**Philippine COVID-19 Living Clinical Practice Guidelines**
*Institute of Clinical Epidemiology, National Institutes of Health, UP Manila*
*In cooperation with the Philippine Society for Microbiology and Infectious Diseases*
*Funded by the Department of Health*

# EVIDENCE SUMMARY

## Among patients with COVID-19, should inhaled corticosteroids be used as treatment?

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## RECOMMENDATION

**There is insufficient evidence to recommend the use of inhaled corticosteroids in treatment of non-hospitalized COVID-19 patients.** *(Very low certainty of evidence)*

*Consensus Issues*
Current evidence shows that inhaled corticosteroids (i.e., budesonide and ciclesonide) had benefit for subjective outcomes such as self-reported recovery on day 14 and day 28/30. However, evidence was inconclusive in terms of objective outcomes such as mortality, emergency room visit, need for hospitalization, duration of hospitalization, and clinical improvement (as evaluated by an assessor). Self-reported recovery may be biased since participants are not blinded, hence a more objective marker of clinical status such as oxygen saturation is more reliable. Only 1 study explicitly excluded patients with asthma or chronic obstructive pulmonary disease (COPD), and the perceived positive effect may have been due to improvement of asthma or COPD and not COVID infection. As of writing, there are 13 ongoing clinical trials, results of which may further elucidate on the effectiveness of inhaled corticosteroids in the treatment of COVID-19.

## PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of inhaled corticosteroids as treatment for non-hospitalized patients with mild to moderate COVID-19 infection. *(Very low certainty of evidence)*

*Previous consensus issues*
Further studies are needed to determine the effectiveness of inhaled corticosteroids for the treatment of COVID-19 infection. Inhaled corticosteroids can be used to provide symptomatic relief for other concomitant conditions such as asthma and COPD.

## What's New

Two (2) randomized controlled trials (RCTs) were added to this review.

## Key Findings

Four (4) randomized controlled trials (RCTs) investigated the effectiveness of inhaled corticosteroids for the treatment of COVID-19. Use of inhaled corticosteroids (e.g., budesonide and ciclesonide) among non-hospitalized patients with mild to moderate COVID-19 demonstrated benefit only for subjective outcomes such as self-reported clinical recovery or improvement at day 14 and day 28/30 but not for objective outcomes such as mortality, need for hospitalization, emergency room visit, and duration of hospitalization. There was no significant difference in serious adverse events and adverse events.

## Introduction

Systemic corticosteroids have demonstrated efficacy against COVID-19 in several studies, probably through decreasing SARS-CoV-2 infection-associated inflammation and have been used for the treatment of COVID-19. One of the major causes of COVID-19-related deaths is acute respiratory distress syndrome which can be attributed to an exaggerated immune response.[1] COVID-19 is postulated to elicit inflammatory cytokine secretion, not only from alveolar macrophages but also from alveolar epithelial type 2 cells leading to the assumption that immunosuppression should be largely directed towards the lungs.[2] Inhaled corticosteroids (ICS) have been used to treat asthma and chronic obstructive pulmonary disease (COPD) by reducing lung inflammation, which led to the premise that ICS may have the potential to protect against severe SARS-CoV-2 infection.[3] Furthermore, administration of corticosteroids via inhalation could effectively reduce inflammation in the lungs with fewer systemic side effects. Two reviews of inhaled corticosteroids for COVID-19 showed no clear evidence on whether use of ICS had adverse or beneficial outcomes in COVID-19 patients.[4,5]. In-vitro studies implied that inhaled glucocorticoid use reduced the replication of SARS-CoV-2 in airway epithelial cells. Furthermore, inhaled glucocorticoids may lead to the downregulation of angiotensin-converting enzyme 2 (*ACE2*) and transmembrane serine protease 2 (*TMPRSS2*) expression, which are both necessary for viral entry.[6] Studies showed that nebulized budesonide improved oxygenation and significantly reduced inflammatory markers (tumor necrosis factor-α, interleukin 1β [IL-1β], and IL-6) in patients with acute respiratory distress syndrome.[7] The anti-inflammatory effect of ciclesonide can be attributed to its blocking effect on PAK1 (RAC/CDC42-activated kinase 1), which is necessary in inflammation.[8] The activity of fluticasone propionate is attributed to the inhibition of cytokine-induced production of pro-inflammatory proteins leading to the suppression of inflammatory mediators and reducing the number of mast cells and lymphocytes.[9] Apart from their anti-inflammatory effects, in-vitro studies showed that ciclesonide and mometasone have antiviral effects and suppressed the replication of SARS-CoV-2 and MERS-CoV.[10]

## Review Methods

A systematic search was done in Medline, Cochrane Library, and Google Scholar from October 9, 2021 to October 13, 2021 using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome, coronavirus 2 or SARS-CoV-2, budesonide, ciclesonide, fluticasone, mometasone, beclomethasone, flunisolide, inhalational steroid, inhalational corticosteroid, inhaled steroid, and inhaled corticosteroid. The COVID-NMA Living Data was also searched and a search for ongoing studies in the WHO clinical trial registry, NIH *clinicaltrials.gov,* and various trial registries was done. Medrxiv, chinaxiv and biorxiv were also searched for preprints. Only randomized controlled trials were included in this review. Outcomes of interest included

hospitalization, emergency department visit, mortality, clinical recovery or improvement, and adverse events.

