicians treating the participants were not given any
18
19 restrictions concerning treatments during the study period. Participants who had been
20
21 discharged were contacted by telephone after day 30 for a follow-up interview.
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29 *Outcomes*

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32 The primary outcome was duration of oxygen therapy (time to termination of oxygen
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34 therapy in days) up to 30 days from randomization. Oxygen therapy was defined as
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36 terminated on the day after which the patient did not receive oxygen therapy during
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38 at least 48 hours, while being alive. This outcome corresponded to clinical
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40 improvement for patients receiving oxygen therapy according to the World Health
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42 Organization clinical progression scale.¹⁸
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48 The key secondary outcome was a composite of invasive mechanical ventilation and
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50 death up to 30 days after randomization. Other secondary outcomes were each
51
52 component of the key secondary outcome, admission to an intensive care unit,
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54 discharge from the hospital and dyspnea in daily living at 30-35 days after
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56 randomization as evaluated by the mMRC (Modified Medical Research Council)
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3 dyspnea scale. The scale ranges from 0 to 4 with a higher score indicating more
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5 severe dyspnea.^{19 20}
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10 Data on serious adverse events²¹ were collected by review of electronic medical
11 records. Information about non-serious adverse events associated with ciclesonide
12 use (dryness of mouth, nausea and oral candidiasis) was reported using a paper-
13 based reporting form which was filled in by the treating physician. Information about
14 non-serious adverse events occurring after hospital discharge was collected during
15 the follow-up interview.
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26 *Data collection*

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30 Patient characteristics at baseline (comorbidities, comedications, clinical parameters)
31 and study outcomes were obtained from electronic medical records. Investigators
32 contacted participants after day 30 after randomization to ask them about non-
33 serious adverse events and dyspnea in daily living (study outcome) at day 30-35 after
34 randomization.
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45 *Statistical analysis*

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48 According to the pre-specified analysis plan in the study protocol, the analyses were
49 performed by an investigator who had not been involved in the enrolment of
50 participants and was blinded to treatment assignment. An intention-to-treat
51 population was used. In the analysis of the duration of oxygen therapy, participants
52 were followed from randomization to termination of oxygen therapy, death, or 30 days
53 after randomization. Kaplan Meier cumulative incidence curves were generated to
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3 illustrate the cumulative incidence of termination of oxygen therapy in the ciclesonide
4 and standard care groups. A Cox proportional hazard regression model, adjusted for
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6 and standard care groups. A Cox proportional hazard regression model, adjusted for
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8 study hospital (Appendix Table 1), age (continuous variable) and sex was used to
9
10 estimate hazard ratios (HR) with 95% CI for time-to-event outcomes. Proportions and
11
12 the absolute risk difference with 95% CI were presented for binary outcomes. In a
13
14 per-protocol analysis of the primary outcome, participants assigned to ciclesonide
15
16 were censored at the time of discontinuing treatment. The median mMRC score was
17
18 compared using the Kruskal-Wallis test. A logistic regression model adjusted for
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20 study hospital, age and sex was used to compare the likelihood of reporting a mMRC
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22 score of 0 (dyspnea only with strenuous exercise).
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30 In an analysis that was not pre-specified, we additionally adjusted the primary
31
32 outcome analysis for baseline variables, including days since symptom onset, c-
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34 reactive protein and white blood count (as continuous variables), and diabetes
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36 mellitus, hypertension and hyperlipidemia.
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39 95% CIs of ratios not including 1 and 95% CIs for absolute risk differences not
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41 including 0 were considered statistically significant. Secondary outcome analyses
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43 were considered hypothesis-generating and no adjustment for multiple testing was
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45 made. Analyses were performed using Stata version 16.1 (StataCorp).
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52 *Patient and Public involvement*

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55 No patients were involved in setting the research question, nor in the design,
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57 conduct, or interpretation of the study.
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Results

Of the 99 participants who underwent randomization 48 were assigned to receive ciclesonide and 51 to standard care (Figure 1). One participant in the standard care group withdrew consent and was excluded from the analysis. Ninety-eight patients (48 in the ciclesonide group and 50 in the standard care group) were included in the final analysis. All participants assigned to ciclesonide received the treatment at least once. None of the participants were lost to follow-up. The median age of participants was 59.5 (IQR 49, 67) years, 68% were men and the median duration of symptoms was 9 (IQR 8, 11) days. There were no relevant between-group differences in demographic characteristics, laboratory test results or comorbidities at enrollment (Table 1).

Table 1 Demographic and clinical characteristics of participants at study enrolment.

	Total (n=98)	Ciclesonide (n=48)	Standard care (n=50)
Age, median (IQR)	59.5 (49, 67)	61 (49, 67)	59 (49, 67)
Age ≥70 years, n (%)	78 (80)	37 (77)	41 (82)
Men, n (%)	67 (68)	34 (71)	33 (66)
Days since symptom onset, median (IQR)	9 (8, 11)	9 (7.5, 11.5)	10 (8, 11)
Days since symptom onset: <10 days, n (%)	51 (52)	27 (56)	24 (48)
Body mass index in kg/m ² , median (IQR)	29.7 (25.6, 34.0)	28.7 (25.4, 34.0)	30.6 (26.8, 34.3)
Oxygen flow of oxygen therapy in L/min, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 2)
Respiratory rate per minute, median (IQR)	20 (18, 24)	20 (19, 25)	20 (18, 23)
C-reactive protein in mg/L, median (IQR)	100 (56, 142)	103 (62, 164)	91.5 (45.5, 124.5)

White cell count in $\times 10^9/L$, median IQR	5.7 (4.5, 7.0)	5.3 (4.3, 6.9)	6.1 (4.9, 7.0)
eGFR in mL/min/1.73m ² , median (IQR)	83 (70.5, 90)	81.5 (70, 90)	87 (73, 90)
Coexisting conditions, n (%)			
Diabetes mellitus	18 (18)	8 (17)	10 (20)
Hypertension ^a	45 (46)	22 (46)	23 (46)
Hyperlipidemia ^b	27 (28)	12 (25)	15 (30)
Chronic obstructive lung disease	3 (3)	1 (2)	2 (4)
Asthma	8 (8)	6 (13)	2 (4)
Current smoker	12 (12)	6 (13)	6 (12)
Ischemic heart disease	8 (8)	2 (4)	6 (12)
Heart failure	3 (3)	2 (4)	1 (2)
Atrial fibrillation	5 (5)	3 (6)	2 (4)
Cancer	10 (10)	5 (10)	5 (10)
Chronic kidney disease	9 (9)	5 (10)	4 (8)

^a Diagnosis of hypertension or use of antihypertensive drugs

^b Diagnosis of hyperlipidemia or use of lipid lowering therapy

Missing values were: n=1 for days since symptom onset, n=20 for body mass index, n=1 for oxygen flow of oxygen therapy, n=1 for body temperature, n=1 for heart rate, n=3 for respiratory rate, n=3 for C-reactive protein, n=7 for white cell count and n=22 for eGFR.

eGFR: estimated glomerular filtration rate

The results of primary and secondary outcome analyses are presented in Table 2.

Kaplan-Meier estimates of the median duration of oxygen therapy were 5.5 (IQR 3, 9) days in the ciclesonide group and 4 (2, 7) days in the standard care group. (Figure 2).

The HR for termination of oxygen therapy during 30 days following randomization, used to compare ciclesonide vs standard care, showed that ciclesonide treatment was not statistically significantly associated with the duration of oxygen therapy (0.73 (95% CI 0.47 to 1.11)).

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3 The research question that we aimed to assess was whether inhaled ciclesonide, as
4 compared with standard care, could reduce the time to clinical improvement (as
5 indicated by duration of oxygen therapy). While the interpretation of statistically non-
6 significant findings is a recurring and well-known subject of debate in the medical
7 literature, it is generally not recommended to use a binary interpretation based on an
8 arbitrary cut-off for statistical significance²²⁻²⁵. This is particularly important in this trial
9 as it was terminated early and thereby underpowered to assess its primary outcome.
10 However, it has been suggested that in trials with statistically non-significant findings,
11 the 95% CIs should be used to rule in or rule out potential effect sizes of the
12 intervention. In this study, we therefore assessed the largest benefit of ciclesonide
13 that was compatible with the confidence interval. Such a benefit was represented by
14 the upper limit of the HR for time to termination of oxygen therapy (a higher HR
15 indicates shorter duration of oxygen therapy for the ciclesonide group), i.e., 1.11. We
16 took the inverse of this HR ($1/1.11 = 0.90$) to calculate the relative reduction in
17 duration of oxygen therapy that the HR was compatible with (i.e., $1-0.90 = 10\%$
18 relative reduction). We then multiplied this 10% relative reduction with the absolute
19 duration of oxygen therapy in the standard care group to calculate the corresponding
20 absolute difference in duration of oxygen therapy ($10\% * 4 \text{ days} = 0.4 \text{ days}$, which is
21 $<1 \text{ day}$). Given the pre-specified minimally clinically important difference of 2 days
22 (which was used for the power calculation of the study), we deemed this best-case
23 difference to be clinically irrelevant.

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55 In the per-protocol analysis, the HR for termination of oxygen therapy during 30 days
56 following randomization was 0.79 (95% CI 0.51 to 1.23). In the additionally adjusted
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analysis, the HR for termination of oxygen therapy was 0.68 (95% CI 0.43 to 1.09) (Table 2).

Table 2 Outcomes. All outcomes are recorded during 30 days following randomization unless otherwise indicated.

