Original article

Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE)

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ABSTRACT

Objectives: To assess the efficacy of inhaled ciclesonide in reducing the risk of adverse outcomes in COVID-19 outpatients at risk of developing severe illness.
Methods: COVERAGE is an open-label, randomized controlled trial. Outpatients with documented COVID-19, risk factors for aggravation, symptoms for ≤7 days, and absence of criteria for hospitalization

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are randomly allocated to either a control arm or one of several experimental arms, including inhaled ciclesonide. The primary efficacy endpoint is COVID-19 worsening (hospitalization, oxygen therapy at home, or death) by Day 14. Other endpoints are adverse events, maximal follow-up score on the WHO Ordinal Scale for Clinical Improvement, sustained alleviation of symptoms, cure, and RT-PCR and blood parameter evolution at Day 7. The trial's Safety Monitoring Board reviewed the first interim analysis of the ciclesonide arm and recommended halting it for futility. The results of this analysis are reported here.
Results: The analysis involved 217 participants (control 107, ciclesonide 110), including 111 women and 106 men. Their median age was 63 years (interquartile range 59−68), and 157 of 217 (72.4%) had at least one comorbidity. The median time since first symptom was 4 days (interquartile range 3−5). During the 28-day follow-up, 2 participants died (control 2/107 [1.9%], ciclesonide 0), 4 received oxygen therapy at home and were not hospitalized (control 2/107 [1.9%], ciclesonide 2/110 [1.8%]), and 24 were hospitalized (control 10/107 [9.3%], ciclesonide 14/110 [12.7%]). In intent-to-treat analysis of observed data, 26 participants reached the composite primary endpoint by Day 14, including 12 of 106 (11.3%, 95% CI: 6.0% −18.9%) in the control arm and 14 of 106 (13.2%; 95% CI: 7.4−21.2%) in the ciclesonide arm. Secondary outcomes were similar for both arms.
Discussion: Our findings are consistent with the European Medicines Agency's COVID-19 task force statement that there is currently insufficient evidence that inhaled corticosteroids are beneficial for patients with COVID-19. **Alexandre Duvignaud, Clin Microbiol Infect 2022;28:1010**

Introduction

Older people and people with comorbid conditions are at increased risk of adverse outcomes from COVID-19 [1−3]. COVID-19 can also affect the health system by overwhelming inpatient care and oxygen supply capacities. There is therefore a need for treatments that could reduce the risk of COVID-19-related hospitalization, oxygen indication, and death. These treatments should have a good safety profile and be administered as early as possible in outpatient care. Since the rationale underpinning the treatment of COVID-19 in patients with recent symptoms is primarily antiviral, the treatment should be active against SARS-CoV-2 [4].

There was no treatment for β-coronavirus infections at the outbreak of the COVID-19 pandemic. In the hope of obtaining rapid results, the research community sought to repurpose drugs with other indications that were already in use and therefore had a known tolerance profile. These drugs were chosen for clinical trials on the basis of preclinical arguments, including _in vitro_ anti-SARS-CoV-2 activity and _in vivo_ efficacy against SARS-CoV-2 in various types of animal. The number of molecules with _in vitro_ anti-SARS-CoV-2 activity was potentially large, and clinical trials had to be adaptive to take into account the most recent data in real time and prioritize the most promising drugs [5−9].

In this context, we initiated a trial (COVERAGE) to study the efficacy of several repurposed drugs for early outpatient treatment of COVID-19. One of the treatments studied was inhaled ciclesonide. Ciclesonide has a favourable safety profile and anti-inflammatory properties for the respiratory tract [10]. The onset of action is faster with ciclesonide than with budesonide for improving lung function in asthmatic patients [11]. Ciclesonide also has _in vitro_ activity against SARS-CoV-2 and MERS-CoV, with a half-maximal effective concentration of 0.55 μM in differentiated human bronchial and tracheal epithelial cells [12−14].

The COVERAGE trial allows the withdrawal of molecules for safety or futility reasons [8,9]. Presented here are the results of the first interim futility analysis of ciclesonide.

