Table 5b. Inhaled Corticosteroids: Selected Clinical Trial Data

Last Updated: December 20, 2023

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for inhaled corticosteroids. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
PRINCIPLE: Open-Label RCT of Inhaled Budesonide in Nonhospitalized Patients With COVID-19 in the United Kingdom[1]		
Key Inclusion Criteria • Aged ≥65 years or aged ≥50 years with comorbidities • PCR-confirmed or suspected COVID-19 • ≤14 days of COVID-19 symptoms **Key Exclusion Criteria** • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Contraindication for inhaled budesonide **Interventions** • Usual care plus inhaled budesonide 800 µg twice daily for 14 days (n = 1,069) • Usual care (n = 787) **Primary Endpoints** • COVID-19–related hospitalization or death by Day 28 • Time to reported recovery up to 28 days from randomization	**Participant Characteristics** • Mean age 64.2 years; 52% women; 92% White • 81% with comorbidities • Median of 6 days from symptom onset to randomization **Primary Outcomes** • COVID-19–related hospitalization or death by Day 28: 6.8% in budesonide arm vs. 8.8% in usual care arm (OR 0.75; 95% CrI, 0.55–1.03) • Median time to reported recovery: 11.8 days in budesonide arm vs. 14.7 days in usual care arm (HR 1.21; 95% CrI, 1.08–1.36)	**Key Limitations** • Open-label trial • Primary endpoint of time to recovery was based on patient self-report. **Interpretation** • Inhaled budesonide reduced the time to reported recovery but not the incidence of COVID-19–related hospitalization or death. • The clinical significance of self-reported time to recovery in an open-label study is unclear.
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults With Early COVID-19 in the United Kingdom[2]		
Key Inclusion Criteria • Aged ≥18 years • ≤7 days of COVID-19 symptoms **Key Exclusion Criteria** • Use of inhaled or systemic glucocorticoids in past 7 days • Known allergy or contraindication to budesonide	**Participant Characteristics** • Mean age 45 years; 58% women • 9% with CVD; 5% with DM • 95% with positive SARS-CoV-2 RT-PCR result • Median of 3 days from symptom onset to randomization	**Key Limitations** • Small, open-label trial • Trial was terminated early after statistical analysis determined that additional patients would not alter study outcome.

Methods	Results	Limitations and Interpretation
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults With Early COVID-19 in the United Kingdom[2], continued		
Interventions • Usual care plus inhaled budesonide 800 µg twice daily until symptom resolution (n = 70) • Usual care (n = 69) **Primary Endpoint** • COVID-19–related urgent care visit, including ED visit or hospitalization **Key Secondary Endpoint** • Time to clinical recovery	**Primary Outcome** • COVID-19–related urgent care visit: 1% in budesonide arm vs. 14% in usual care arm (difference in proportion 0.131; 95% CI, 0.043–0.218; *P* = 0.004) **Secondary Outcome** • Median time to clinical recovery: 7 days in budesonide arm vs. 8 days in usual care arm	• Secondary endpoint of time to recovery was based on patient self-report. **Interpretation** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care, ED visit, or hospitalization. • The clinical significance of self-reported time to recovery in an open-label study is unclear.
Phase 3, Double-Blind, Placebo-Controlled RCT of Inhaled Ciclesonide in Nonhospitalized Patients With COVID-19 in the United States[3]		
Key Inclusion Criteria • Aged ≥12 years • Positive SARS-CoV-2 molecular or antigen diagnostic test result in previous 72 hours • ≥1 symptoms of COVID-19 (i.e., fever, cough, dyspnea) **Key Exclusion Criteria** • Use of inhaled or intranasal corticosteroid within 14 days of enrollment or systemic corticosteroid within 90 days of enrollment • Unable to use an inhaler **Interventions** • Ciclesonide MDI 160 µg/actuation, administered as 2 actuations twice daily for 30 days (n = 197) • Placebo MDI twice daily for 30 days (n = 203) **Primary Endpoint** • Time to alleviation of all COVID-19–related symptoms by Day 30 **Key Secondary Endpoints** • Alleviation of COVID-19–related symptoms by Day 30	**Participant Characteristics** • Mean age 43.3 years; 55.3% women; 86.3% White • Mean BMI 29.4 • 22.3% with HTN; 7.5% with type 2 DM • Higher rates of DM and asthma in ciclesonide arm **Primary Outcome** • Median of 19 days in both arms for alleviation of all COVID-19–related symptoms (HR 1.08; 95% CI, 0.84–1.38) **Secondary Outcomes** • Alleviation of COVID-19–related symptoms by Day 30: 70.6% in ciclesonide arm vs. 63.5% in placebo arm (OR 1.28; 95% CI, 0.84–19.7) • ED visit or hospital admission for COVID-19 by Day 30: 1.0% in ciclesonide arm vs. 5.4% in placebo arm (OR 0.18; 95% CI, 0.04–0.85) • Hospital admission or death by Day 30: 1.5% in ciclesonide arm vs. 3.4% in placebo arm (OR 0.45; 95% CI, 0.11–1.84) • No deaths by Day 30 in either arm	**Key Limitations** • ED visit or hospital admission outcome was based on a small number of events. • Primary endpoint of time to alleviation of all symptoms was based on patient self-report. **Interpretation** • Inhaled ciclesonide did not reduce the time to reported recovery in nonhospitalized patients with COVID-19. • The robustness of the conclusion that inhaled ciclesonide reduced COVID-19-related ED visits or hospital admissions is uncertain. The small number of events is most likely due to the relatively low rate of comorbidities in the study population.