	Ciclesonide	Standard care	Difference^a
Primary outcome			
Duration of oxygen therapy, median (IQR) days	5.5 (3, 9)	4 (2, 7)	0.73 (0.47 to 1.11)
Key secondary outcome			
Death or invasive mechanical ventilation, n (%)	3 (6)	3 (6)	0 (-9 to 10)
Time to death or invasive mechanical ventilation, median (IQR) days	2 (2, 10)	4 (2, 7)	0.90 (0.15 to 5.32)
Secondary outcomes			
Death, n (%)	2 (4)	1 (2)	-
Invasive mechanical ventilation, n (%)	1 (2)	3 (6)	-
Admission to an intensive care unit, n (%)	4 (8)	4 (8)	-
mMRC dyspnea scale score at day 30-35, median (IQR) ^b	3 (2, 4)	3 (2, 4)	0.97
mMRC dyspnea scale score 0 at day 30-35, n (%) ^b	4 (9)	7 (15)	0.48 (0.11 to 2.04)
Per protocol analysis^c			
Duration of oxygen therapy, median (IQR) days	5 (3, 9)	4 (2, 7)	0.79 (0.51 to 1.23)
Additionally adjusted analysis^d			
Duration of oxygen therapy, median (IQR) days	5 (3, 9)	4.5 (2, 7)	0.68 (0.43 to 1.09)

^a. Differences are expressed as hazard ratios (95% CI) estimated using a Cox proportional hazards model for time to event outcomes and as absolute risk difference (95% CI) in percent for outcomes of absolute risk. The comparison of the mMRC dyspnea score was done using the Kruskal-Wallis test and the difference is expressed as a p-value. The comparison of the likelihood of reporting a mMRC score of 0 was done using a logistic regression model and the difference is expressed as an odds ratio (95% CI). Statistical testing for differences in proportions and time-to-event analyses were not performed for the secondary outcome events, including death, invasive mechanical ventilation, and admission to an intensive care unit due to few events.

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3 ^b. Not including 1 participant in the standard care group and 2 participants in the ciclesonide group who died within
4 30 days of randomization and 1 participant in the standard care group and 1 participant in the ciclesonide group with
5 missing data on this outcome.
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9 ^c. In the per-protocol analysis for duration of oxygen therapy, patients assigned to ciclesonide were censored at the
10 time of discontinuing treatment.
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13 ^d. In addition to age, sex and study center, this analysis of duration of oxygen therapy was adjusted for days since
14 symptom onset, c-reactive protein, white blood count (as continuous variables) and diabetes mellitus, hypertension
15 and hyperlipidemia (as categorical variables). The analyses included n=46 in the standard care group and n=45 in the
16 ciclesonide group without missing data on any of the variables included in the model.
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24 In total, 3 (6%) participants assigned to ciclesonide and 3 (6%) participants assigned
25 to standard care experienced the key secondary outcome of mechanical invasive
26 ventilation or death (absolute difference 0% (95% CI -10 to 9%; HR 0.90 (95% CI
27 0.15 to 5.32)). Median mMRC dyspnea score at 30-35 days after randomization was
28 3 (IQR 2, 4) in both groups (p-value for difference 0.97) (Table 2).
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39 There were no apparent differences between the groups in treatments that
40 participants received after randomization (Table 3); 26 (54%) of the participants
41 assigned to ciclesonide and 22 (44%) of the participants in the standard care group
42 received treatment with systemic corticosteroids after randomization.
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51 Few serious adverse clinical events occurred during the study. The most frequently
52 reported adverse event was dry mouth (7 (15%) participants in the ciclesonide group
53 and 11 (22%) participants in the standard care group). Two participants assigned to
54 ciclesonide and 0 in the placebo group reported that they experienced oral
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candidiasis (Table 3).

Table 3 Participants' treatments and adverse clinical events through day 30 after randomization.

	Ciclesonide (n=48)	Standard care (n=50)
Received treatment, n (%)		
Systemic corticosteroids	26 (54)	22 (44)
Remdesivir	4 (8)	5 (10)
Low-molecular-weight heparin	45 (94)	45 (90)
Oral anticoagulants	32 (67)	30 (60)
Vasopressors	4 (8)	3 (6)
Non-invasive mechanical ventilation	8 (17)	7 (14)
Serious clinical events, n (%)		
Renal failure	2 (4)	3 (6)
Cardiac arrest	1 (2)	0 (0)
New onset atrial fibrillation	0 (0)	1 (2)
Pulmonary embolism	4 (8)	2 (4)
Other thromboembolic events	0 (0)	1 (2)
Sepsis	3 (6)	2 (4)
Other serious event	1 (2)	0 (0)
Non-serious adverse events, n (%)		
Nausea	6 (13)	8 (16)
Dry mouth	7 (15)	11 (22)
Oral candidiasis	2 (4)	0 (0)
Other non-serious adverse event	3 (6)	1 (2)

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3 Some pre-specified analyses were not performed due to small sample size or low
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5 number of events. These included statistical testing of differences in proportions and
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7 time-to-event analyses for non-key secondary outcomes, including death, invasive
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9 mechanical ventilation, and admission to an intensive care unit; the secondary
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11 outcome analyses of discharge from hospital; subgroup analyses, and the primary
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13 outcome analysis after exclusion of participants who received invasive mechanical
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15 ventilation or died.
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22 Discussion

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27 In this randomized open-label, controlled trial, including 98 hospitalized Covid-19
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29 patients with ongoing oxygen therapy, treatment with inhaled ciclesonide did not
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31 result in a statistically significant reduction in the duration of oxygen therapy, used as
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33 a measure of time to clinical improvement. The trial ruled out, with 0.95 confidence,
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35 treatments effects of ciclesonide corresponding to more than a one-day reduction in
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37 duration of oxygen therapy.
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43 While previous randomized controlled trials have assessed effects of inhaled
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45 corticosteroids, including budesonide^{14 15} and ciclesonide^{16 17}, in non-hospitalized
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47 patients with Covid-19, this is the first trial that includes hospitalized patients with
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49 more severe forms of the disease. In contrast to our hypothesis, the median duration
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51 of oxygen therapy was nominally longer among patients assigned to ciclesonide vs
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53 standard care (5.5 vs 4 days; HR for termination of oxygen therapy 0.73 (95% CI
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55 0.47 to 1.11)). As such, the 95% CI indicates that,²⁴ even in the best case,
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57 ciclesonide may reduce the duration of oxygen therapy with only 10% (1-1/1.11; less
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3 than 1 day in our study) while it may in the worst case result in an over 2-fold
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5 increase. Thus, the results of this trial indicate that ciclesonide is unlikely to provide a
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7 clinically meaningful beneficial effect on the duration of oxygen therapy in
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9 hospitalized Covid-19 patients receiving oxygen therapy.
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14 To date, 2 randomized controlled trials of ciclesonide in non-hospitalized patients with
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16 Covid-19 have been presented. In the CONTAIN study,¹⁶ which was terminated early
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18 due to slow recruitment, 215 non-hospitalized patients with a median of 3 days
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20 symptom duration were randomized to combination treatment with intranasal and
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22 inhaled ciclesonide or placebo. No statistically significant difference between the
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24 groups was observed for the primary endpoint, resolution of respiratory symptoms at
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26 day 7 after randomization, which was reached by 40% of the patients in the treatment
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28 group vs 35% in the placebo group (adjusted risk difference of 5.5% (95% CI -7.8%
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30 to 18.8%).¹⁶ Six (6%) patients assigned to ciclesonide vs 3 (3%) in the placebo group
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32 were hospitalized within 14 days; none died. In another clinical trial of ciclesonide,
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34 including 400 non-hospitalized patients with Covid-19,¹⁷ randomization to ciclesonid
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36 vs placebo did not result in a reduced time to alleviation of all Covid-19 related
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38 symptoms. However, in secondary outcome analyses, patients assigned to
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40 ciclesonide had fewer emergency department visits or hospital admissions for
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42 reasons related to COVID-19 (odds ratio, 0.18, 95% CI, 0.04 to 0.85).
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51 In addition, 2 randomized clinical trials of the inhaled corticosteroid budesonide in
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53 non-hospitalized patients with Covid-19 have been presented. The STOIC trial was
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55 an open-label trial comparing inhaled budesonide vs standard care in 146 Covid-19
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57 patients with mild symptoms.¹⁴ Compared to standard care, budesonide treatment
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3 led to a statistically significant reduction in Covid-19-related emergency department
4 assessment and hospitalization (difference in proportions 0.123 (95% CI 0.043 to
5 0.218)).¹⁴ Furthermore, budesonide treatment was associated with 1 day shorter time
6 to clinical recovery. The PRINCIPLE trial was another open-label trial that included
7 4700 primary care patients at high risk of developing severe Covid-19 (1073
8 randomized to budesonide treatment; 1988 to standard care; 1639 to other
9 treatments).¹⁵ Compared to standard care, randomization to budesonide led to a
10 shorter time to self-reported recovery (difference 2.94 days (95% Bayesian credible
11 interval 1.19 to 5.12) and a reduced likelihood of hospital admission or death,
12 although the results for the latter outcomes did not meet the superiority threshold.
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28 Taken together, the previous studies indicate that inhaled corticosteroids might be
29 useful for preventing deterioration of Covid-19 in non-hospitalized patients with mild
30 symptoms. It is possible that the low likelihood of benefit associated with ciclesonide
31 treatment observed in our study reflects the more severe pulmonary inflammation in
32 our study population, as indicated by the need for hospitalization with oxygen therapy
33 and a median symptom duration of 9 days: at such stages of disease progression, it
34 could be speculated that pulmonary administration of corticosteroids may not suffice
35 to confer benefit and that systemic treatment is needed. Accordingly, in the Recovery
36 trial of hospitalized Covid-19 patients,²⁶ dexamethasone treatment reduced risk of
37 death and the time to discharge from hospital, with these benefits primarily being
38 observed among patients receiving oxygen therapy or invasive mechanical ventilation
39 at baseline.
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58 Similar to other clinical trials including patients with Covid-19,^{15 26 27} we used a
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3 pragmatic, open-label design. With this design, we intended to assess the effect of
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5 adding ciclesonide to standard care, rather than to examine the effect of ciclesonide
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7 compared to placebo. The research question that our study aimed to answer was
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9 “what is the effect of using ciclesonide as an addition to standard care as compared
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11 with standard care alone?” While this is a research question of relevance to clinical
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13 decision-making, the open-label design and the possible expectations of effect
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15 among both patients²⁸ and physicians might have affected the outcomes in our study,
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17 including when to terminate oxygen therapy. Another limitation of our study is that we
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19 were unable to recruit the intended number of patients due to the substantial
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21 decrease in hospitalized Covid-19 patients in Sweden during 2021. Importantly, the
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23 study could not provide much information regarding the key secondary outcome of
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25 death or invasive mechanical intervention. Further research in hospitalized Covid-19
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27 patients is needed to determine the potential effect of ciclesonide treatment on these
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29 outcomes. Moreover, it is a possibility that effects of ciclesonide differ as compared to
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31 other inhaled corticosteroids (e.g., budesonide). Patients were instructed to use
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33 ciclesonide without a spacer after discharge from the hospital; this may have affected
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35 drug delivery. Finally, results from the Recovery Trial were released 5 weeks after the
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37 initiation of our study and around half of the patients in both the ciclesonide group
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39 and the control group received systemic corticosteroids after randomization. Further
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41 studies would be needed to assess the comparative effectiveness and safety of
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43 ciclesonide vs systemic corticosteroids.
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53 **Conclusions**