Methods

Study design

COVERAGE France is a phase-3, multicentre, open-label, randomized controlled trial of COVID-19 early treatment. The trial began in April 2020 and is currently underway at 14 trial centres in 9 French regions (Appendix S1, section SA1-2). The full original version and current version of the protocol are shown in Appendix S2.

The trial participants are randomly allocated to a control arm or one of the experimental arms ongoing at the time. For each experimental arm, the trial involves two phases: a pilot phase, the objective of which is to assess the safety of the drug in outpatients with COVID-19; and an efficacy phase, the objective of which is to assess the drug's efficacy in reducing the risk of hospitalisation, need for oxygen therapy, or death. The Scientific Advisory Board (SAB) can propose the opening of a new arm at any time, or the withdrawal of an ongoing arm if new external data suggest the drug is unsafe or insufficiently active against SARS-CoV-2. At the end of the pilot phase and at pre-established interim sample sizes during the efficacy phase, the Data Safety Monitoring Board (DSMB) conducts interim analyses and advises the SAB on continuation of the arm analyzed. The DSMB can also advise the SAB to withdraw an arm for safety or futility reasons at any time between analyses. Fig. SA1-3 in Appendix S1 shows all the experimental drugs included in the trial to date, as well as the date and reasons for withdrawing those that were halted prematurely.

The ciclesonide arm was opened on 29 December 2020. On 9 June 2021, the DSMB decided to run an interim analysis to ascertain whether the magnitude of the effect of ciclesonide observed in COVERAGE was within the range of that reported for budesonide in the PRINCIPLE trial [15]. The DSMB reviewed this interim analysis on 2 July 2021 and advised the SAB that continuing the ciclesonide arm would be futile. Based on this recommendation and blind to the results, the SAB decided to halt the ciclesonide arm on 22 July 2021. The arm was closed on 23 July 2021.

Reported here are the data from the participants randomized to the ciclesonide arm and those randomized to the control arm in the period when the ciclesonide arm was open.

Participants

Criteria for inclusion in the trial are as follows: (a) age ≥60 years regardless of the presence of other risk factors, or ≥50 years with at least one of the following risk factors: high blood pressure, body mass index ≥30 kg/m^2, diabetes, ischemic heart disease, heart failure, history of stroke, chronic obstructive pulmonary disease, stage ≥3 chronic kidney disease, solid or haematological

malignancy diagnosed <5 years earlier, immunosuppressive therapy, or HIV infection with CD4 $<200/mm^3$); (b) COVID-19 with first symptoms ≤7 days earlier; (c) positive SARS-CoV-2 nasopharyngeal RT-PCR or antigen test; (d) no criteria for hospitalization or acute oxygen therapy; and (e) written informed consent. Exclusion criteria are inability to understand or decide on participation; lack of health insurance; and conditions or treatment contraindicating the use of one trial drugs. For ciclesonide, the latter included chronic inhaled corticosteroid therapy, hypersensitivity to ciclesonide, history of incompletely treated pulmonary tuberculosis, pulmonary fungal infection, inability to use the inhalation chamber, and ongoing treatment with a potent CYP3A4 inhibitor.

Randomization and masking

Participants who met all the inclusion criteria and none of the exclusion criteria were randomly assigned 1:1 to one of the trial arms, using a secure online system. The randomization list had balanced blocks of fixed size and was stratified by study region. The allocated treatment was not masked from participants or investigators.

Treatment

Participants allocated to the control arm receive a 10-day treatment with a combination of vitamins and trace elements (Azinc Vitality, 2 pills per day). Participants allocated to the inhaled ciclesonide arm received a 10-day treatment with ALVESCO 160 μg, two puffs twice a day using an inhalation chamber (640 μg of ciclesonide per day).

Follow-up

Participants were randomised at home or in an outpatient facility on day (D)0 and then visited on D1, D3, D5, D7, D9, D14, and D28. D7 visits were face to face; other visits were by phone. Both patients and trial staff were allowed to request an additional visit at any time between scheduled visits for closer monitoring of clinical progress. Blood samples were collected from all participants at each trial centre on D0 to measure blood cell count, C-reactive protein, ferritin, lactate deshydrogenase, transaminases, and creatinine. At some centres, blood samples were also collected on D7 for the same tests, and a nasopharyngeal swab was collected on D7 for SARS-CoV-2 RT-PCR testing.