## Results

Four (3 published and 1 preprint) RCTs [11-14] compared the effect of inhaled corticosteroid against placebo and/or standard of care among confirmed COVID-19 patients (n = 2,463). Two trials were conducted in the UK [11,12], and 2 multicenter trials were conducted in the US [14] and South Korea.[13] Two studies evaluated inhaled budesonide [11,12], while 2 studies evaluated inhaled ciclesonide.[13,14] Three studies [11,12,14] included patients with chronic respiratory disease [e.g., bronchial asthma and chronic obstructive pulmonary disease (COPD)] who were not on maintenance medication of inhaled corticosteroids or not currently using inhaled corticosteroids during the time of the trial. One study [13] however, excluded patients diagnosed with bronchial asthma and COPD. Appendix 3 summarizes the characteristics of included studies in this review.

The overall methodological quality of evidence was rated very low due to serious risk of bias (performance, detection, and attrition), and imprecision in majority of the critical outcomes (e.g., hospitalization, death, self-reported clinical recovery, and serious adverse events). The risk of bias summary is in Appendix 4. The GRADE evidence summary is in Appendix 5.

Pooled estimates of objective outcomes, namely hospitalization/death (RR 0.82, 95% CI 0.62-1.08; $I^2$ = 0%; n = 2,256, 2 RCTs), hospitalization/emergency department visit (RR 0.36, 95% CI 0.11-1.20; $I^2$ = 73%; n = 2,132, 3 RCTs), mortality (RR 0.74, 95% CI 0.28-1.99; n = 1,856, 1 RCT), hospitalization (RR 0.85, 95% CI 0.64-1.15; n = 1,856, 1 RCT) and duration of hospitalization (MD -0.25 days, 95% CI -0.75 to 0.25; $I^2$ = 0%; n = 1,917, 2 RCTs) did not reach statistical significance.

In terms of subjective outcomes, inhaled corticosteroids showed statistically significant benefit in self-reported clinical recovery/improvement at day 14 (RR 1.18, 95% CI 1.10-1.27; $I^2$ = 0%, n = 2,463, 4 RCTs) and day 28/30 (RR 1.10, 95% CI 1.04-1.16, $I^2$ = 0%; n = 2,317, 3 RCTs) compared with placebo and/or standard of care. There was benefit in self-reported clinical recovery at day 14 (RR 1.15, 95% CI 1.07-1.24; n = 2,402, 3 RCTs) and at day 28/30 (RR 1.09, 95% CI 1.03-1.15; n = 2,256, 2 RCTs). However, there was no significant benefit for self-reported clinical recovery/improvement at day 7 (RR 1.07, 95% CI 0.95-1.20; $I^2$ = 0%; n = 2,317, 3 RCTs) and self-reported clinical recovery at day 7 (RR 1.08, 95% CI 0.95-1.22; $I^2$ = 0%; n = 2,256, 3 RCTs). The findings were inconclusive for clinical improvement at day 7 (RR 0.94, 95% CI 0.60 to 1.47; n = 61, 1 RCT) as well as clinical improvement at day 14 (RR 1.38, 95% CI 0.92-2.07; n = 61, 1 RCT) and did not reach statistical significance but showed potential towards benefit for the outcome clinical improvement at day 28/30 (RR 1.20, 95% CI 0.99-1.46; n = 61, 1 RCT). Time to self-reported clinical recovery/improvement also demonstrated to be statistically beneficial for inhaled corticosteroids (MD -1.72 days, 95% CI -3.28 to -0.17; n = 2,402, 3 RCTs) but with substantial heterogeneity ($I^2$ = 91%).

Pooled estimate for viral eradication at day 14 (RR 6.45, 95% CI 0.89-46.60; n = 51, 1 RCT) did not reach statistical significance but showed potential towards benefit. The forest plots are shown in Appendix 6.

Sensitivity analysis excluding the preprint study still showed statistically significant benefit for the following outcomes: time to self-reported clinical recovery/improvement (MD -2.04 days, 95% CI -4.0 to -0.08, $I^2$ = 94%; n = 2,002, 2 RCTs), self-reported clinical recovery/improvement at day 14 (RR 1.19, 95% CI 1.10-1.28; $I^2$ = 0%; n = 2,063, 3 RCTs), self-reported clinical

recovery/improvement at day 28/30 (RR 1.09, 95% CI 1.03-1.17; $I^2$ = 3%; n = 1,917, 2 RCTs), self-reported clinical recovery at day 14 (RR 1.15, 95% CI 1.07-1.25; $I^2$ = 0%; n = 2,002, 2 RCTs), and self-reported clinical recovery at day 28 (RR 1.08, 95% CI 1.02 to 1.15, n=1,856, 1 RCT). Sensitivity analysis excluding the preprint study for self-reported clinical recovery at day 7 (RR 1.16, 95% CI 1.06-1.27; n = 1,856, 1 RCT) showed statistically significant benefit. Sensitivity analysis excluding the preprint study for the rest of the outcomes including hospitalization/death (RR 0.78, 95% CI 0.57-1.08; n = 1,856, 1 RCT), hospitalization/emergency department visit (RR 0.46, 95% CI 0.11-1.93; n = 1,732, 2 RCTs), duration of hospitalization (MD -0.25 days, 95% CI -0.75 to 0.25; n = 1,917, 2 RCTs) and self-reported clinical recovery/improvement at day 7 (RR 1.07, 95% CI 0.95-1.21; n=1,917, 2 RCTs) was similar with primary analysis and remained statistically insignificant.