Methods	Results	Limitations and Interpretation
Phase 3, Double-Blind, Placebo-Controlled RCT of Inhaled Ciclesonide in Nonhospitalized Patients With COVID-19 in the United States[3], continued		
• ED visit or hospital admission for COVID-19 by Day 30 • Hospital admission or death by Day 30		
CONTAIN: Double-Blind RCT of Inhaled Ciclesonide Plus Intranasal Ciclesonide in Nonhospitalized Patients With COVID-19 in Canada[4]		
Key Inclusion Criteria • Aged ≥18 years • Positive SARS-CoV-2 molecular diagnostic test result • ≥1 symptoms of COVID-19 (i.e., fever, cough, shortness of breath) • ≤5 days of COVID-19 symptoms **Key Exclusion Criteria** • Receiving an inhaled corticosteroid or received a PO or IM corticosteroid within 7 days of enrollment • Unable to use an inhaler • Has only nonrespiratory symptoms • Use of oxygen at home • Vaccinated against COVID-19 **Interventions** • Ciclesonide MDI 600 µg/actuation plus intranasal ciclesonide 100 µg, both twice daily for 14 days (n = 105) • Saline placebo MDI plus intranasal saline, both twice daily for 14 days (n = 98) **Primary Endpoint** • Resolution of fever and all respiratory symptoms at Day 7 **Key Secondary Endpoints** • Resolution of fever and all respiratory symptoms at Day 14 • Hospital admission by Day 14	**Participant Characteristics** • Median age 35 years; 54% women; 61% White • 20% with comorbidities **Primary Outcome** • Resolution of fever and all respiratory symptoms at Day 7: 40% in ciclesonide arm vs. 35% in placebo arm (adjusted risk difference 5.5%; 95% CI, -7.8% to 18.8%) **Secondary Outcomes** • Resolution of fever and all respiratory symptoms at Day 14: 66% in ciclesonide arm vs. 58% in placebo arm (adjusted risk difference 7.5%; 95% CI, -5.9% to 20.8%) • Hospital admission by Day 14: 6% in ciclesonide arm vs. 3% in placebo arm (adjusted risk difference 2.3%; 95% CI, -3.0% to 7.6%)	**Key Limitation** • Small study with a relatively young, healthy population **Interpretation** • The use of inhaled ciclesonide plus intranasal ciclesonide did not improve resolution of fever and respiratory symptoms in nonhospitalized patients with COVID-19.