Endpoints

The primary endpoint of the pilot phase is the occurrence of grade 3-4-5 adverse events. The primary endpoint of the efficacy phase is a combination of hospitalization and need for COVID-19-related oxygen therapy at home or death. Secondary endpoints are adverse events of any grade, maximal follow-up score on the WHO Ordinal Scale for Clinical Improvement, sustained alleviation of symptoms (body temperature ≤37.5°C and reports of all following symptoms as minor or none, with no subsequent relapse: asthenia, headache, cough, retrosternal discomfort/pain, thoracic oppression, thoracic pain, dyspnoea, nausea, vomiting, diarrhoea, abdominal pain, anorexia, myalgia, or arthralgia), cure (participant report return to normal activity with no subsequent relapse), and RT-PCR and blood parameter evolution at D7.
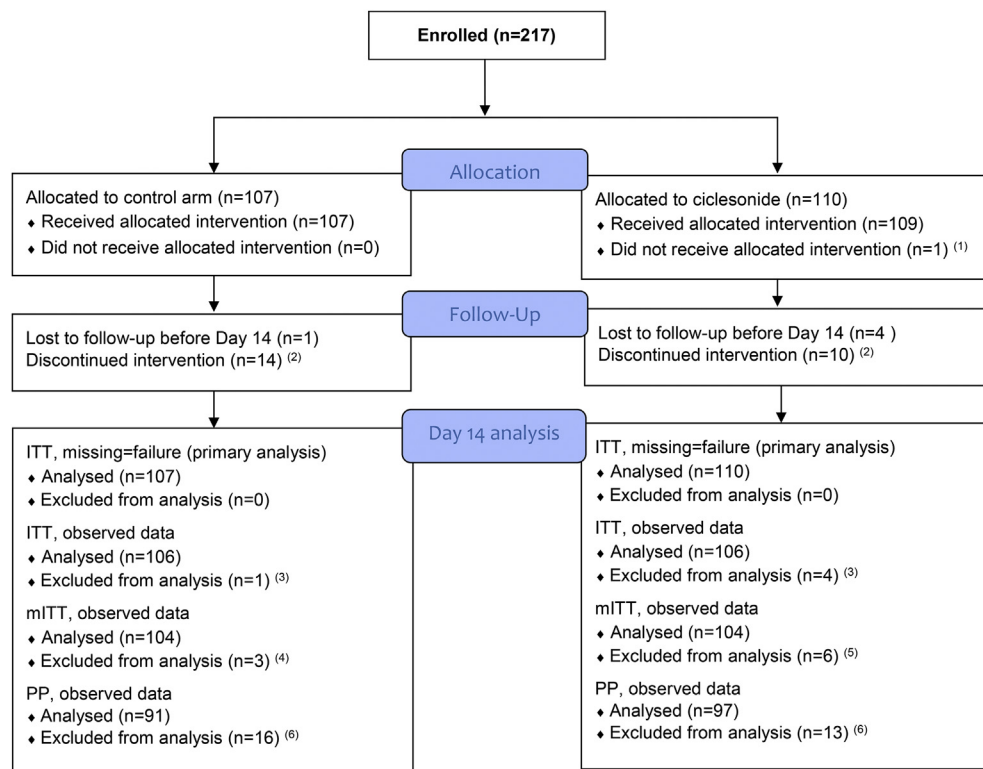

Fig. 1. CONSORT flow diagram. This figure shows the flow of participants through Day 14. The number of participants included in the analyses covering the 28-day follow-up is shown in Tables 2 and 3. ITT, intention-to-treat; mITT, modified intention-to-treat; PP, per protocol. 1. Participant on chronic inhaled corticosteroid therapy (exclusion criteria). 2. Participants who have not been lost to follow-up before Day 9 and have not completed the 10-day treatment for reasons other than the occurrence of an adverse event. 3. Patients lost to follow-up were excluded from the ITT analysis. 4. Reasons: lost to follow-up, $n = 1$; major violation of eligibility criteria, $n = 2$ (untreated diabetes, $n = 1$; patient requiring oxygen therapy before randomisation, $n = 1$). 5. Reasons: lost to follow-up, $n = 4$; major violation of eligibility criteria, $n = 2$ (already on chronic inhaled corticosteroid therapy, $n = 1$; patient requiring oxygen therapy before randomisation, $n = 1$). 6. Patients who did not receive allocated intervention were lost to follow-up or did not complete the 10-day treatment for reasons other than the occurrence of an adverse event were excluded from PP analysis.

