Supplemental Online Content

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*. Published online November 22, 2021. doi:10.1001/jamainternmed.2021.
6759

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods: Changes to Primary Efficacy Endpoint and Sample Size Plan

The following is the relevant text from the 4 versions of the protocol.

May 1, 2020; Version 1.0
This study is designed to assess the efficacy and safety of ciclesonide MDI plus standard supportive care compared with placebo MDI plus standard supportive care. The primary endpoint is percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30. Assuming an odds ratio of approximately 0.5 for the odds of patients meeting the primary endpoint for the ciclesonide arm to the placebo arm, a total of 400 patients (200 per arm) is required to achieve 90% power at $\alpha = 0.05$ for the study. It is anticipated that approximately 40% of placebo treated patients will have a subsequent emergency department visit or hospital admission compared to approximately 25% for those treated with ciclesonide. Note that these are best estimates at this point as there is still much uncertainty regarding COVID-19.

May 18, 2020; Version 2.0 (Protocol Amendment 1)
This study is designed to assess the efficacy and safety of ciclesonide MDI plus standard supportive care compared with placebo MDI plus standard supportive care. The primary endpoint is percentage of patients with hospital admission or death by day 30. Assuming an odds ratio of approximately 0.5 for the odds of patients meeting the primary endpoint for the ciclesonide arm to the placebo arm, a total of 400 patients (200 per arm) is required to achieve 90% power at $\alpha = 0.05$ for the study. It is anticipated that approximately 40% of placebo treated patients will have a hospital admission or death compared to approximately 25% for those treated with ciclesonide. Note that these are best estimates at this point as there is still much uncertainty regarding COVID-19.

August 31, 2020; Version 3.0 (Protocol Amendment 2)
No Change to Primary Efficacy Endpoint or Sample Size Plan from the previous version.

December 21, 2020; Version 4.0 (Protocol Amendment 3)
This study is designed to assess the efficacy and safety of ciclesonide MDI plus standard supportive care compared with placebo MDI plus standard supportive care. The primary endpoint is time to alleviation of COVID-19-related symptoms of cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell, defined as symptom-free for a continuous period of 24 hours (ie, ≥ 3 AM/PM assessments) by day 30. Assuming a median time to alleviation of 7 days for the ciclesonide arm and 11 days for the placebo arm (hazard ratio of approximately 1.58) with a total study duration of 30 days and a total of 201 events observed in the 2 arms combined, a sample size of approximately 232 patients (116 in each arm) is required to achieve 90% power at $\alpha = 0.05$ for the study. To account for an unknown drop-out rate in this patient population as well as other factors that may impact the overall power of the study, the planned sample size was increased to 400 patients (200 in each arm) for this study. Note that these are best estimates at this point as there is still much uncertainty regarding COVID-19.

eTable 1: Number of Participants Enrollment by Month and Location

	June	July	August	September	October	November	Total
Miami, FL				29	60	10	99
Easley, SC		4	7	19	22	3	55
Buffalo, NY	8	16	5	8	9	1	47
Williamsburg, VA	7	24	6	4	4	2	47
Riverton, UT				26	15	1	42
Miami Springs, FL			29	7	1		37
Boca Raton, FL		28					28
Dallas, TX		4		12	1		17
Nashville TN		1	1	9	4	2	17
Winston-Salem, NC			4	3	3	1	11
Total	15	77	52	117	119	20	400

Patients were screened and enrolled from June 11, 2020 to November 3, 2020

eTable 2: Cox Regression of Time to Alleviation of COVID-19-Related Symptoms of Cough, Dyspnea, Chills, Feeling Feverish Based on Severity of Symptoms at time of Enrollment

	Subjects in Treatment Arm	Subjects in Placebo Arm	Hazard Ratio [a]	95% CI
One or more severe symptoms	5 (2.5%)	9 (4.4%)	5.64	(0.39 - 80.78)
No severe symptoms	192 (97.5%)	194 (95.6%)	1.06	(0.83 - 1.35)
One or more moderate or severe symptoms	80 (40.6%)	74 (36.5%)	1.10	(0.72 - 1.68)
No Moderate or severe symptoms	117 (59.4%)	129 (63.5%)	1.13	(0.83 - 1.54)

[a] Hazard Ratio > 1 implies a better outcome (faster resolution of symptoms with treatment compared to placebo).