**Safety**

There was no significant difference in the incidence of adverse events (RR 2.31, 95% CI 0.35-15.07; $I^2$ = 59%; n = 607, 3RCTs) and serious adverse events (RR 0.68, 95% CI 0.12-3.70; n = 1,856, 1 RCT) between the inhaled corticosteroids and standard of care or placebo group. Sensitivity analysis excluding the preprint study for the outcome adverse events showed potential towards harm, although results did not reach statistical significance (RR 7.64, 95% CI 0.98-59.34; $I^2$ = 0%; n = 207, 2 RCTs). Reported adverse events included headache, dizziness, nausea, bruising, odynophagia, sore throat, dry mouth, and oral candidiasis. The adverse events were non-fatal and self-limiting with full recovery upon cessation of the inhaled corticosteroid. Serious adverse events were reported in only one study (PRINCIPLE trial) but these serious adverse events requiring hospital admission were not specified in the trial.

## Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

| Regulatory Agency | Recommendation |
|---|---|
| Canadian Thoracic Society (CTS)<br>(as of October 15, 2021) | Recommends the use of inhaled corticosteroids as regular maintenance and exacerbation management for asthma and chronic obstructive pulmonary disease (COPD) be continued according to current treatment guidelines. They do not recommend the use of a nebulizer unless absolutely necessary (no other alternative available).[15-17] |
| UK NICE<br>(as of April 16, 2021) | |
| Public Health Agency of Canada (PHAC)<br>(as of December 22, 2020) | |
| British Thoracic Society<br>(as of October 4, 2021) | Recommends the use of inhaled corticosteroids as regular maintenance and exacerbation management for asthma and chronic obstructive pulmonary disease (COPD) be continued according to current treatment guidelines and supports the use of nebulizers, claiming that there is no evidence supporting an increased risk of viral transmission.[18] |
| Australian Guideline<br>(as of October 21, 2021) | Conditionally recommends inhaled corticosteroid (budesonide) for treating patients with confirmed COVID-19 who do not require oxygen but have 1 or more risk factors for disease progression and recommends the use of inhaled or oral steroids for |

| | |
|---|---|
| | the management of people with co-existing asthma or chronic obstructive pulmonary disease (COPD) and COVID-19 as one would normally do for viral exacerbation of asthma or COPD but do not recommend the use of a nebulizer.[19] |
| Philippine Society for Microbiology and Infectious Diseases (PSMID)<br>(as of July 20, 2020) | Do not recommend the use of inhaled corticosteroid (ICS) as treatment nor for prophylaxis against COVID-19 pending the results of ongoing studies.[20] |
| US-NIH<br>(as of August 25, 2021) | No recommendation on the use of inhaled corticosteroids for the treatment of COVID-19. |
| World Health Organization (WHO)<br>(as of September 21, 2021) | |
| Infectious Diseases Society of America (IDSA)<br>(as of October 1, 2021) | |
| American Thoracic Society and European Respiratory Society | |

## Research Gaps

As of October 13, 2021, there are 13 ongoing clinical trials on inhaled corticosteroids registered (Appendix 6).

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# Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 4)

| FACTORS | JUDGEMENT (N = 4) | | | | | | RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS |
|---|---|---|---|---|---|---|---|
| **Problem** | No | Yes (4) | | | | | |
| **Benefits** | Large | Moderate (2) | Small (2) | Uncertain | | | • Inconclusive in terms of objective outcomes: mortality, hospitalization/death, hospitalization/ER visit, duration of hospitalization<br>• Benefit in self-reported clinical recovery/improvement at day 14 (RR 1.18, 95% CI 1.10-1.27) and day 28/30 (RR 1.10, 95% CI 1.04-1.16) |
| **Harm** | Large | Small (2) | Uncertain (2) | | | | • No significant difference in adverse events (RR 2.31, 95% CI 0.35-15.07; $I^2$ = 59%; n = 607, 3RCTs) and serious adverse events (RR 0.68, 95% CI 0.12-3.70; n = 1,856, 1 RCT) |
| **Certainty of Evidence** | High | Moderate | Low (4) | Very low | | | • Serious risk of bias (performance, detection, and attrition), and imprecision in majority of the critical outcomes (e.g., hospitalization, death, self-reported clinical recovery, and serious adverse events) |
| **Balance of effects** | Favors drug (3) | Does not favor drug | Uncertain (1) | | | | • Net potential benefit in terms of subjective (self-reported) outcomes, with no significant harm |
| **Values** | Important uncertainty or variability (3) | Possibly important uncertainty or variability (1) | Possibly NO important uncertainty or variability | No important uncertainty or variability | | | |
| **Resources Required** | Uncertain | Large cost | Moderate cost (4) | Negligible cost | Moderate savings | Large savings | • Budesonide 800 mcg/dose 2x a day for 14 days = Php 1,862.00 to Php 12,091.24 (nebule), Php 796.32 to 1,422.00 (dry powder inhaler)<br>• Ciclesonide 160 mcg/dose 2x a day for 14 to 30 days = Php 6,641.37 to 14,231.50 |
| **Certainty of evidence of required resources** | No included studies | Very low (1) | Low | Moderate (2) | High (1) | | • Prices were from the 2020 Philippine Drug Price Reference Index, the DOH Memorandum (9/9/2020) on suggested retail price, and Amazon Pharmacy. |
| **Cost effectiveness** | No included studies (4) | Favors the comparison | Does not favor either the intervention or the comparison | Favors the intervention | | | |
| **Equity** | Uncertain (2) | Reduced (1) | Probably no impact (1) | Increased | | | |
| **Acceptability** | Uncertain (3) | No | Yes (1) | | | | |
| **Feasibility** | Uncertain (1) | No | Yes (3) | | | | |