Sample size

For the pilot phase, the sample size calculation is detailed in Appendix S2. For the efficacy phase, a sample size of 666 participants per arm was calculated as the number required to demonstrate that the proportion reaching the primary endpoint by D14 is at least 50% lower in one experimental arm than in the control arm, with the following assumptions: 7.5% reaching the primary endpoint in the control arm; $1-\beta = 95\%$; three interim analyses with 119, 235, and 403 participants in the arm; and one-sided type-I error 6.5%, 4.5%, 2.5%, and 2.5% at the first, second, and third interim analyses and final analysis.

Statistical analysis

For the pilot phase, the analysis is detailed in Appendix S2. For the efficacy phase, the primary analysis compares the proportion of participants reaching the primary endpoint by Day 14 in the two arms and is intention-to-treat (ITT) with a missing-equals-failure approach. Sensitivity analyses include an ITT analysis of observed data, excluding participants with missing data for the main outcome; a modified ITT (mITT) analysis of observed data, additionally excluding participants wrongly included; an ITT maximum bias analysis; and a per-protocol analysis of observed data. It was

Table 1
Baseline characteristics

	Control ($n = 107$)	Ciclesonide ($n = 110$)
Age (y), median (IQR)	63 (59; 70)	62 (58; 67)
Sex (female), n (%)	59 (55.1%)	52 (47.3%)
Previous COVID-19 vaccine		
No, n (%)	93 (86.9%)	94 (85.5%)
Yes, n (%)	14 (13.1%)	16 (14.5%)
One dose, n (%)	13	15
Two doses, n (%)	1	1
Time since last dose (d), median (IQR)	12 (8; 24)	16 (13; 21)
Time since first COVID-19 symptom (d), median (IQR)	4 (3–6)	4 (3–5)
At least one comorbidity, n (%)	73 (68.2%)	84 (76.4%)
High blood pressure	38 (35.5%)	51 (46.4%)
Body mass index $\geq$30 kg/m^{2}[a]	31 (29.0%)	33 (30.0%)
Diabetes	16 (15.0%)	17 (15.5%)
Stroke	9 (8.4%)	10 (9.1%)
Ischemic heart disease	7 (6.5%)	4 (3.6%)
Solid tumour or haematological malignancy <5 y	6 (5.6%)	7 (6.4%)
Chronic obstructive pulmonary disease	4 (3.7%)	3 (2.7%)
Cardiac insufficiency	3 (2.8%)	2 (1.8%)
HIV infection	1 (0.9%)	0
Body mass index (kg/m^{2}), median (IQR)	27 (24; 31)	27 (24; 32)
SpO2 under room air, median (IQR)	98 (97; 99)	98 (97; 98)
Body temperature (°C), median (IQR)	37.0 (36.5; 37.3)	36.8 (36.4; 37.3)
WHO Ordinal Scale for Clinical Improvement, n (%)		
1 - No limitation of activities	85 (79.4%)	82 (74.5%)
2 - Limitation of activities	22 (20.6%)	28 (25.5%)
Symptoms, moderate or severe, n (%)[b]		
General symptoms	81 (75.7%)	80 (72.7%)
Upper respiratory tract	39 (36.4%)	37 (33.6%)
Lower respiratory tract	39 (36.4%)	39 (35.5%)
Digestive	16 (15.0%)	25 (22.7%)
Anosmia or dysgeusia	18 (16.8%)	18 (16.4%)
Biological characteristics, median (IQR)		
Blood cell count		
Total leucocytes, $\times 10^{6}$/L	4.7 (4.0; 5.6)	4.6 (3.8; 5.6)
Lymphocytes, $\times 10^{6}$/L	1.34 (1.02; 1.78)	1.35 (1.05; 1.74)
Neutrophils, $\times 10^{6}$/L	2.67 (2.04; 3.40)	2.69 (1.86; 3.39)
Haemoglobin, g/dL	14.3 (13.3; 15.3)	14.4 (13.8; 15.5)
Platelet count, $\times 10^{6}$/L	190 (166; 229)	195 (165; 229)
C-reactive protein (CRP), mg/L	6.9 (2.2; 16.1)	9.7 (3.5; 18.8)
Ferritinemia, µg/L	263 (161; 444)	266 (158; 509)
Albuminemia, g/L	40.8 (38.0; 43.0)	40.8 (38.0; 43.7)
Creatininemia, µmol/L	71 (64; 84)	74 (64; 85)
Lactate deshydrogenase, IU/L	214 (192; 246)	211 (193; 239)
Aspartate amino transferase, IU/L	31 (23; 37)	32 (25; 44)
Alanine amino transferase, IU/L	31 (22; 44)	35 (25; 55)