Methods	Results	Limitations and Interpretation
COVERAGE: Open-Label RCT of Inhaled Ciclesonide in Nonhospitalized Adults With COVID-19 in France[5]		
Key Inclusion Criteria • Aged ≥60 years or aged ≥50 years with comorbidities • Positive SARS-CoV-2 nasopharyngeal RT-PCR result or antigen test result • ≤7 days of COVID-19 symptoms **Key Exclusion Criteria** • Chronic use of inhaled corticosteroid therapy • Unable to use an inhalation chamber • Ongoing therapy with a potent CYP3A4 inhibitor **Interventions** • Ciclesonide 160 µg via inhalation chamber, 2 puffs twice daily for 10 days (n = 110) • Vitamin and trace element supplement, 2 capsules PO once or twice daily for 10 days (n = 107) **Primary Endpoint** • Composite of hospitalization from any cause, need for COVID-19–related oxygen therapy at home, or death by Day 14 **Key Secondary Endpoint** • Sustained alleviation of symptoms by Day 14	**Participant Characteristics** • Median age 63 years; 51% women • 72% with ≥1 comorbidities • 14% received ≥1 COVID-19 vaccine doses. **Primary Outcome** • Composite of hospitalization from any cause, need for COVID-19–related oxygen therapy at home, or death by Day 14: 16% in ciclesonide arm vs. 12% in control arm **Secondary Outcome** • Sustained alleviation of symptoms by Day 14: 54% in ciclesonide arm vs. 57% in control arm	**Key Limitation** • Small, open-label study **Interpretation** • In adult outpatients with mild COVID-19, inhaled ciclesonide did not reduce the proportion of patients who died, were hospitalized, or required COVID-19–related oxygen therapy at home.

Methods	Results	Limitations and Interpretation
ACTIV-6: Decentralized, Placebo-Controlled, Platform RCT of Inhaled Fluticasone in Outpatients With COVID-19 in the United States[6]		
Key Inclusion Criteria • Aged ≥30 years • Positive SARS-CoV-2 nasopharyngeal RT-PCR result or antigen test result • ≤7 days of ≥2 COVID-19 symptoms **Key Exclusion Criterion** • Use of inhaled or systemic corticosteroids in preceding 30 days **Interventions** • Inhaled fluticasone 200 µg once daily for 14 days (n = 656) • Matching inhaled placebo (n = 350) or placebo from a different study (n = 271) **Primary Endpoint** • Time to sustained recovery (i.e., the last of 3 consecutive days without symptoms) **Key Secondary Endpoints** • Hospitalization or death by Day 28 • Urgent care visit, ED visit, or hospitalization by Day 28 • Number of days unwell with ongoing symptoms	**Participant Characteristics** • Median age 45 years; 63% women • 39% with BMI >30; 26% with HTN • 65% received ≥2 COVID-19 vaccine doses. **Primary Outcome** • No difference between arms in time to sustained recovery (HR 1.01; 95% CrI, 0.91–1.12) **Secondary Outcomes** • Hospitalization or death by Day 28: 0.5% in fluticasone arm vs. 0.5% in placebo arm • Urgent care visit, ED visit, or hospitalization by Day 28: 3.7% in fluticasone arm vs. in 2.1% placebo arm (HR 1.9; 95% CrI, 0.8–3.5) • Mean number of days unwell with ongoing symptoms: 11.2 in fluticasone arm vs. 11.3 in placebo arm	**Key Limitations** • Low numbers of some clinical endpoints limited the ability to assess the effect of inhaled fluticasone on the key secondary endpoints. • Not all patients in the placebo arm received a matched placebo. **Interpretation** • In adult outpatients with mild COVID-19, inhaled fluticasone did not reduce the time to sustained symptom recovery or the occurrence of urgent care visits, ED visits, or hospitalizations.