eTable 3: Adverse Events

		Ciclesonde	Placebo	Overall
Participants with at least one adverse event		22 (11.2%)	29 (14.3%)	51 (12.8%)
Respiratory, thoracic and mediastinal disorders		6 (3.0%)	9 (4.4%)	15 (3.8%)
	Dyspnoea	1 (0.5%)	4 (2.0%)	5 (1.3%)
	Dysphonia	2 (1.0%)	0	2 (0.5%)
	Hypoxia	0	2 (1.0%)	2 (0.5%)
	Cough	0	1 (0.5%)	1 (0.3%)
	Nasal Congestion	1 (0.5%)	0	1 (0.3%)
	Productive cough	1 (0.5%)	0	1 (0.3%)
	Sinus pain	1 (0.5%)	0	1 (0.3%)
	Throat tightness	0	1 (0.5%)	1 (0.3%)
	Wheezing	0	1 (0.5%)	1 (0.3%)
Infections and infestations		6 (3.0%)	7 (3.4%)	13 (3.3%)
	COVID-19	1 (0.5%)	3 (1.5%)	4 (1.0%)
	COVID-19 pneumonia	1 (0.5%)	2 (1.0%)	3 (0.8%)
	Oral candidiasis	1 (0.5%)	1 (0.5%)	2 (0.5%)
	Cellulitis	1 (0.5%)	0	1 (0.3%)
	Conjunctivitis	1 (0.5%)	0	1 (0.3%)
	Urinary tract infection	1 (0.5%)	0	1 (0.3%)
	Varicella zoster virus infection	0	1 (0.5%)	1 (0.3%)
Gastrointestinal disorders		3 (1.5%)	6 (3.0%)	9 (2.3%)
	Dry mouth	3 (1.5%)	1 (0.5%)	4 (1.0%)
	Dyspepsia	0	2 (1.0%)	2 (0.5%)
	Diarrhoea	0	1 (0.5%)	1 (0.3%)
	Intestinal obstruction	0	1 (0.5%)	1 (0.3%)
	Nausea	0	1 (0.5%)	1 (0.3%)
Nervous system disorders		2 (1.0%)	6 (3.0%)	8 (2.0%)
	Headache	1 (0.5%)	0	1 (0.3%)
	Dizziness	0	1 (0.5%)	1 (0.3%)
	Hypoaesthesia	1 (0.5%)	0	1 (0.3%)
	Paraesthesia	1 (0.5%)	0	1 (0.3%)
	Piriformis syndrome	0	1 (0.5%)	1 (0.3%)
General disorders and administration site conditions		1 (0.5%)	2 (1.0%)	3 (0.8%)
	Chest discomfort	1 (0.5%)	1 (0.5%)	2 (0.5%)
	Fatigue	0	1 (0.5%)	1 (0.3%)
Cardiac disorders		0	2 (1.0%)	2 (0.5%)
	Atrial fibrillation	0	1 (0.5%)	1 (0.3%)
	Bradycardia	0	1 (0.5%)	1 (0.3%)
Injury, poisoning and procedural complications		2 (1.0%)	0	2 (0.5%)
	Animal bite	1 (0.5%)	0	1 (0.3%)
	Tendon injury	1 (0.5%)	0	1 (0.3%)
Musculoskeletal and connective tissue disorders		2 (1.0%)	0	2 (0.5%)
	Back pain	1 (0.5%)	0	1 (0.3%)
	Neck pain	1 (0.5%)	0	1 (0.3%)
Psychiatric disorders		0	2 (1.0%)	2 (0.5%)
	Insomnia	0	1 (0.5%)	1 (0.3%)
	Panic attack	0	1 (0.5%)	1 (0.3%)
Renal and urinary disorders		2 (1.0%)	0	2 (0.5%)

	Nephrolithiasis	1 (0.5%)	0	1 (0.3%)
	Renal failure	1 (0.5%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders		1 (0.5%)	1 (0.5%)	2 (0.5%)
	Dermatitis atopic	1 (0.5%)	0	1 (0.3%)
	Rash	0	1 (0.5%)	1 (0.3%)
Investigations		0	1 (0.5%)	1 (0.3%)
	Oxygen saturation decreased	0	1 (0.5%)	1 (0.3%)
Metabolism and nutrition disorders		1 (0.5%)	0	1 (0.3%)
	Decreased appetite	1 (0.5%)	0	1 (0.3%)

Specific symptoms were adjudicated to be an adverse event if, in the opinion of the PI, they were outside of what would be expected of the participants' COVID-19 disease progression or if they were associated with a need for emergency care or hospitalization.