IQR, interquartile range; IU, international unit; SD, standard deviation.
[a] Including eight participants with a BMI $\geq$40 kg/m^{2} (four control, four ciclesonide).
[b] Symptoms: patients were asked to report symptoms in four grades: absent, mild, moderate, and severe. We describe here the numbers and percentages of patients reporting moderate or severe symptoms for at least one symptom of the following groups:
- General symptoms: asthenia, anorexia, myalgia/arthralgia, headache
- Upper respiratory tract: rhinorrhoea/nasal obstruction/sneezing, sore throat (includes pruritus of the throat or throat irritation)
- Lower respiratory tract: cough, chest pain, chest tightness, retro sternal discomfort or pain, dyspnoea
- Digestive: nausea, vomiting, diarrhoea, abdominal pai
- Anosmia or dysgeusia
The details for each grade per symptom are shown in Appendix S1 (Section SA1-4).

decided *a priori* that all secondary analyses would be descriptive and not subject to statistical testing.

The analyses were carried out using SAS version 9.4.

Ethics

The trial protocol was approved by a French Ethics Committee (CPPIDF1-2020-ND45). Written informed consent was obtained from all participants.

Results

During the period when the ciclesonide arm was open, 217 participants were enrolled on the ciclesonide arm or the control arm (Fig. 1). Their characteristics at baseline are detailed in Table 1. Fifty-one percent were women. The median age was 63 years (range 50–86 years), with 4 (1.8%) participants aged ≥80, 40 (18.4%) between 70 and 79, 107 (49.3%) between 60 and 69, and 66 (30.4%) between 50 and 59. One hundred fifty-seven (72.4%) participants had at least one comorbidity, including 4 (100%), 28 (70%), 60 (56%), and 65 (98%) of those aged ≥80, 70–79, 60–69, and 50–59, respectively. Overall, 171 (78.8%) participants had at least one symptom reported as moderate to severe, including 78 (36%) with moderate-to-severe lower respiratory tract symptoms and 41 (19%) with moderate-to-severe digestive symptoms (Table 1). The list of baseline symptoms by severity level and arm is given in Appendix S1 (Table SA1-4).

During follow-up, the 217 participants had 1653 protocol visits (control 815, ciclesonide 838), 18 had 19 additional unscheduled visits (control 11, ciclesonide 8), 4 were prescribed oxygen therapy at home with no subsequent hospitalisation (control 2/107 [1.9%], ciclesonide 2/110 [1.8%]), 24 were hospitalized (control 10/107 [9.3%], ciclesonide 14/110 [12.7%]), and 2 died (control 2/107 [1.9%], ciclesonide 0). The median time between enrolment and admission to hospital was 6 days (IQR 4–9; control 5 [4–7], ciclesonide 6 [5–9]). The median length of hospital stay was 6.5 days (IQR 4.5–14.5; control 7.0 [5.0–14.0], ciclesonide 6.5 [3.0–15.0]).