Methods	Results	Limitations and Interpretation
TOGETHER: Placebo-Controlled, Platform RCT of Oral Fluvoxamine and Inhaled Budesonide in Adults With Early-Onset COVID-19 in Brazil[7]		
Key Inclusion Criteria • Aged ≥50 years or aged ≥18 years with comorbidities • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of COVID-19 symptoms **Key Exclusion Criteria** • Use of an SSRI • Severe mental illness • Cirrhosis, recent seizures, or severe ventricular cardiac arrythmia **Interventions** • Fluvoxamine 100 mg PO twice daily plus inhaled budesonide 800 mcg twice daily for 10 days (n = 738) • Placebo (n = 738; route, dosing frequency, and duration may have differed from fluvoxamine arm) **Primary Endpoint** • Composite of ED observation >6 hours or hospitalization for COVID-19 by Day 28 **Key Secondary Endpoints** • Hospitalization by Day 28 • Health care attendance by Day 28 • Any ED visit by Day 28 • Occurrence of treatment-emergent AEs	**Participant Characteristics** • Median age 51 years; 61% women • 42% with BMI >30 • 44% with HTN; 68% with ≥2 comorbidities • 94% received ≥2 COVID-19 vaccine doses. **Primary Outcome** • Composite of ED observation >6 hours or hospitalization by Day 28: 1.8% in fluvoxamine and budesonide arm vs. 3.7% in placebo arm (relative risk 0.50; 95% CrI, 0.25–0.92) **Secondary Outcomes** • Hospitalization by Day 28: 0.9% in fluvoxamine plus budesonide arm vs. 1.1% in placebo arm • Health care attendance by Day 28: 2.6% in fluvoxamine plus budesonide arm vs. 4.1% in placebo arm (relative risk 0.64; 95% CrI, 0.36–1.11) • Any ED visit by Day 28: 12.2% in fluvoxamine plus budesonide arm vs. 13.0% in placebo arm • Occurrence of treatment-emergent AEs: 17.6% in fluvoxamine plus budesonide arm vs. 12.9% in placebo arm (relative risk 1.37; 95% CrI, 1.07–1.75) • Most AEs were grade 2 events.	**Key Limitation** • Multiple investigational treatments or placebos were evaluated simultaneously. Not all patients in the placebo arm received a matched placebo. **Interpretation** • Adult outpatients with mild COVID-19 who received a combination of fluvoxamine and inhaled budesonide had fewer ED observations >6 hours or hospitalizations for COVID-19 by Day 28 than those who received placebo. • The use of fluvoxamine plus inhaled budesonide did not reduce the risk of hospitalization, health care attendance, or ED visits. • It is difficult to define the clinical relevance of the >6-hour ED observation endpoint and apply it to practice settings in different countries. • More AEs occurred with the use of fluvoxamine plus inhaled budesonide than with placebo.

Key: AE = adverse event; BMI = body mass index; CVD = cardiovascular disease; CYP = cytochrome P450; DM = diabetes mellitus; ED = emergency department; HTN = hypertension; IM = intramuscular; MDI = metered dose inhaler; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SSRI = selective serotonin reuptake inhibitor

References

1. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;398(10303):843-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388395.
2. Ramakrishnan S, Nicolau DV Jr, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9(7):763-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33844996.
3. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med*. 2022;182(1):42-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34807241.
4. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of COVID-19 in adult outpatients: CONTAIN Phase II randomised controlled trial. *BMJ*. 2021;375:e068060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34728476.
5. Duvignaud A, Lhomme E, Onaisi R, et al. Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE). *Clin Microbiol Infect*. 2022;28(7):1010-1016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35304280.
6. Boulware DR, Lindsell CJ, Stewart TG, et al. Inhaled fluticasone furoate for outpatient treatment of COVID-19. *N Engl J Med*. 2023;389(12):1085-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37733308.
7. Reis G, Dos Santos Moreira Silva EA, Medeiros Silva DC, et al. Oral fluvoxamine with inhaled budesonide for treatment of early-onset COVID-19: a randomized platform trial. *Ann Intern Med*. 2023;176(5):667-675. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37068273.