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56 In this open-label randomized controlled trial in patients hospitalized with Covid-19
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58 and receiving oxygen therapy, the findings indicated that treatment with ciclesonide
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3 vs standard care is unlikely to result in a clinically meaningful reduction in the
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5 duration of oxygen therapy.
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10 11 **Acknowledgements**

12
13
14 We would like to thank the following individuals that did not qualify for authorship but
15
16 contributed to the study: Dr Oscar Bakhouch (Skaraborg Hospital), Dr Eva-Marie
17
18 Boman and Dr Anders Lundqvist (Southern Älvsborg Hospital).
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24 **Contributorship statement**

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28 DB, PU, PT, OB and DPA conceived the study and were responsible for the
29
30 methods. OB and DPA were responsible for the study conduct. DB, PU, OB and DPA
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32 were responsible for the financing. PT validated the data. PU performed the main
33
34 analysis. DPA, PU and PT wrote the original draft of the manuscript. All authors
35
36 wrote, reviewed, and edited the manuscript. OB and DPA supervised the study. DB,
37
38 DPA, PU, PT and OB were responsible for administration of the project. DPA and OB
39
40 are the guarantors. DB, PT, AK, EW, SA, SW, OE, AN, AE, JG, JEK, SB, CU, ML,
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42 BJ, JL, JLI, JH, OB and DPA enrolled participants in the study. The corresponding
43
44 author attests that all listed authors meet authorship criteria and that no others
45
46 meeting the criteria have been omitted.
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54 **Competing interests**

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56 This study received non-financial support from COVIS Pharma (study drug donation).
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58 The authors have no conflict of interest to disclose.
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Funding/Support

This study was funded by the Swedish Heart and Lung Foundation (Number 20200421), The Axel and Margaret Ax:son Johnson Foundation (N/A), CIMED (N/A), and Strategic Research Program at Karolinska Institutet (Number 961507), the Stockholm County Council (Number: 954970, 963296, 962029), and the Västmanland County Council (Grant nr LTV-938409). PU was supported by grants from the Strategic Research Program in Epidemiology at Karolinska Institutet (N/A), and a Faculty Funded Career Position at Karolinska Institutet (N/A).

The funders had no role in the study design, conduct, collection, management, analysis, interpretation of data, writing or reviewing the manuscript or decision to submit the manuscript for publication. The study drug was donated by COVIS Pharma but COVIS pharma did not participate in any other part of the study.

Data sharing statement

Data are available upon reasonable request

Ethics Approval

All participants provided written informed consent. The study was approved by the Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and registered at clinicaltrials.gov (NCT04381364).

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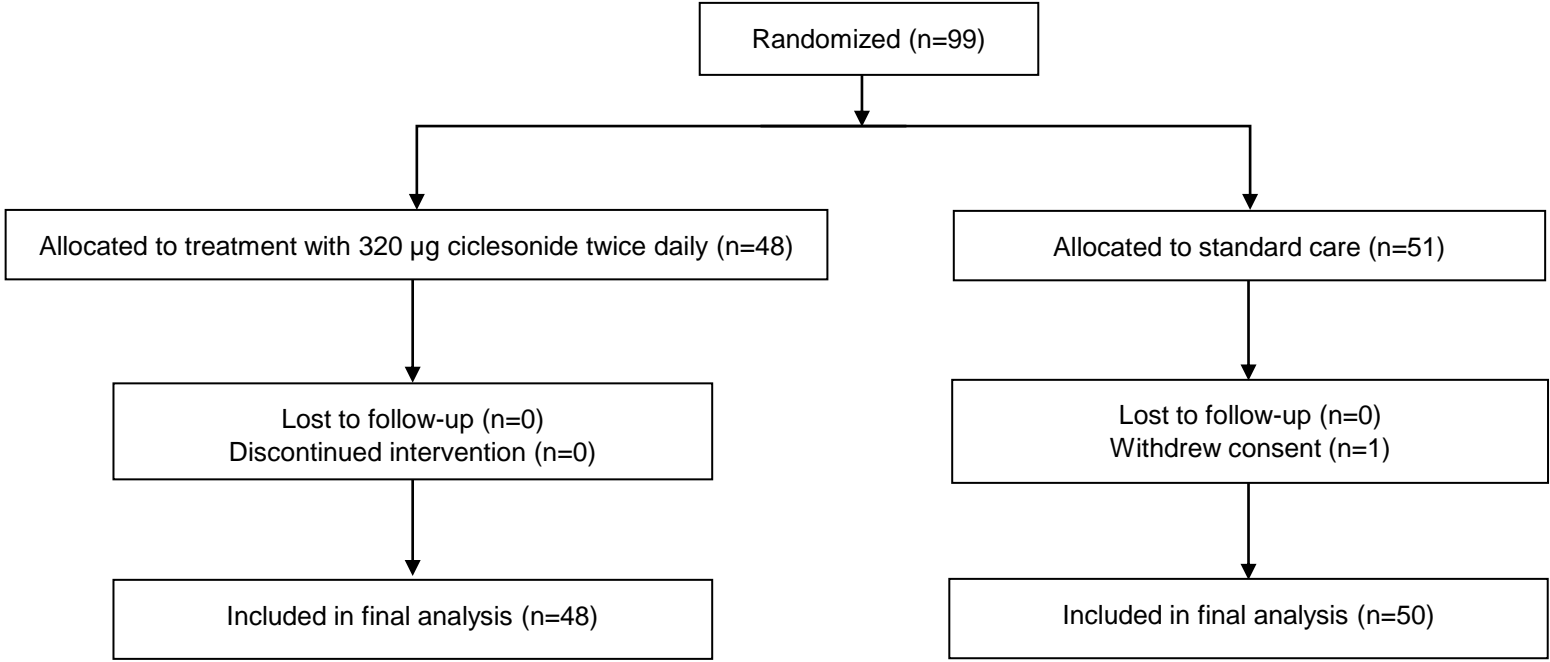
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3 **Figure 1** Flow diagram for study participants.
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5 **Figure 2** Time to termination of oxygen therapy during 30 days after randomization.
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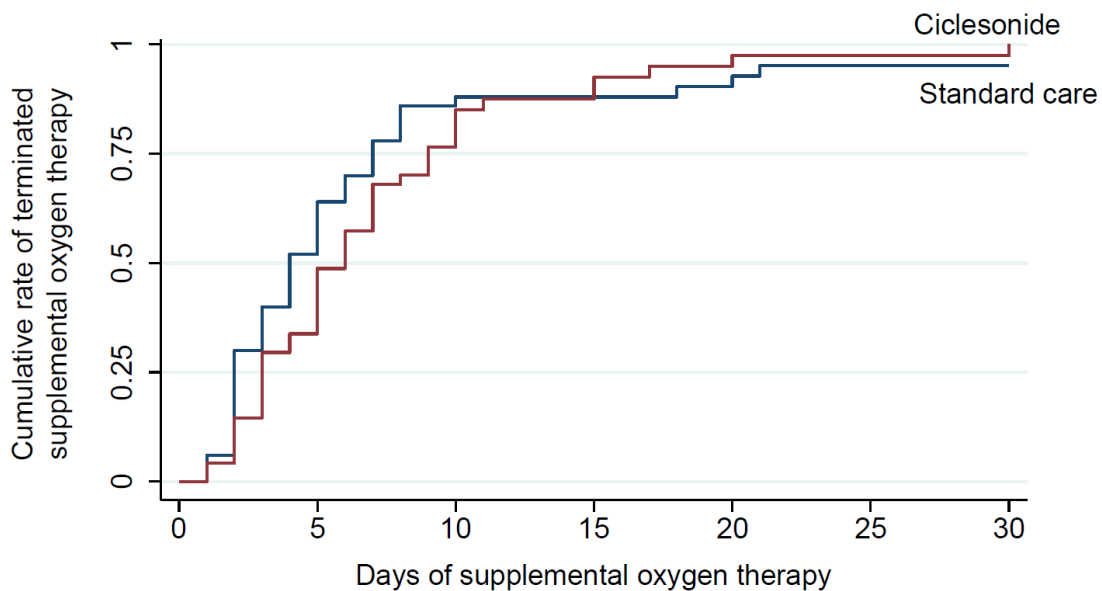
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1 **Figure 1**
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Figure 2 Time to termination of oxygen therapy.



No at risk		0	5	10	15	20	25	30
Standard care	50	24	7	6	4	2	2	
Ciclesonide	48	31	11	5	2	1	1	

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3 **ONLINE APPENDIX**
4

5 Brodin D, Tornhammar P, Ueda P, Krifors A, Westerlund E, Athlin S, Wojt S, Elvstam O,
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Protocol changes and rationale

The trial was designed in the beginning of the covid-19 pandemic when data from randomized clinical trials of Covid-19 treatment were scarce. After trial initiation, treatments for patients with Covid-19 and hospitalization rates of such patients changed rapidly. Therefore, we made changes to the protocol and the trial was stopped early.

5 weeks after the start of patient inclusion in our study, in July 2020, the Recovery Collaborative group presented preliminary data¹ showing protective effects of dexamethasone treatment in patients hospitalized for covid-19; a subgroup analysis of this study indicated that the effect was driven by patients receiving invasive mechanical ventilation or oxygen therapy. These data, in combination with local experience from treating patients with Covid-19,² led to most patients receiving oxygen therapy with ≥ 4 L oxygen/min at the study hospitals being treated with systemic corticosteroids. As use of systemic corticosteroids was an exclusion criterion, the change in practice made a large proportion of the Covid-19 patients ineligible for participation.