Table 2 shows the proportion of participants who reached the primary efficacy endpoint or any of its components in each arm and the results of the primary and sensitivity analyses. In intent-to-treat analysis of observed data, 26 participants reached the composite primary endpoint by Day 14, including 12 of 106 (11.3%, 95% CI: 6.0–18.9%) in the control arm and 14 of 106 (13.2%; 95% CI: 7.4–21.2%) in the ciclesonide arm. The analysis package of the primary endpoint provided robust arguments to conclude that continuing the ciclesonide arm would be futile.

Table 3 shows the description of the secondary outcomes.

Discussion

Our data should be considered alongside others from randomised trials of inhaled corticosteroids in COVID-19 outpatients. In a phase 2 trial conducted by Song et al. [16], 61 adult patients of any age with COVID-19 were randomized to inhaled ciclesonide or standard care (SC). The number (%) of participants reaching the primary endpoint (SARS-CoV-2 RT-PCR negativation by Day 14) was 10 (32.3%) in the ciclesonide group and 1 (5.0%) in the SC group (p = 0.021) [16]. In the phase 2 STOIC trial, 146 adults of any age were randomized to inhaled ciclesonide or SC. The number (%) of participants reaching the primary endpoint (COVID-19-related emergency department assessment or hospitalization) was 2 (3%) in the ciclesonide group and 11 (15%) in the SC group (p = 0.009) [17]. In a phase 2 trial conducted by Clemency et al. [18], 413 adults of any age were randomized to inhaled ciclesonide or a placebo. The median time to alleviation of all COVID-19–related symptoms was 19.0 days (95% CI: 14.0–21.0) in the ciclesonide arm and 19.0 days (95% CI: 16.0–23.0) in the placebo arm. The number (percentage) of participants with hospital admission by day 30 was three (1.5%) in the ciclesonide arm and seven (3.4%) in the placebo arm (OR 0.45, 95% CI: 0.11–1.84, p = 0.26) [18]. The phase 2/3 CONTAIN trial compared inhaled plus intranasal ciclesonide with a placebo in COVID-19 patients of any age with

Table 2
Oxygen therapy at home, hospitalization, or death, according to randomization arm

	Control				Ciclesonide			
	N	n	Percentage	(95% CI)	N	n	Percentage (95% CI)	
Oxygen need, hospitalization, or death by Day 14								
Composite outcome								
Intention-to-treat, missing = failure[a]	107	13	12.1%	(6.6–19.9)	110	18	16.4%	(10.0–24.6)
Intention-to-treat, observed data[b]	106	12	11.3%	(6.0–18.9)	106	14	13.2%	(7.4–21.2)
Modified intention-to-treat, observed data[b]	104	11	10.6%	(5.4–18.1)	104	13	12.5%	(6.8–20.4)
Intention-to-treat, maximum bias in favour of control[b]	107	12	11.2%	(5.9–18.8)	110	18	16.4%	(10.0–24.6)
Intention-to-treat, maximum bias in favour of ciclesonide[b]	107	13	12.1%	(6.6–19.9)	110	14	12.7%	(7.1–20.4)
Per protocol analysis[b]	91	9	9.9%	(4.6–17.9)	97	11	11.3%	(5.8–19.4)
Events included in the composite outcome								
Death[c]		1				0		
Oxygen therapy at home, no hospitalization		2				2		
Hospitalization		9				12		
Oxygen need, hospitalization, or death by Day 28								
Composite outcome								
Intention-to-treat, observed data[b]	100	13	13.0%	(7.1 to 21.2)	104	16	15.4%	(9.1–23.8)
Modified intention-to-treat, observed data[b]	98	12	12.2%	(6.5 to 20.4)	102	15	14.7%	(8.5–23.1)
Events included in the composite outcome								
Death[c]		2				0		
Oxygen therapy at home, no hospitalization		2				2		
Hospitalization		10				14		

[a] Primary analysis, as per the trial protocol.
[b] Sensitivity analyses, as per the trial protocol.
[c] One participant died at home at Day 5 from undocumented cause and had no previous severe claims. One participant died at hospital at Day 16 from COVID19-related acute respiratory distress syndrome.

