Table 6b. Inhaled Corticosteroids: Selected Clinical Data

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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[1]		
Key Inclusion Criteria: • Aged ≥65 years or aged ≥50 years with comorbidities • PCR-confirmed or suspected COVID-19 • ≤14 days of symptoms **Key Exclusion Criteria:** • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Contraindication to inhaled budesonide **Interventions:** • Usual care plus budesonide 800 mcg inhaled twice daily for 14 days (n = 1,069) • Usual care (n = 787) **Primary Endpoints:** • COVID-19-related hospitalization or death up to 28 days from randomization • 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 time from symptom onset to randomization: 6 days **Primary Outcomes:** • Percentage of patients who were hospitalized or died due to COVID-19 within 28 days: 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 reported recovery based on participant self-report **Interpretation:** • Inhaled budesonide reduced time to reported recovery but not 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[2]		
Key Inclusion Criteria: • Aged ≥18 years • ≤7 days of 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 time from symptom onset to randomization: 3 days	**Key Limitations:** • Small, open-label trial • Early termination after statistical analysis determined that additional participants 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[2], continued		
Interventions: • Usual care plus budesonide 800 mcg inhaled twice daily until symptom resolution (n = 73) • Usual care (n = 73) **Primary Endpoint:** • COVID-19-related urgent care visit, including ED visit or hospitalization	**Primary Outcomes:** • Median duration of budesonide use: 7 days. • Percentage of patients with COVID-19-related urgent care visit or hospitalization: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%).	**Interpretation:** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization.
Phase 3, Double-Blind RCT of Inhaled Ciclesonide in Nonhospitalized Patients With COVID-19[3]		

Key Inclusion Criteria:
• Aged ≥12 years
• Positive SARS-CoV-2 molecular or antigen diagnostic test result in previous 72 hours
• ≥1 symptom of fever, cough, or dyspnea
Key Exclusion Criteria:
• Taken 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, 2 actuations twice a day for 30 days (n = 197)
• Placebo MDI twice a day 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
• ED visit or hospital admission for COVID-19 by Day 30
• Hospital admission or death 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 time to alleviation of all COVID-19-related symptoms: 19.0 days in ciclesonide arm vs. 19.0 days in placebo arm (HR 1.08; 95% CI, 0.84–1.38).
	Secondary Outcomes:
	• By Day 30, percentage of patients in whom the following outcomes occurred:
	  • Alleviation of COVID-19-related symptoms: 70.6% in ciclesonide arm vs. 63.5% in placebo arm.
	  • Subsequent ED visit or hospital admission for COVID-19: 1.0% in ciclesonide arm vs. 5.4% in placebo arm (OR 0.18; 95% CI, 0.04–0.85).
	  • Hospital admission or death: 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 or hospitalization outcome based on small number of events
		• Primary endpoint of time to alleviation of all symptoms based on participant self-report
		Interpretation:
		• Inhaled ciclesonide did not reduce time to reported recovery.
		• The robustness of the conclusion that inhaled ciclesonide reduced COVID-19-related ED visits or hospitalization is uncertain; there were only a small number of events, which is most likely due to the relatively low rate of comorbidities in the study population.

Methods	Results	Limitations and Interpretation
CONTAIN: Double-Blind RCT of Inhaled and Intranasal Ciclesonide in Nonhospitalized Patients With COVID-19[4]		
Key Inclusion Criteria: • Aged ≥18 years • Positive SARS-CoV-2 molecular diagnostic test result • ≥1 symptom of fever, cough, or shortness of breath • Symptom duration ≤6 days **Key Exclusion Criteria:** • Already taking an inhaled corticosteroid or taken PO or IM corticosteroids within 7 days of enrollment • Unable to use an inhaler • No respiratory symptoms • Use of oxygen at home • COVID-19 vaccinated **Interventions:** • Ciclesonide MDI 600 µg/actuation and intranasal ciclesonide 100 µg, both twice a day for 14 days (n = 105) • Saline placebo MDI and intranasal saline, both twice a day 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 comorbid condition **Primary Outcome:** • Percentage of patients with 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:** • Percentage of patients with 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%). • Percentage of patients who were admitted to the hospital 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.

Key: BMI = body mass index; CVD = cardiovascular disease; 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

References

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