## Appendix 2. Search Yield and Results

| DATABASE | SEARCH STRATEGY / SEARCH TERMS | DATE AND TIME OF SEARCH | RESULTS | |
|---|---|---|---|---|
| | | | Yield | Eligible |
| Medline | ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "ncov"[All Fields])) AND ("budesonide"[All Fields] OR "ciclesonide"[All Fields] OR "fluticasone"[All Fields] OR "mometasone"[All Fields] OR "beclomethasone"[All Fields] OR "flunisolide"[All Fields] OR "inhalational steroid"[All Fields] OR "inhalational corticosteroid"[All Fields] OR "inhaled steroid"[All Fields] OR "inhaled corticosteroid"[All Fields]) | 10/9/21 5:55:16 AM | 124 | 3 |
| CENTRAL | (Coronaviridae Infections OR Coronavirus OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-20 AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") AND Randomized trial | 10/12/21 | 100 | 3 |
| COVID-NMA Initiative | Corticosteroids | 10/12/21 | 2 | 2 |
| Google Scholar | {Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {Inhaled Corticosteroid} AND {Randomized trial} | 10/12/21 | 706 | 3 |
| | | | | |
| ClinicalTrials.gov | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/12/21 | 29 | 3 |
| Chinese Clinical Trial Registry | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 1 | 0 |
| EU Clinical Trials Register | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational | 10/13/21 | 291 | 1 |

| | | | | |
|---|---|---|---|---|
| | corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | | | |
| Republic of Korea - Clinical Research Information Service | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 2 | 0 |
| Japan Primary Registries Network/ NIPH Clinical Trials Search | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 2 | 0 |
| CenterWatch | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 420 | 0 |
| WHO database COVID-19 studies | ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 389 | 3 |
| | | | | |
| chinaxiv.org | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 0 | 0 |
| Medrxiv.org | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 101 | 4 |
| Biorxiv.org | Coronavirus AND ("budesonide" OR "ciclesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "flunisolide" OR "inhalational steroid" OR "inhalational corticosteroid" OR "inhaled steroid"OR "inhaled corticosteroid") | 10/13/21 | 18 | 0 |