Table 3
Secondary outcomes, according to randomization arm

	Control			Ciclesonide		
	N	n	%	N	n	%
Positive SARS-CoV-2 PCR at Day 7[a]	54	41	75.9%	53	43	81.1%
AEs over the entire follow-up[b]						
At least one AE of any grade	96	30	31.3%	105	39	37.1%
At least one grade 1 AE	91	15	16.5%	104	22	21.2%
At least one grade 2 AE	93	11	11.8%	104	13	12.5%
At least one grade 3 AE	94	9	9.6%	103	15	14.6%
At least one grade 4 or 5 AE	91	2	2.2%	102	1	1.0%
Highest WHO OSCI grade during the entire follow-up						
1 - Ambulatory, no limitation of activities	107	20	18.7%	108	20	18.5%
2 - Ambulatory, limitation of activities	107	74	69.2%	108	72	66.7%
3 - Hospitalization, no oxygen therapy	107	1	0.9%	108	2	1.9%
4 - Hospitalization, oxygen by mask or nasal prongs[c]	107	10	9.3%	108	10	9.3%
5 - Hospitalization, noninvasive ventilation, or high-flow oxygenrowhead	107	0		108	3	2.8%
6 - Hospitalization, intubation, and mechanical ventilation	107	0		108	1	0.9%
7 - Hospitalization, ventilation, plus additional organ support	107	0		108	0	
8 - Death	107	2	1.9%	108	0	
Sustained alleviation of symptoms[d]						
By Day 7	104	31	29.8%	107	37	34.6%
By Day 14	100	57	57.0%	105	57	54.3%
Sustained self-reported cure[e]						
By Day 7	104	13	12.5%	107	13	12.1%
By Day 14	100	51	51.0%	106	47	44.3%
	N	Mean	SD	N	Mean	SD
Time to sustained alleviation of symptoms (d)[d]	78	12.1	(9.8)	79	13.3	(11.0)
Time to sustained self-reported cure (d)[e]	81	16.9	(9.0)	87	18.5	(10.2)
Ferritinemia (µg/L)[a]						
Measure at Day 7	59	384	(347)	59	460	(430)
Evolution D0 to Day 7	58	+71.7	(282)	59	+92.7	(326)
Plasma C-reactive protein at Day 7 (mg/L)[a]						
Measure at Day 7	61	15.9	(22.5)	59	23.9	(32.7)
Evolution D0 to Day 7	59	+6.1	(26.5)	59	+10.2	(36.1)
Plasma lactate dehydrogenase at Day 7 (IU/mL)[a]						
Measure at Day 7	58	241	(60)	57	246	(63)
Evolution D0 to Day 7	57	+19	(53)	57	+33	(55)

All figures showed in this Table are from observed data. OSCI, Ordinal Scale for Clinical Improvement; SD, standard deviation.

  [a] Nasopharyngeal and blood samplings were performed at Day 7 in a limited number of centres (Bordeaux, Nancy, Dijon, Montpellier). Blood samplings were performed at Day 7 in a limited number of centres (Bordeaux, Nancy, Dijon, Montpellier, Toulouse).

  [b] Severity grade according to the Common Terminology Criteria for Adverse Events (CTCAE). Eleven participants had 13 grade $\geq$ 3 adverse events in the control group: worsening of COVID-19−related pulmonary signs or symptoms ($n = 9$), intestinal ischaemia ($n = 1$), bacterial pneumonia ($n = 1$), appendicitis ($n = 1$), and death of unknown cause ($n = 1$). Sixteen participants had 26 grade $\geq$ 3 adverse events in the ciclesonide group: worsening of COVID-19−related pulmonary signs or symptoms ($n = 15$), pulmonary embolism ($n = 2$), myocardial infarction ($n = 1$), bacterial pneumonia ($n = 1$), angioedema ($n = 1$), and worsening of general symptoms ($n = 6$).

  [c] Includes the four patients who received oxygen therapy at home and were never hospitalized.