Initially the trial was conducted at 4 hospitals. To increase the inclusion rate, 9 additional hospitals were included as study sites, although only 5 of them ended up recruiting patients to the study. We also removed the previous upper age limit of 85 years for inclusion and allowed for inclusion of patients based on a positive antigen test for SARS-CoV-2. Moreover, because some patients may start receiving oxygen therapy before hospital admission (e.g., at nursing homes before being transported

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2
3 to the hospital) or a period after hospital admission (e.g., if the patient's condition
4 deteriorated) and we aimed to include patients shortly after initiation of such therapy,
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6 we changed the inclusion criteria from hospitalization within 48 hours prior to
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8 enrollment to initiation of oxygen therapy no longer than 48 hours prior to enrollment.
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14 All changes were approved by the Data Monitoring Committee, Ethical Review
15 Authority and the Swedish Medical Products Agency and implemented from
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17 December 2020.
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24 In June 2021, when 99 patients had been included in the study, a large and
25 increasing proportion of the adult Swedish population had received vaccination for
26
27 Covid-19. The number of patients hospitalized with Covid-19 had dropped
28
29 substantially and there were none to only a few Covid-19 patients admitted to the
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31 study hospitals per week. We determined that it was unlikely that we would reach the
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33 intended sample size and asked the Data Monitoring Committee to convene for a
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35 meeting. Following the recommendation of the Data Monitoring Committee, the study
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37 was terminated early due to expected futility to meet total enrolment.
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Inclusion and exclusion criteria^a

Participants were eligible for inclusion if, at the time of study inclusion, they (1) were aged ≥ 18 years, (2) had a polymerase chain reaction confirmed SARS-CoV-2 infection or a positive antigen test for SARS-CoV-2, (3) were hospitalized at any of the study hospitals and (4) were receiving oxygen therapy with not more than 48 hours having passed since initiation of this treatment.

Patients were not eligible for inclusion if they (1) had a history of hypersensitivity to ciclesonide or other substances included in the treatment, (2) received ongoing treatment with inhaled or oral corticosteroids, ketokonazol, itrakonazol, ritonavir or nelfinavir, (3) received >8 L oxygen/min or >50 % oxygen with nasal high-flow therapy, (4) were receiving or under consideration for palliative care or had an expected survival of less than 72 h, (5) were expected to be admitted to an intensive care unit within 48 h, (6) had active or inactive pulmonary tuberculosis, severe liver failure (Child-Pugh C), pulmonary arterial hypertension or fibrosis, cognitive or physical impairment, (7) had insufficient language skills to understand information given about the study, (8) had been included in a clinical trial within 30 days, or (9) were women and pregnant, breastfeeding or did not agree to take highly effective contraceptive measures while receiving treatment plus an additional 7 days.

^a The presentation of these inclusion and exclusion criteria have been modified for readability as compared with the version presented in the study protocol.

Appendix table 1 Number of participants included in the final study population by study center.

<i>Study center</i>	<i>n participants</i>
Danderyd Hospital	26
Capio S:t Göran Hospital	24
Karolinska University Hospital	21
Västmanland County Hospital	13
Örebro University Hospital ^a	6
Växjö Central Hospital ^a	3
Halland County Hospital ^a	2
Östersund Hospital ^a	2
Visby Hospital ^a	1

^a In the analyses adjusted for study center, these hospitals were categorized into one group.

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2. Kan B, Ahl M, Blennow O, et al. *Lakartidningen* 2020;117 [published Online First: 2020/10/07]

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	5-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,7,9
Participants	4a	Eligibility criteria for participants	7,8
	4b	Settings and locations where the data were collected	6,7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6,7
Sample size	7a	How sample size was determined	6-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6,7
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8,11

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10,11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10,11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11-13
	13b	For each group, losses and exclusions after randomisation, together with reasons	11-13
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6,7
	14b	Why the trial ended or was stopped	7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Yes
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10,11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-17
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18,19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064374.R3
Article Type:	Original research
Date Submitted by the Author:	02-Feb-2023
Complete List of Authors:	<p>Brodin, Daniel; Capio Sankt Görans Sjukhus Tornhammar, Per; Karolinska Institute, Functional Area of Emergency Medicine Ueda, Peter; Karolinska Institutet Krifors, Anders; Karolinska Institutet, Department of Physiology and Pharmacology; Västmanlands sjukhus Västerås Westerlund, Eli; Danderyd University Hospital, Department of Clinical Sciences Athlin, Simon; Örebro University Wojt, Sandra; Danderyd University Hospital, Department of Internal Medicine Elvstam, Olof; Central Hospital Växjö, Department of Infectious Diseases Neumann, Anca; Capio Sankt Görans Sjukhus Elshani, Arsim; Karlskoga Hospital Giasecke, Julia; Karolinska Universitetssjukhuset Edvardsson-Källkvist, Jens; Karolinska University Hospital Bunpuckdee, Sayam; Karolinska Institutet Unge, Christian; Danderyd University Hospital, Department of Internal Medicine Larsson, Martin; Karolinska Institutet Department of Clinical Science and Education Sodersjukhuset Johansson, Björn; Halland County Ljungberg, Johan; Halland County Lindell, Jonas; Visby Hospital, Department of Infectious Diseases Hansson, Johan; Östersund Hospital, Department of Infectious Diseases Blennow, Ola; Karolinska University Hospital, Department of Infectious Diseases Andersson, Daniel Peter; Karolinska University Hospital, Department of Medicine Huddinge H7, Karolinska Institutet; Karolinska Institute, Medicine (H7)</p>
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Respiratory medicine
Keywords:	COVID-19, Clinical trials < THERAPEUTICS, Respiratory infections < THORACIC MEDICINE

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Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19)

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*Equal contributions

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8 Word count: 3288
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11 Abstract word count: 250
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For peer review only

Abstract

Objective: To assess the efficacy of inhaled ciclesonide in reducing the duration of oxygen therapy (an indicator of time to clinical improvement) among adults hospitalized with Covid-19.

Design: Multicenter, randomized, controlled, open-label trial.

Setting: 9 hospitals (3 academic hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May 17, 2021.

Participants: Adults hospitalized with Covid-19 and receiving oxygen therapy.

Intervention: Inhaled ciclesonide 320 µg twice daily for 14 days versus standard care.

Main outcome measures: Primary outcome was duration of oxygen therapy, an indicator of time to clinical improvement. Key secondary outcome was a composite of invasive mechanical ventilation/death.

Results: Data from 98 participants were analyzed (48 receiving ciclesonide and 50 receiving standard care; median (IQR) age, 59.5 (49-67) years; 67 (68%) male). Median (IQR) duration of oxygen therapy was 5.5 (3-9) days in the ciclesonide group and 4 (2-7) days in the standard care group (hazard ratio (HR) for termination of oxygen therapy 0.73 (95% CI 0.47-1.11), with the upper 95% CI being compatible with a 10% relative reduction in oxygen therapy duration, corresponding to a <1-day absolute reduction in a post-hoc calculation). Three participants in each group died/received invasive mechanical ventilation (HR 0.90 (95% CI 0.15-5.32)). The trial was discontinued early due to slow enrollment.

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3 **Conclusions:** In hospitalized Covid-19 patients receiving oxygen therapy, this trial
4 ruled out, with 0.95 confidence, a treatment effect of ciclesonide corresponding to
5 more than a one-day reduction in duration of oxygen therapy. Ciclesonide is unlikely
6 to improve this outcome meaningfully.
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16 **Strengths and limitations of this study**

- 17 • This was a multicenter, randomized, controlled, open-label trial comparing
18 treatment with the inhaled corticosteroid ciclesonide 320 µg twice daily for 14
19 days versus standard care.
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- 21 • Healthcare providers and participants were not blinded to treatment
22 assignment.
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- 24 • The trial was terminated early due to slow recruitment.
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Introduction

Patients with Covid-19 can develop acute respiratory failure that may require invasive mechanical ventilation, associated with high mortality. The unregulated inflammation in the lungs, poor oxygenation and pulmonary infiltrates characterizing severe Covid-19 have been considered as a type of acute respiratory distress syndrome (ARDS).^{1 2}

Prior to the Covid-19 pandemic, studies have indicated that inhaled corticosteroids may reduce the risk of ARDS. In a randomized controlled trial including 61 patients at risk of ARDS, none of the patients assigned to aerosolized budesonide/formoterol vs 7 assigned to placebo developed ARDS,³ and 6 (20%) and 16 (53%) of the patients, respectively, received mechanical ventilation. In another trial including 60 patients with acute lung injury or ARDS, nebulized budesonide improved oxygenation and peak and plateau airway pressures, and reduced inflammatory markers.⁴ Moreover, potentially protective and preventive effects of inhaled corticosteroids for ARDS is supported by animals models of lung injury,⁵⁻⁸ and *in vitro* studies,⁹ and it has been speculated that local administration of the drug in the lung may maximize therapeutic benefits with fewer systemic side effects, as compared with systemic steroids.³

Therefore, it could be hypothesized that inhaled corticosteroids may be beneficial for patients with severe Covid-19. The hypothesis is further supported by reports that inhaled corticosteroids reduce the epithelial expression of genes linked to SARS-CoV-2 entry into host cells.^{10 11} Among the inhaled corticosteroids, ciclesonide has been identified as a particularly promising treatment as it can suppress replication of SARS-CoV-2 *in vitro*.^{12 13}

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3 While previous randomized controlled trials have assessed the effects of inhaled
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5 budesonide^{14 15} or ciclesonide^{16 17} in non-hospitalized Covid-19 patients, no study
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7 has been performed in hospitalized patients with more severe Covid-19.
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10 This open-label randomized controlled trial investigated the effects of inhaled
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12 ciclesonide, compared to standard care, in adult patients hospitalized with Covid-19
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14 and requiring oxygen therapy.
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21 **Methods**