## Appendix 3. Characteristics of Included Studies

| Study ID | Participants | Sample Size | Comparisons | | Design | Outcomes |
|---|---|---|---|---|---|---|
| | | | Intervention | Control | | |
| Ramakrishnan S, et al, 2021 (STOIC Trial) | Adults aged older than 18 years with symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days in Oxfordshire, UK | N = 146 | Budesonide (N = 73) | Usual care (N = 73) | Randomized, open-label, parallel-group, phase 2 clinical trial | The primary endpoint was COVID-19-related urgent care visits, including emergency department assessment or hospitalization<br><br>The secondary outcomes were self-reported clinical recovery (symptom resolution), viral symptoms measured using the Common Cold Questionnaire (CCQ) and the InFLUenza Patient Reported Outcome Questionnaire (FLUPro), body temperature, blood oxygen saturations, and SARS-CoV-2 viral load |
| Yu LM, et al, 2021 (PRINCIPLE Trial) | People in the community in the UK aged at least 65 years, or at least 50 years with comorbidities, and had ongoing symptoms from PCR-confirmed or suspected COVID-19 (in accordance with the UK National Health Service definition of high temperature, new, continuous cough, or change in sense of smell or taste) which had started within the previous 14 days | N = 2530<br><br>SARS-CoV-2-positive participants (787 in the budesonide group, 1,069 in the usual care group, and 974 receiving other treatments) | Budesonide (N = 787) | Usual care (N = 1,069) | Multicenter, open-label, multi-arm, randomized, controlled, adaptive platform trial | The coprimary endpoints are time to first self-reported recovery and hospital admission or death related to COVID-19, within 28 days;<br><br>Secondary outcomes include a binary outcome of early, sustained recovery (recovered by day 14 and remains recovered until day 28), time to sustained recovery (date participant first reports recovery and subsequently remains well until 28 days), daily rating of 1–10 of how well participants feel, time to initial alleviation of symptoms (date symptoms first reported as minor or none), time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remain minor or none until 28 days), time to initial reduction of severity of symptoms (date symptom severity reported at least one grade lower), contacts with health services, hospital assessment without admission, oxygen administration, intensive care unit admission, mechanical ventilation, adherence to study treatment, WHO-5 Well-Being Index and reports of new household infections; Serious adverse events other than the coprimary outcome of hospital admission or death related to COVID-19 were measured in all trial groups |
| Song JY, et al, 2021 | Patients (aged ≥19 years) with mild-to-moderate COVID-19, confirmed by quantitative reverse transcription polymerase chain reaction (qRT-PCR), were enrolled in the study within 3 days of diagnosis or within 7 days from symptom onset (6 hospitals in South Korea ) | N = 61 | Ciclesonide group (N = 35) | Standard care group (N = 26) | Randomized, open-label, multicenter clinical trial | Primary endpoint was the SARS-CoV-2 eradication rate based on qRT-PCR on day 14 of study enrollment. SARS-CoV-2 eradication was defined as negative conversion of two consecutive negative results of qRT-PCR<br><br>Secondary endpoints were as follows: SARS-CoV-2 eradication rate based on qRT-PCR at days 7 and 10 from study enrollment; rate of clinical improvement (resolution of all systemic and respiratory symptoms) at days 7, 10, and 14 from study enrollment; rate of clinical failure within 28 days; safety/tolerability of ciclesonide |

| | | | | | | |
|---|---|---|---|---|---|---|
| Clemency, B, et al, 2021 | Participants were eligible for inclusion if, at the time of enrollment, they (1) were at least 12 years of age, (2) had a positive SARS-CoV-2 molecular or antigen diagnostic sample obtained in the previous 72 hours, (3) were not hospitalized or under consideration for hospitalization, (4) had an oxygen saturation of at least 93% on room air, (5) were able to demonstrate successful use of an MDI, and (6) had at least one of the following symptoms of COVID: fever, cough, or dyspnea (10 centers in the US) | N = 400 | Ciclesonide (N = 197) | Placebo (N = 203) | Phase III, multicenter, double-blind, randomized controlled trial | The primary endpoint was time to alleviation of all COVID-19 related symptoms (cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell) by Day 30<br><br>Secondary endpoints included subsequent emergency department visits or hospital admissions for reasons attributable to COVID-19. |