  [d] Sustained alleviation of symptoms: Body temperature $\leq$37.5°C and participant reports all of the following symptoms as minor or none, with no subsequent relapse: asthenia, anorexia, myalgia or arthralgia, headache, cough, retrosternal discomfort/pain, thoracic oppression, thoracic pain, dyspnoea, nausea, vomiting, diarrhoea, abdominal pain. When restricting the list of symptoms to those that might be helped by inhaling steroids (cough, retrosternal discomfort/pain, thoracic oppression, thoracic pain, dyspnoea), the results were as follows:

- Sustained alleviation by Day 7: control 61/104 (58.7%), ciclesonide 65/107 (60.7%)
- Sustained alleviation by Day 14: control 77/100 (77.0%), ciclesonide 81/105 (77.1%)

  [e] Cure: Participant reports return to normal activity with no subsequent relapse.

cough, dyspnoea, or fever. The trial was stopped early after enrolling 203 participants. The percentage of patients reaching the primary endpoint (resolution of symptoms by day 7) was 40% in the ciclesonide group and 35% in the placebo group (adjusted risk difference 5.5% (95% CI: 7.8%−18.8%). The number (percentage) of participants with hospital admission by Day 14 was six (6%) in the ciclesonide arm and three (3%) in the placebo arm (adjusted risk difference 2.3% (95% CI: 3.0%−7.6%) [19]. Finally, in the phase 3 PRINCIPLE trial, 1856 adults aged over 50 years with comorbidities, or over 65 with or without comorbidities, were randomized to inhaled budesonide or SC. The rate of hospitalization or death was 6.8% in the budesonide group and 8.8% in the SC group. The time to recovery was 11.8 days in the budesonide group and 14.7 days in the SC group. In Bayesian piecewise exponential analysis, the former was considered nonsignificant and the latter significant [15].

PRINCIPLE and COVERAGE have similar target populations and a similar hard primary endpoint (including hospitalization and death). The difference between arms for this endpoint was nonsignificant in PRINCIPLE and led to the conclusion of futility in COVERAGE. Although the former used budesonide and the latter ciclesonide, both trials suggest that it will be difficult to prove that inhaled corticosteroid reduces the risk of clinical worsening in trials designed to include hundreds of participants, also suggesting that the efficacy of inhaled corticosteroid in reducing this risk, if any, would be small.

There were several limitations to our trial. First, it was open label. It is therefore possible that some hospitalization decisions were influenced by knowing what treatment was being provided. Second, daily symptoms were self-reported on fixed occasions. Time to clinical improvement and cure are therefore to be interpreted with caution because of the risk of interval censoring. Third, we did not record information of the number of people approached for the study and the reasons for exclusion. Finally, morbidity data collected during the study do not allow for

conclusions about the safety profile of inhaled ciclesonide in this population.

In conclusion, it is now considered acceptable to include repurposed drugs with good safety profiles in efficacy trials on the basis of *in vitro* or *ex vivo* arguments alone, on two conditions: first, that animal research is conducted in parallel to provide the preclinical arguments that usually precede a clinical trial [9,20]; second, that interim analyses allow for early withdrawal of the drug if there are convincing arguments that the trial will never reach a conclusion on efficacy. This reasoning led to discontinuation of our ciclesonide arm. Our findings are consistent with the European Medicines Agency's COVID-19 taskforce (COVID-ETF) statement that there is currently insufficient evidence that inhaled corticosteroids are beneficial for people with COVID-19 [21]. The COVERAGE trial is currently continuing with an inhaled interferon-β1b arm.

Transparency declaration

Author contributions

AD and EL contributed equally to this work. LW, XA, and DM contributed equally to this work. AD, EL, RO, RS, DN, TP, RT, J-PJ, LR, LW, SB, RL, XA, and DM designed the study. AD, RO, XA, DM, JC, LP, CB, JD, AM, BL, J-MN, DN, TP, and OS-L enrolled and followed the patients and recorded clinical data. SD, M-EL, and MM supervised the virological and pharmacological aspects. CW, CR, AG, SK, VJ, EL, RS, RT, LR, and LW monitored the study. XdL chaired the Scientific Advisory Board. AD, XA, EL and RS performed the analysis. AD, EL, XA, and DM drafted the first version of the manuscript. All authors revised the manuscript critically for important intellectual content and approved the final version before submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.02.031.

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