24 *Study design*

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28 The HALT Covid-19 (inHALation of ciclesonide for Treatment of Covid-19) trial was a
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30 multicenter, open-label randomized controlled trial to assess the efficacy and safety
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32 of inhaled ciclesonide for the treatment of hospitalized patients with Covid-19
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34 receiving oxygen therapy. The trial was conducted at 9 hospitals (3 academic
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36 hospitals and 6 non-academic hospitals) in Sweden between June 1, 2020, and May
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38 17, 2021.
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44 All participants provided written informed consent. The study was approved by the
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46 Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the
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48 Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and
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50 registered at clinicaltrials.gov (NCT04381364).
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56 *Protocol changes and rationale*

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5 The trial was designed in the beginning of the Covid-19 pandemic. After trial initiation,
6 treatments for, and hospitalization rates of, patients with Covid-19 changed rapidly.
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8 Therefore, we made protocol changes (described in detail in the Online Appendix)
9
10 and the trial was stopped early.
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17 In brief, we increased the number of study centers, removed the upper age limit (≤ 85
18 years) for patient inclusion, changed the inclusion criteria from ≤ 48 hours since
19 hospital admission to ≤ 48 hours from initiation of oxygen therapy and allowed for
20 patients to be included on the basis of a positive antigen test for SARS-Cov-2. All
21 changes were approved by the Data Monitoring Committee, Ethical Review Authority
22 and the Swedish Medical Products Agency and implemented from December 2020.
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33 In June 2021, 99 patients had been included in the study, a large and increasing
34 proportion of the adult Swedish population had received Covid-19 vaccination and
35 hospitalizations for Covid-19 had dropped substantially. We determined that it was
36 unlikely that the intended sample size would be reached and asked the Data
37 Monitoring Committee to convene for a meeting. Following the recommendation of
38 the Data Monitoring Committee, the study was terminated for futility to meet the
39 targeted enrolment.
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52 *Participants*

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56 Based on observations from Covid-19 patients treated at the study centers, we
57 expected that 85% of the standard care group would survive and terminate oxygen
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3 therapy within 30 days (median 8 days). We considered a 25% (2 days) reduction in
4 the duration of oxygen therapy to be a clinically meaningful effect. We estimated that
5 such an effect could be detected with α of 0.05, and 80% power if 446 participants
6 (223 in each group) were enrolled.
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15 Participants were eligible for inclusion if, they (1) were aged ≥ 18 years, (2) had a
16 polymerase chain reaction confirmed SARS-CoV-2 infection or a positive SARS-CoV-
17 2 antigen test from the upper respiratory tract, (3) were hospitalized at any of the
18 study hospitals and (4) were receiving oxygen therapy, initiated within 48 hours
19 before inclusion. Key exclusion criteria were ongoing treatment with inhaled or oral
20 corticosteroids (previous use was accepted), oxygen therapy with >8 L oxygen/min or
21 >50 % oxygen on nasal high-flow cannula, and ongoing or expected intensive care or
22 palliative care (Online Appendix).
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36 *Randomization*

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38 Patients were randomized 1:1 in blocks of 8, stratified by sex and hospital to receive
39 ciclesonide or standard care. The randomization sequence was prepared by a
40 statistician not involved in the trial. Treatment allocation was provided through a web-
41 based interface. The participants and the physicians treating them were unblinded to
42 the treatment assignment.
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52 *Intervention*

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55 The treatment was 320 μg of inhaled ciclesonide (80 μg per actuation, for a total of 4
56 actuations, or 160 μg per actuation, for a total of 2 actuations) twice daily (total daily
57 dose 640 μg) for 14 days. Ciclesonide was administered using a spacer (L'espace,
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3 Nordic Infucare, Stockholm Sweden). Participants randomized to ciclesonide
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5 received written instructions, including pictures, and practical instructions on how to
6
7 use the inhalator and spacer; the first dose was taken under supervision. Ciclesonide
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9 was then prescribed in the participant's electronic medical record and each given
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11 dose during the hospitalization was recorded. Participants discharged before day 14
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13 were instructed to continue the treatment at home for a total treatment duration of 14
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15 days. Participants randomized to standard care did not receive any intervention
16
17 related to the study. Physicians treating the participants were not given any
18
19 restrictions concerning treatments during the study period. Participants who had been
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21 discharged were contacted by telephone after day 30 for a follow-up interview.
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29 *Outcomes*

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32 The primary outcome was duration of oxygen therapy (time to termination of oxygen
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34 therapy in days) up to 30 days from randomization. Oxygen therapy was defined as
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36 terminated on the day after which the patient did not receive oxygen therapy during
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38 at least 48 hours, while being alive. This outcome corresponded to clinical
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40 improvement for patients receiving oxygen therapy according to the World Health
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42 Organization clinical progression scale.¹⁸
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49 The key secondary outcome was a composite of invasive mechanical ventilation and
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51 death up to 30 days after randomization. Other secondary outcomes were each
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53 component of the key secondary outcome, admission to an intensive care unit,
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55 discharge from the hospital and dyspnea in daily living at 30-35 days after
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57 randomization as evaluated by the mMRC (Modified Medical Research Council)
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3 dyspnea scale. The scale ranges from 0 to 4 with a higher score indicating more
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5 severe dyspnea.^{19 20}
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10 Data on serious adverse events²¹ were collected by review of electronic medical
11 records. Information about non-serious adverse events associated with ciclesonide
12 use (dryness of mouth, nausea and oral candidiasis) was reported using a paper-
13 based reporting form which was filled in by the treating physician. Information about
14 non-serious adverse events occurring after hospital discharge was collected during
15 the follow-up interview.
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26 *Data collection*

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30 Patient characteristics at baseline (comorbidities, comedications, clinical parameters)
31 and study outcomes were obtained from electronic medical records. Investigators
32 contacted participants after day 30 after randomization to ask them about non-
33 serious adverse events and dyspnea in daily living (study outcome) at day 30-35 after
34 randomization.
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45 *Statistical analysis*

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48 According to the pre-specified analysis plan in the study protocol, the analyses were
49 performed by an investigator who had not been involved in the enrolment of
50 participants and was blinded to treatment assignment. An intention-to-treat
51 population was used. In the analysis of the duration of oxygen therapy, participants
52 were followed from randomization to termination of oxygen therapy, death, or 30 days
53 after randomization. Kaplan Meier cumulative incidence curves were generated to
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3 illustrate the cumulative incidence of termination of oxygen therapy in the ciclesonide
4 and standard care groups. A Cox proportional hazard regression model, adjusted for
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6 and standard care groups. A Cox proportional hazard regression model, adjusted for
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8 study hospital (Appendix Table 1), age (continuous variable) and sex was used to
9
10 estimate hazard ratios (HR) with 95% CI for time-to-event outcomes. Proportions and
11
12 the absolute risk difference with 95% CI were presented for binary outcomes. In a
13
14 per-protocol analysis of the primary outcome, participants assigned to ciclesonide
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16 were censored at the time of discontinuing treatment. The median mMRC score was
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18 compared using the Kruskal-Wallis test. A logistic regression model adjusted for
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20 study hospital, age and sex was used to compare the likelihood of reporting a mMRC
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22 score of 0 (dyspnea only with strenuous exercise).
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30 In an analysis that was not pre-specified, we additionally adjusted the primary
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32 outcome analysis for baseline variables, including days since symptom onset, c-
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34 reactive protein and white blood count (as continuous variables), and diabetes
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36 mellitus, hypertension and hyperlipidemia.
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39 95% CIs of ratios not including 1 and 95% CIs for absolute risk differences not
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41 including 0 were considered statistically significant. Secondary outcome analyses
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43 were considered hypothesis-generating and no adjustment for multiple testing was
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45 made. Analyses were performed using Stata version 16.1 (StataCorp).
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52 *Patient and Public involvement*

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55 No patients were involved in setting the research question, nor in the design,
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57 conduct, or interpretation of the study.
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Results

Of the 99 participants who underwent randomization 48 were assigned to receive ciclesonide and 51 to standard care (Figure 1). One participant in the standard care group withdrew consent and was excluded from the analysis. Ninety-eight patients (48 in the ciclesonide group and 50 in the standard care group) were included in the final analysis. All participants assigned to ciclesonide received the treatment at least once. None of the participants were lost to follow-up. The median age of participants was 59.5 (IQR 49, 67) years, 68% were men and the median duration of symptoms was 9 (IQR 8, 11) days. There were no relevant between-group differences in demographic characteristics, laboratory test results or comorbidities at enrollment (Table 1).

Table 1 Demographic and clinical characteristics of participants at study enrolment.

	Total (n=98)	Ciclesonide (n=48)	Standard care (n=50)
Age, median (IQR)	59.5 (49, 67)	61 (49, 67)	59 (49, 67)
Age ≥70 years, n (%)	78 (80)	37 (77)	41 (82)
Men, n (%)	67 (68)	34 (71)	33 (66)
Days since symptom onset, median (IQR)	9 (8, 11)	9 (7.5, 11.5)	10 (8, 11)
Days since symptom onset: <10 days, n (%)	51 (52)	27 (56)	24 (48)
Body mass index in kg/m ² , median (IQR)	29.7 (25.6, 34.0)	28.7 (25.4, 34.0)	30.6 (26.8, 34.3)
Oxygen flow of oxygen therapy in L/min, median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 2)
Respiratory rate per minute, median (IQR)	20 (18, 24)	20 (19, 25)	20 (18, 23)
C-reactive protein in mg/L, median (IQR)	100 (56, 142)	103 (62, 164)	91.5 (45.5, 124.5)

White cell count in $\times 10^9/L$, median IQR	5.7 (4.5, 7.0)	5.3 (4.3, 6.9)	6.1 (4.9, 7.0)
eGFR in mL/min/1.73m ² , median (IQR)	83 (70.5, 90)	81.5 (70, 90)	87 (73, 90)
Coexisting conditions, n (%)			
Diabetes mellitus	18 (18)	8 (17)	10 (20)
Hypertension ^a	45 (46)	22 (46)	23 (46)
Hyperlipidemia ^b	27 (28)	12 (25)	15 (30)
Chronic obstructive lung disease	3 (3)	1 (2)	2 (4)
Asthma	8 (8)	6 (13)	2 (4)
Current smoker	12 (12)	6 (13)	6 (12)
Ischemic heart disease	8 (8)	2 (4)	6 (12)
Heart failure	3 (3)	2 (4)	1 (2)
Atrial fibrillation	5 (5)	3 (6)	2 (4)
Cancer	10 (10)	5 (10)	5 (10)
Chronic kidney disease	9 (9)	5 (10)	4 (8)

^a Diagnosis of hypertension or use of antihypertensive drugs

^b Diagnosis of hyperlipidemia or use of lipid lowering therapy

Missing values were: n=1 for days since symptom onset, n=20 for body mass index, n=1 for oxygen flow of oxygen therapy, n=1 for body temperature, n=1 for heart rate, n=3 for respiratory rate, n=3 for C-reactive protein, n=7 for white cell count and n=22 for eGFR.

eGFR: estimated glomerular filtration rate

The results of primary and secondary outcome analyses are presented in Table 2.