## Appendix 4. Methodological assessment of included studies

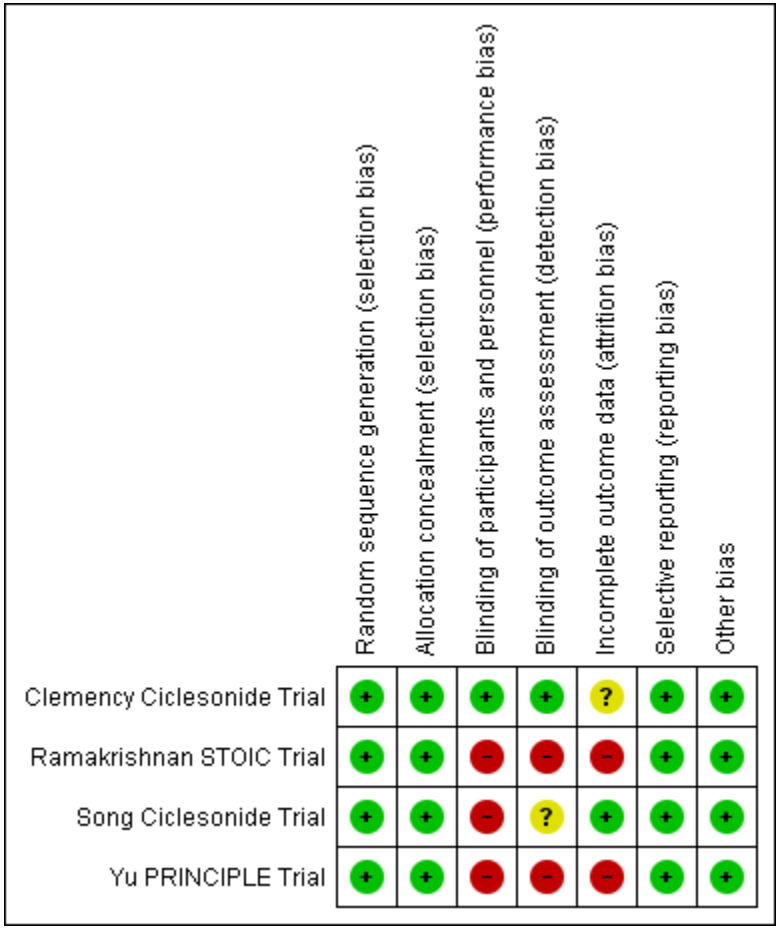


Figure 1. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study

# Appendix 5. GRADE Evidence Summary

**Question:** Inhaled Corticosteroids compared to Standard Care and/or Placebo for COVID 19 infection

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Inhaled Corticosteroids | Standard Care and/or Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Hospitalization/Death** | | | | | | | | | | | | |
| 2 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 75/984 (7.6%) | 123/1272 ( 9.7%) | **RR 0.82** (0.62 to 1.08) | **17 fewer per 1,000** (from 37 fewer to 8 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Hospitalization/Emergency Department Visit** | | | | | | | | | | | | |
| 3 | randomised trials | serious[c] | serious[d] | not serious | serious[b] | none | 92/1057 (8.7%) | 132/1075 (12.3%) | **RR 0.36** (0.11 to 1.20) | **79 fewer per 1,000** (from 109 fewer to 25 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Clinical Recovery/Clinical Improvement D7** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | not serious | none | 319/1019 (31.3%) | 385/1298 (29.7%) | **RR 1.07** (0.95 to 1.20) | **21 more per 1,000** (from 15 fewer to 59 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Clinical Recovery/Clinical Improvement D14** | | | | | | | | | | | | |
| 4 | randomised trials | serious[c] | not serious | not serious | not serious | none | 619/1092 (56.7%) | 664/1371 (48.4%) | **RR 1.18** (1.10 to 1.27) | **87 more per 1,000** (from 48 more to 131 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Clinical Recovery/Clinical Improvement D28/D30** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | not serious | none | 739/1019 (72.5%) | 860/1298 (66.3%) | **RR 1.10** (1.04 to 1.16) | **66 more per 1,000** (from 27 more to 106 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| **Adverse Events** | | | | | | | | | | | | |
| 3 | randomised trials | serious[c] | serious[d] | not serious | serious[b] | none | 30/305 (9.8%) | 29/302 (9.6%) | **RR 2.31** (0.35 to 15.07) | **126 more per 1,000** (from 62 fewer to 1,000 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Serious Adverse Events** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 2/787 (0.3%) | 4/1069 (0.4%) | **RR 0.68** (0.12 to 3.70) | **1 fewer per 1,000** (from 3 fewer to 10 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 6/787 (0.8%) | 11/1069 (1.0%) | **RR 0.74** (0.28 to 1.99) | **3 fewer per 1,000** (from 7 fewer to 10 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Hospitalization** | | | | | | | | | | | | |
| 1 | randomised trials | serious[a] | not serious | not serious | serious[b] | none | 66/787 (8.4%) | 105/1069 (9.8%) | **RR 0.85** (0.64 to 1.15) | **15 fewer per 1,000** (from 35 fewer to 15 more) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## *Explanations*

a. Risk of bias downgraded by 1 level: some concerns regarding performance and attrition bias.
b. Imprecision was downgraded by 1 level due to the wide confidence interval
c. Risk of bias downgraded by 1 level: some concerns regarding performance, detection and attrition bias.
d. Inconsistency was downgraded by 1 level due to substantial heterogeneity

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Inhaled Corticosteroids | Standard Care and/or Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Time to Clinical Recovery/Clinical Improvement** | | | | | | | | | | | | |
| 3 | randomised trials | serious[b] | serious[c] | not serious | not serious | none | 1057 | 1345 | - | MD **1.72 lower** (3.28 lower to 0.17 lower) | ⊕⊕◯◯ LOW | IMPORTANT |
| **Duration of Hospitalization** | | | | | | | | | | | | |
| 2 | randomised trials | serious[a] | not serious | not serious | not serious | none | 822 | 1095 | - | MD **0.25 lower** (0.75 lower to 0.25 higher) | ⊕⊕⊕◯ MODERATE | IMPORTANT |
| **Viral Eradication D14** | | | | | | | | | | | | |
| 1 | randomised trials | serious[d] | not serious | not serious | very serious[e] | none | 10/31 (32.3%) | 1/20 (5.0%) | **RR 6.45** (0.89 to 46.60) | **273 more per 1,000** (from 6 fewer to 1,000 more) | ⊕◯◯◯ VERY LOW | IMPORTANT |

**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

## *Explanations*

a. Risk of bias downgraded by 1 level: some concerns regarding performance and attrition bias.
b. Risk of bias downgraded by 1 level: some concerns regarding performance, detection and attrition bias.
c. Inconsistency was downgraded by 1 level due to substantial heterogeneity
d. Risk of bias downgraded by 1 level: some concerns regarding performance bias.
e. Imprecision was downgraded by 2 level due to the very wide confidence interval

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Inhaled Corticosteroids | Standard Care and/or Placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Self-reported Clinical Recovery D7** | | | | | | | | | | | | |
| 2 | randomised trials | serious[a] | not serious | not serious | not serious | none | 300/984 (30.5%) | 370/1272 (29.1%) | **RR 1.08** (0.95 to 1.22) | **23 more per 1,000** (from 15 fewer to 64 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Self-Reported Clinical Recovery D14** | | | | | | | | | | | | |
| 3 | randomised trials | serious[a] | not serious | not serious | not serious | none | 582/1057 (55.1%) | 647/1345 (48.1%) | **RR 1.15** (1.07 to 1.24) | **72 more per 1,000** (from 34 more to 115 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Self-Reported Clinical Recovery D28/D30** | | | | | | | | | | | | |
| 2 | randomised trials | serious[a] | not serious | not serious | not serious | none | 705/984 (71.6%) | 839/1272 (66.0%) | **RR 1.09** (1.03 to 1.15) | **59 more per 1,000** (from 20 more to 99 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |
| **Clinical Improvement D7** | | | | | | | | | | | | |
| 1 | randomised trials | serious[b] | not serious | not serious | serious[c] | none | 19/35 (54.3%) | 15/26 (57.7%) | **RR 0.94** (0.60 to 1.47) | **35 fewer per 1,000** (from 231 fewer to 271 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Clinical Improvement D14** | | | | | | | | | | | | |
| 1 | randomised trials | serious[b] | not serious | not serious | serious[c] | none | 26/35 (74.3%) | 14/26 (53.8%) | **RR 1.38** (0.92 to 2.07) | **205 more per 1,000** (from 43 fewer to 576 more) | ⊕⊕◯◯ LOW | CRITICAL |
| **Clinical Improvement D28/D30** | | | | | | | | | | | | |
| 1 | randomised trials | serious[b] | not serious | not serious | not serious | none | 34/35 (97.1%) | 21/26 (80.8%) | **RR 1.20** (0.99 to 1.46) | **162 more per 1,000** (from 8 fewer to 372 more) | ⊕⊕⊕◯ MODERATE | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

## *Explanations*

a. Risk of bias downgraded by 1 level: some concerns regarding performance, detection and attrition bias.
b. Risk of bias downgraded by 1 level: some concerns regarding performance bias.
c. Imprecision was downgraded by 1 level due to the wide confidence interval

## Appendix 6. Forest Plots

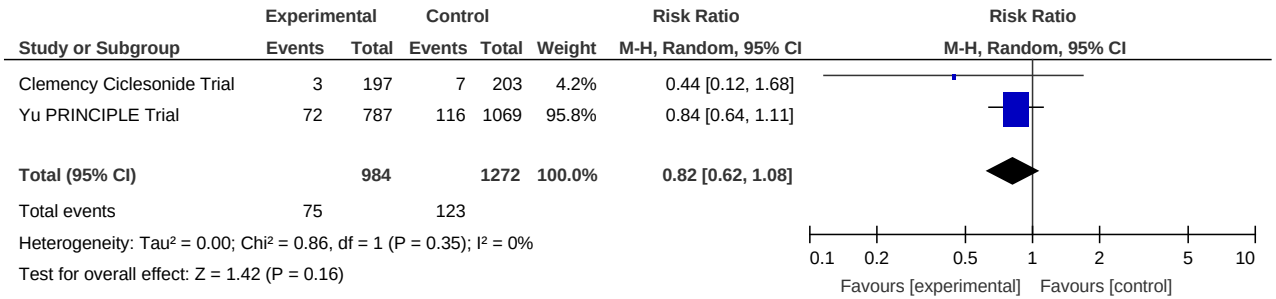


Figure 1a. Hospitalization/Death

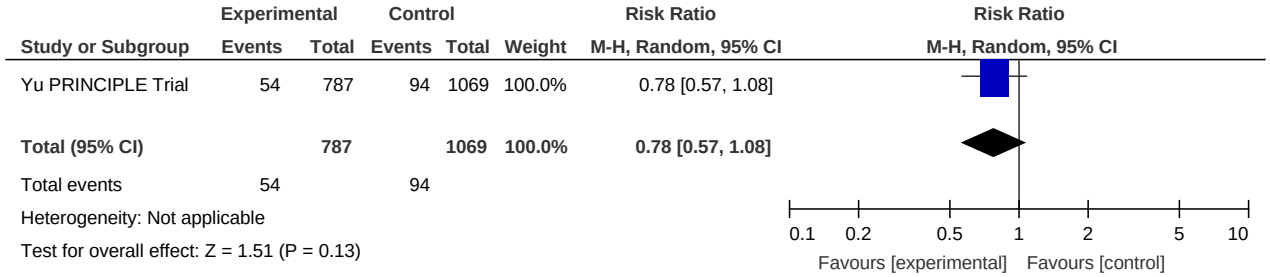


Figure 1b. Hospitalization/Death (Sensitivity Analysis excluding preprint)