Kaplan-Meier estimates of the median duration of oxygen therapy were 5.5 (IQR 3, 9) days in the ciclesonide group and 4 (2, 7) days in the standard care group. (Figure 2).

The HR for termination of oxygen therapy during 30 days following randomization, used to compare ciclesonide vs standard care, showed that ciclesonide treatment was not statistically significantly associated with the duration of oxygen therapy (0.73 (95% CI 0.47 to 1.11)).

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3 The research question that we aimed to assess was whether inhaled ciclesonide, as
4 compared with standard care, could reduce the time to clinical improvement (as
5 indicated by duration of oxygen therapy). While the interpretation of statistically non-
6 significant findings is a recurring and well-known subject of debate in the medical
7 literature, it is generally not recommended to use a binary interpretation based on an
8 arbitrary cut-off for statistical significance²²⁻²⁵. This is particularly important in this trial
9 as it was terminated early and thereby underpowered to assess its primary outcome.
10 However, it has been suggested that in trials with statistically non-significant findings,
11 the 95% CIs should be used to rule in or rule out potential effect sizes of the
12 intervention. In this study, we therefore assessed the largest benefit of ciclesonide
13 that was compatible with the confidence interval. Such a benefit was represented by
14 the upper limit of the HR for time to termination of oxygen therapy (a higher HR
15 indicates shorter duration of oxygen therapy for the ciclesonide group), i.e., 1.11. We
16 took the inverse of this HR ($1/1.11 = 0.90$) to calculate the relative reduction in
17 duration of oxygen therapy that the HR was compatible with (i.e., $1-0.90 = 10\%$
18 relative reduction). We then multiplied this 10% relative reduction with the absolute
19 duration of oxygen therapy in the standard care group to calculate the corresponding
20 absolute difference in duration of oxygen therapy ($10\% * 4 \text{ days} = 0.4 \text{ days}$, which is
21 $<1 \text{ day}$). Given the pre-specified minimally clinically important difference of 2 days
22 (which was used for the power calculation of the study), we deemed this best-case
23 difference to be clinically irrelevant.

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55 In the per-protocol analysis, the HR for termination of oxygen therapy during 30 days
56 following randomization was 0.79 (95% CI 0.51 to 1.23). In the additionally adjusted
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analysis (Appendix table 2) the HR for termination of oxygen therapy was 0.68 (95% CI 0.43 to 1.09) (Table 2).

Table 2 Outcomes. All outcomes are recorded during 30 days following randomization unless otherwise indicated.

	Ciclesonide	Standard care	Difference^a
Primary outcome			
Duration of oxygen therapy, median (IQR) days	5.5 (3, 9)	4 (2, 7)	0.73 (0.47 to 1.11)
Key secondary outcome			
Death or invasive mechanical ventilation, n (%)	3 (6)	3 (6)	0 (-9 to 10)
Time to death or invasive mechanical ventilation, median (IQR) days	2 (2, 10)	4 (2, 7)	0.90 (0.15 to 5.32)
Secondary outcomes			
Death, n (%)	2 (4)	1 (2)	-
Invasive mechanical ventilation, n (%)	1 (2)	3 (6)	-
Admission to an intensive care unit, n (%)	4 (8)	4 (8)	-
mMRC dyspnea scale score at day 30-35, median (IQR) ^b	3 (2, 4)	3 (2, 4)	0.97
mMRC dyspnea scale score 0 at day 30-35, n (%) ^b	4 (9)	7 (15)	0.48 (0.11 to 2.04)
Per protocol analysis^c			
Duration of oxygen therapy, median (IQR) days	5 (3, 9)	4 (2, 7)	0.79 (0.51 to 1.23)
Additionally adjusted analysis^d			
Duration of oxygen therapy, median (IQR) days	5 (3, 9)	4.5 (2, 7)	0.68 (0.43 to 1.09)

^a. Differences are expressed as hazard ratios (95% CI) estimated using a Cox proportional hazards model for time to event outcomes and as absolute risk difference (95% CI) in percent for outcomes of absolute risk. The comparison of the mMRC dyspnea score was done using the Kruskal-Wallis test and the difference is expressed as a p-value. The comparison of the likelihood of reporting a mMRC score of 0 was done using a logistic regression model and the difference is expressed as an odds ratio (95% CI). Statistical testing for differences in proportions and time-to-event analyses were not performed for the secondary outcome events, including death, invasive mechanical ventilation, and admission to an intensive care unit due to few events.

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3 ^b. Not including 1 participant in the standard care group and 2 participants in the ciclesonide group who died within
4 30 days of randomization and 1 participant in the standard care group and 1 participant in the ciclesonide group with
5 missing data on this outcome.
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9 ^c. In the per-protocol analysis for duration of oxygen therapy, patients assigned to ciclesonide were censored at the
10 time of discontinuing treatment.
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13 ^d. In addition to age, sex and study center, this analysis of duration of oxygen therapy was adjusted for days since
14 symptom onset, c-reactive protein, white blood count (as continuous variables) and diabetes mellitus, hypertension
15 and hyperlipidemia (as categorical variables). The analyses included n=46 in the standard care group and n=45 in the
16 ciclesonide group without missing data on any of the variables included in the model.
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24 In total, 3 (6%) participants assigned to ciclesonide and 3 (6%) participants assigned
25 to standard care experienced the key secondary outcome of mechanical invasive
26 ventilation or death (absolute difference 0% (95% CI -10 to 9%; HR 0.90 (95% CI
27 0.15 to 5.32)). Median mMRC dyspnea score at 30-35 days after randomization was
28 3 (IQR 2, 4) in both groups (p-value for difference 0.97) (Table 2).
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39 There were no apparent differences between the groups in treatments that
40 participants received after randomization (Table 3); 26 (54%) of the participants
41 assigned to ciclesonide and 22 (44%) of the participants in the standard care group
42 received treatment with systemic corticosteroids after randomization.
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51 Few serious adverse clinical events occurred during the study. The most frequently
52 reported adverse event was dry mouth (7 (15%) participants in the ciclesonide group
53 and 11 (22%) participants in the standard care group). Two participants assigned to
54 ciclesonide and 0 in the placebo group reported that they experienced oral
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candidiasis (Table 3).

Table 3 Participants' treatments and adverse clinical events through day 30 after randomization.

	Ciclesonide (n=48)	Standard care (n=50)
Received treatment, n (%)		
Systemic corticosteroids	26 (54)	22 (44)
Remdesivir	4 (8)	5 (10)
Low-molecular-weight heparin	45 (94)	45 (90)
Oral anticoagulants	32 (67)	30 (60)
Vasopressors	4 (8)	3 (6)
Non-invasive mechanical ventilation	8 (17)	7 (14)
Serious clinical events, n (%)		
Renal failure	2 (4)	3 (6)
Cardiac arrest	1 (2)	0 (0)
New onset atrial fibrillation	0 (0)	1 (2)
Pulmonary embolism	4 (8)	2 (4)
Other thromboembolic events	0 (0)	1 (2)
Sepsis	3 (6)	2 (4)
Other serious event	1 (2)	0 (0)
Non-serious adverse events, n (%)		
Nausea	6 (13)	8 (16)
Dry mouth	7 (15)	11 (22)
Oral candidiasis	2 (4)	0 (0)
Other non-serious adverse event	3 (6)	1 (2)

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3 Some pre-specified analyses were not performed due to small sample size or low
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5 number of events. These included statistical testing of differences in proportions and
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7 time-to-event analyses for non-key secondary outcomes, including death, invasive
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9 mechanical ventilation, and admission to an intensive care unit; the secondary
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11 outcome analyses of discharge from hospital; subgroup analyses, and the primary
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13 outcome analysis after exclusion of participants who received invasive mechanical
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15 ventilation or died.
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22 Discussion

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27 In this randomized open-label, controlled trial, including 98 hospitalized Covid-19
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29 patients with ongoing oxygen therapy, treatment with inhaled ciclesonide did not
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31 result in a statistically significant reduction in the duration of oxygen therapy, used as
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33 a measure of time to clinical improvement. The trial ruled out, with 0.95 confidence,
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35 treatments effects of ciclesonide corresponding to more than a one-day reduction in
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37 duration of oxygen therapy.
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43 While previous randomized controlled trials have assessed effects of inhaled
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45 corticosteroids, including budesonide^{14 15} and ciclesonide^{16 17}, in non-hospitalized
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47 patients with Covid-19, this is the first trial that includes hospitalized patients with
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49 more severe forms of the disease. In contrast to our hypothesis, the median duration
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51 of oxygen therapy was nominally longer among patients assigned to ciclesonide vs
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53 standard care (5.5 vs 4 days; HR for termination of oxygen therapy 0.73 (95% CI
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55 0.47 to 1.11)). As such, the 95% CI indicates that,²⁴ even in the best case,
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57 ciclesonide may reduce the duration of oxygen therapy with only 10% (1-1/1.11; less
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3 than 1 day in our study) while it may in the worst case result in an over 2-fold
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5 increase. Thus, the results of this trial indicate that ciclesonide is unlikely to provide a
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7 clinically meaningful beneficial effect on the duration of oxygen therapy in
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9 hospitalized Covid-19 patients receiving oxygen therapy.
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14 To date, 2 randomized controlled trials of ciclesonide in non-hospitalized patients with
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16 Covid-19 have been presented. In the CONTAIN study,¹⁶ which was terminated early
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18 due to slow recruitment, 215 non-hospitalized patients with a median of 3 days
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20 symptom duration were randomized to combination treatment with intranasal and
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22 inhaled ciclesonide or placebo. No statistically significant difference between the
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24 groups was observed for the primary endpoint, resolution of respiratory symptoms at
25
26 day 7 after randomization, which was reached by 40% of the patients in the treatment
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28 group vs 35% in the placebo group (adjusted risk difference of 5.5% (95% CI -7.8%
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30 to 18.8%).¹⁶ Six (6%) patients assigned to ciclesonide vs 3 (3%) in the placebo group
31
32 were hospitalized within 14 days; none died. In another clinical trial of ciclesonide,
33
34 including 400 non-hospitalized patients with Covid-19,¹⁷ randomization to ciclesonid
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36 vs placebo did not result in a reduced time to alleviation of all Covid-19 related
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38 symptoms. However, in secondary outcome analyses, patients assigned to
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40 ciclesonide had fewer emergency department visits or hospital admissions for
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42 reasons related to COVID-19 (odds ratio, 0.18, 95% CI, 0.04 to 0.85).
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51 In addition, 2 randomized clinical trials of the inhaled corticosteroid budesonide in
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53 non-hospitalized patients with Covid-19 have been presented. The STOIC trial was
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55 an open-label trial comparing inhaled budesonide vs standard care in 146 Covid-19
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57 patients with mild symptoms.¹⁴ Compared to standard care, budesonide treatment
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3 led to a statistically significant reduction in Covid-19-related emergency department
4 assessment and hospitalization (difference in proportions 0.123 (95% CI 0.043 to
5 0.218)).¹⁴ Furthermore, budesonide treatment was associated with 1 day shorter time
6 to clinical recovery. The PRINCIPLE trial was another open-label trial that included
7 4700 primary care patients at high risk of developing severe Covid-19 (1073
8 randomized to budesonide treatment; 1988 to standard care; 1639 to other
9 treatments).¹⁵ Compared to standard care, randomization to budesonide led to a
10 shorter time to self-reported recovery (difference 2.94 days (95% Bayesian credible
11 interval 1.19 to 5.12) and a reduced likelihood of hospital admission or death,
12 although the results for the latter outcomes did not meet the superiority threshold.
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28 Taken together, the previous studies indicate that inhaled corticosteroids might be
29 useful for preventing deterioration of Covid-19 in non-hospitalized patients with mild
30 symptoms. It is possible that the low likelihood of benefit associated with ciclesonide
31 treatment observed in our study reflects the more severe pulmonary inflammation in
32 our study population, as indicated by the need for hospitalization with oxygen therapy
33 and a median symptom duration of 9 days: at such stages of disease progression, it
34 could be speculated that pulmonary administration of corticosteroids may not suffice
35 to confer benefit and that systemic treatment is needed. Accordingly, in the Recovery
36 trial of hospitalized Covid-19 patients,²⁶ dexamethasone treatment reduced risk of
37 death and the time to discharge from hospital, with these benefits primarily being
38 observed among patients receiving oxygen therapy or invasive mechanical ventilation
39 at baseline.
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58 Similar to other clinical trials including patients with Covid-19,^{15 26 27} we used a
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3 pragmatic, open-label design. With this design, we intended to assess the effect of
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5 adding ciclesonide to standard care, rather than to examine the effect of ciclesonide
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7 compared to placebo. The research question that our study aimed to answer was
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9 “what is the effect of using ciclesonide as an addition to standard care as compared
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11 with standard care alone?” While this is a research question of relevance to clinical
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13 decision-making, the open-label design and the possible expectations of effect
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15 among both patients²⁸ and physicians might have affected the outcomes in our study,
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17 including when to terminate oxygen therapy. Another limitation of our study is that we
18
19 were unable to recruit the intended number of patients due to the substantial
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21 decrease in hospitalized Covid-19 patients in Sweden during 2021. Importantly, the
22
23 study could not provide much information regarding the key secondary outcome of
24
25 death or invasive mechanical intervention. Further research in hospitalized Covid-19
26
27 patients is needed to determine the potential effect of ciclesonide treatment on these
28
29 outcomes. Moreover, it is a possibility that effects of ciclesonide differ as compared to
30
31 other inhaled corticosteroids (e.g., budesonide). Patients were instructed to use
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33 ciclesonide without a spacer after discharge from the hospital; this may have affected
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35 drug delivery. Finally, results from the Recovery Trial were released 5 weeks after the
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37 initiation of our study and around half of the patients in both the ciclesonide group
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39 and the control group received systemic corticosteroids after randomization. Further
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41 studies would be needed to assess the comparative effectiveness and safety of
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43 ciclesonide vs systemic corticosteroids.
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53 **Conclusions**

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56 In this open-label randomized controlled trial in patients hospitalized with Covid-19
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58 and receiving oxygen therapy, the findings indicated that treatment with ciclesonide
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3 vs standard care is unlikely to result in a clinically meaningful reduction in the
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5 duration of oxygen therapy.
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10 11 **Acknowledgements**

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14 We would like to thank the following individuals that did not qualify for authorship but
15
16 contributed to the study: Dr Oscar Bakhouch (Skaraborg Hospital), Dr Eva-Marie
17
18 Boman and Dr Anders Lundqvist (Southern Älvsborg Hospital).
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24 **Contributorship statement**

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28 DB, PU, PT, OB and DPA conceived the study and were responsible for the
29
30 methods. OB and DPA were responsible for the study conduct. DB, PU, OB and DPA
31
32 were responsible for the financing. PT validated the data. PU performed the main
33
34 analysis. DPA, PU and PT wrote the original draft of the manuscript. All authors
35
36 wrote, reviewed, and edited the manuscript. OB and DPA supervised the study. DB,
37
38 DPA, PU, PT and OB were responsible for administration of the project. DPA and OB
39
40 are the guarantors. DB, PT, AK, EW, SA, SW, OE, AN, AE, JG, JEK, SB, CU, ML,
41
42 BJ, JL, JLI, JH, OB and DPA enrolled participants in the study. The corresponding
43
44 author attests that all listed authors meet authorship criteria and that no others
45
46 meeting the criteria have been omitted.
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54 **Competing interests**

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56 This study received non-financial support from COVIS Pharma (study drug donation).
57
58 The authors have no conflict of interest to disclose.
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Funding/Support

This study was funded by the Swedish Heart and Lung Foundation (Number 20200421), The Axel and Margaret Ax:son Johnson Foundation (N/A), CIMED (N/A), and Strategic Research Program at Karolinska Institutet (Number 961507), the Stockholm County Council (Number: 954970, 963296, 962029), and the Västmanland County Council (Grant nr LTV-938409). PU was supported by grants from the Strategic Research Program in Epidemiology at Karolinska Institutet (N/A), and a Faculty Funded Career Position at Karolinska Institutet (N/A).

The funders had no role in the study design, conduct, collection, management, analysis, interpretation of data, writing or reviewing the manuscript or decision to submit the manuscript for publication. The study drug was donated by COVIS Pharma but COVIS pharma did not participate in any other part of the study.

Data sharing statement

Data are available upon reasonable request

Ethics Approval

All participants provided written informed consent. The study was approved by the Swedish Ethical Review Authority (Ethics committee number 2020-02183) and the Swedish Medical Products Agency (Eudra-CT number 2020-001928-34) and registered at clinicaltrials.gov (NCT04381364).

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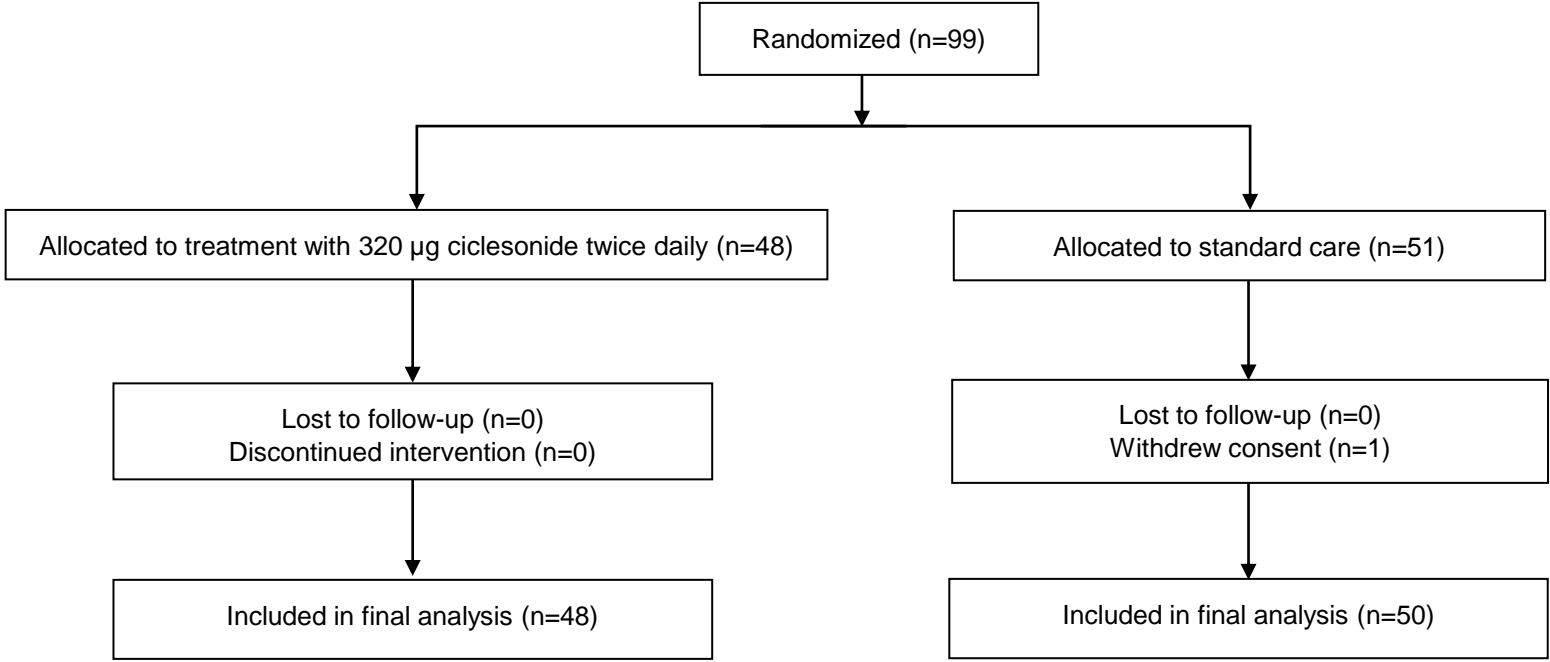
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3 **Figure 1** Flow diagram for study participants.
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5 **Figure 2** Time to termination of oxygen therapy during 30 days after randomization.
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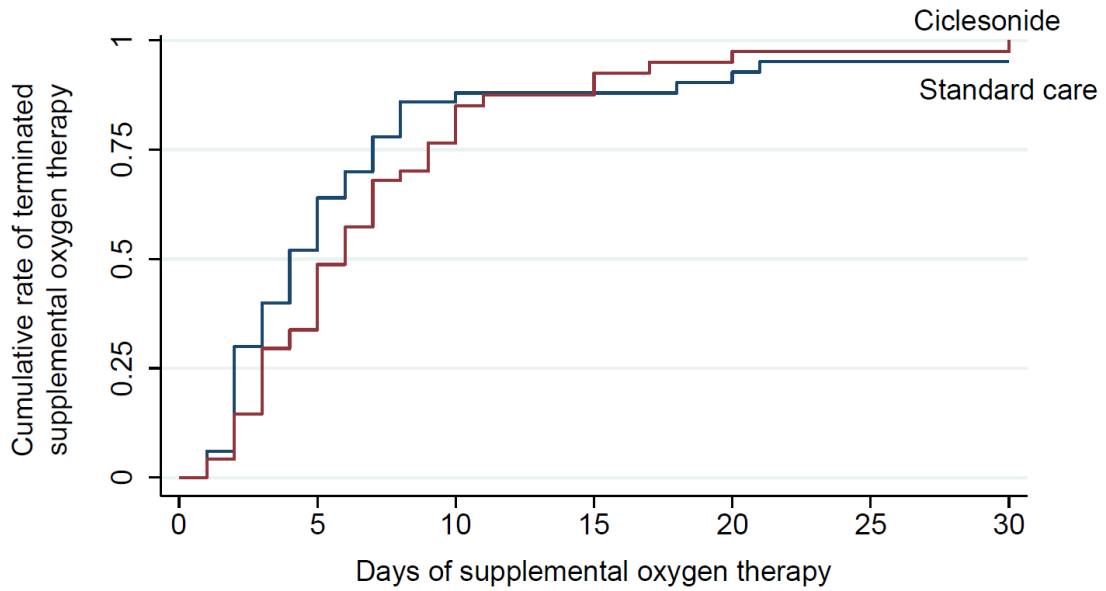
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1 **Figure 1**
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Figure 2 Time to termination of oxygen therapy.



No at risk								
Standard care	50	24	7	6	4	2	2	
Ciclesonide	48	31	11	5	2	1	1	

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ONLINE APPENDIX

Brodin D, Tornhammar P, Ueda P, Krifors A, Westerlund E, Athlin S, Wojt S, Elvstam O, Neumann A, Elshani A, Giesecke J, Edvardsson J, Bunpuckdee S, Unge C, Larsson M, Johansson B, Ljungberg J, Lindell J, Hansson J, Blennow O, Andersson DP. Inhaled Ciclesonide in Adults Hospitalized with Covid-19: a Randomized Controlled Open-label Trial (HALT Covid-19).

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Protocol changes and rationale

The trial was designed in the beginning of the covid-19 pandemic when data from randomized clinical trials of Covid-19 treatment were scarce. After trial initiation, treatments for patients with Covid-19 and hospitalization rates of such patients changed rapidly. Therefore, we made changes to the protocol and the trial was stopped early.

5 weeks after the start of patient inclusion in our study, in July 2020, the Recovery Collaborative group presented preliminary data¹ showing protective effects of dexamethasone treatment in patients hospitalized for covid-19; a subgroup analysis of this study indicated that the effect was driven by patients receiving invasive mechanical ventilation or oxygen therapy. These data, in combination with local experience from treating patients with Covid-19,² led to most patients receiving oxygen therapy with ≥ 4 L oxygen/min at the study hospitals being treated with systemic corticosteroids. As use of systemic corticosteroids was an exclusion criterion, the change in practice made a large proportion of the Covid-19 patients ineligible for participation.

Initially the trial was conducted at 4 hospitals. To increase the inclusion rate, 9 additional hospitals were included as study sites, although only 5 of them ended up recruiting patients to the study. We also removed the previous upper age limit of 85 years for inclusion and allowed for inclusion of patients based on a positive antigen test for SARS-CoV-2. Moreover, because some patients may start receiving oxygen therapy before hospital admission (e.g., at nursing homes before being transported

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3 to the hospital) or a period after hospital admission (e.g., if the patient's condition
4 deteriorated) and we aimed to include patients shortly after initiation of such therapy,
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6 we changed the inclusion criteria from hospitalization within 48 hours prior to
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8 enrollment to initiation of oxygen therapy no longer than 48 hours prior to enrollment.
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14 All changes were approved by the Data Monitoring Committee, Ethical Review
15 Authority and the Swedish Medical Products Agency and implemented from
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17 December 2020.
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24 In June 2021, when 99 patients had been included in the study, a large and
25 increasing proportion of the adult Swedish population had received vaccination for
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27 Covid-19. The number of patients hospitalized with Covid-19 had dropped
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29 substantially and there were none to only a few Covid-19 patients admitted to the
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31 study hospitals per week. We determined that it was unlikely that we would reach the
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33 intended sample size and asked the Data Monitoring Committee to convene for a
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35 meeting. Following the recommendation of the Data Monitoring Committee, the study
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37 was terminated early due to expected futility to meet total enrolment.
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Inclusion and exclusion criteria^a

Participants were eligible for inclusion if, at the time of study inclusion, they (1) were aged ≥ 18 years, (2) had a polymerase chain reaction confirmed SARS-CoV-2 infection or a positive antigen test for SARS-CoV-2, (3) were hospitalized at any of the study hospitals and (4) were receiving oxygen therapy with not more than 48 hours having passed since initiation of this treatment.

Patients were not eligible for inclusion if they (1) had a history of hypersensitivity to ciclesonide or other substances included in the treatment, (2) received ongoing treatment with inhaled or oral corticosteroids, ketokonazol, itrakonazol, ritonavir or nelfinavir, (3) received >8 L oxygen/min or >50 % oxygen with nasal high-flow therapy, (4) were receiving or under consideration for palliative care or had an expected survival of less than 72 h, (5) were expected to be admitted to an intensive care unit within 48 h, (6) had active or inactive pulmonary tuberculosis, severe liver failure (Child-Pugh C), pulmonary arterial hypertension or fibrosis, cognitive or physical impairment, (7) had insufficient language skills to understand information given about the study, (8) had been included in a clinical trial within 30 days, or (9) were women and pregnant, breastfeeding or did not agree to take highly effective contraceptive measures while receiving treatment plus an additional 7 days.

^a The presentation of these inclusion and exclusion criteria have been modified for readability as compared with the version presented in the study protocol.

Appendix table 1 Number of participants included in the final study population by study center.

<i>Study center</i>	<i>n participants</i>
Danderyd Hospital	26
Capio S:t Göran Hospital	24
Karolinska University Hospital	21
Västmanland County Hospital	13
Örebro University Hospital ^a	6
Växjö Central Hospital ^a	3
Halland County Hospital ^a	2
Östersund Hospital ^a	2
Visby Hospital ^a	1

^a In the analyses adjusted for study center, these hospitals were categorized into one group.

Appendix table 2 Additionally adjusted model.

Variable	Hazard ratio (95% CI) for termination of oxygen therapy
Ciclesonide (vs standard care)	0.68 (0.43 to 1.09)
Age (per year increase)	0.97 (0.95 to 0.99)
Female (vs male)	0.81 (0.46 to 1.40)
Days since symptom onset (per day increase)	0.99 (0.93 to 1.06)
C-reactive protein (per mg/L increase)	1.00 (1.00 to 1.00)
White cell count (per 10 ⁹ /L increase)	1.07 (0.95 to 1.19)
Diabetes	0.84 (0.44 to 1.58)
Hypertension	1.42 (0.79 to 2.56)
Hyperlipidemia	0.86 (0.45 to 1.64)

The model was also adjusted for study center.

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2. Kan B, Ahl M, Blennow O, et al. *Lakartidningen* 2020;117 [published Online First: 2020/10/07]

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	5-7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6,7,9
Participants	4a	Eligibility criteria for participants	7,8
	4b	Settings and locations where the data were collected	6,7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6,7
Sample size	7a	How sample size was determined	6-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6,7
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8,11

1		assessing outcomes) and how	
2		11b If relevant, description of the similarity of interventions	-
3	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	10,11
4		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	10,11
5			
6	Results		
7	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	11-13
8	diagram is strongly	were analysed for the primary outcome	
9	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	11-13
10	Recruitment	14a Dates defining the periods of recruitment and follow-up	6,7
11		14b Why the trial ended or was stopped	7
12	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	Yes
13	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	Yes
14		by original assigned groups	
15	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	Yes
16	estimation	precision (such as 95% confidence interval)	
17		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
18	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	10,11
19		pre-specified from exploratory	
20	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
21			
22	Discussion		
23	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-17
24	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	13-17
25	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-17
26			
27	Other information		
28	Registration	23 Registration number and name of trial registry	6
29	Protocol	24 Where the full trial protocol can be accessed, if available	-
30	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	18,19

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37 *We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also

38 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.

39 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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