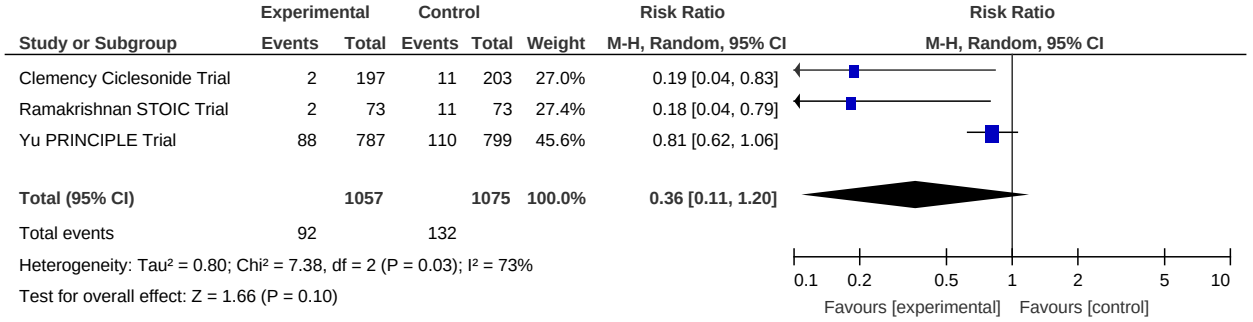


Figure 2a. Hospitalization/Emergency Department Visit

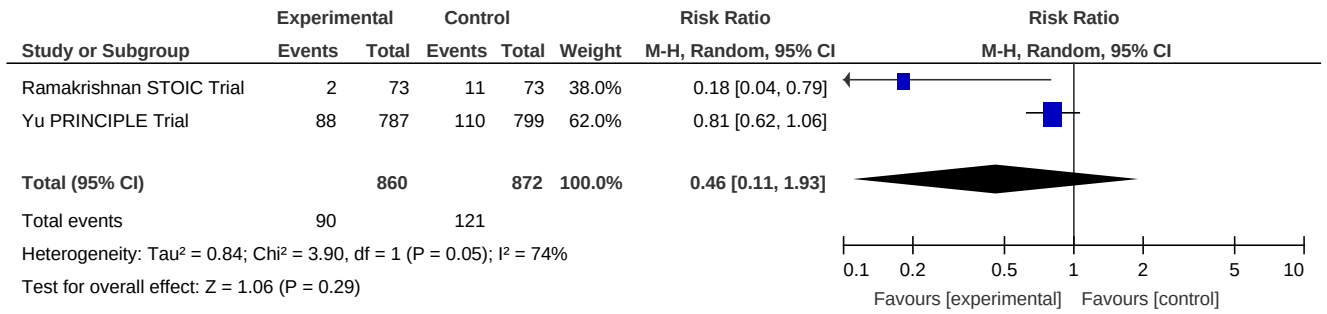


Figure 2b. Hospitalization/Emergency Department Visit (Sensitivity Analysis excluding preprint)

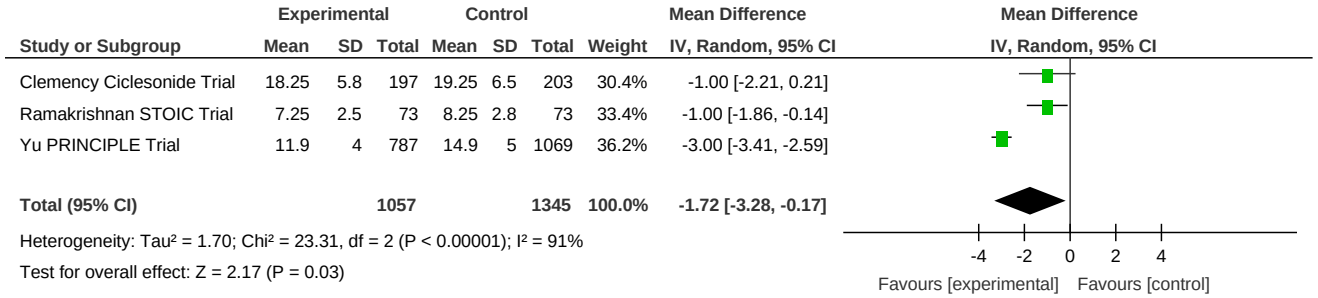


Figure 3a. Time to Clinical Recovery/Clinical Improvement

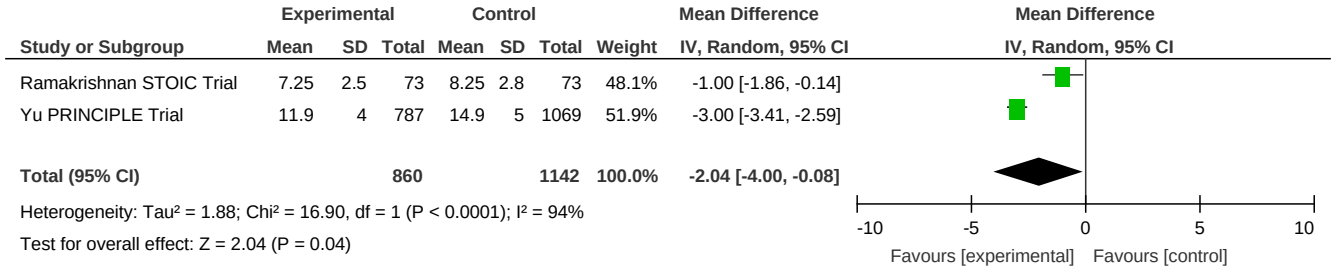


Figure 3b. Time to Clinical Recovery/Improvement (Sensitivity Analysis excluding preprint)

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Clemency Ciclesonide Trial | 28 | 197 | 29 | 203 | 6.3% | 0.99 [0.62, 1.61] |
| Song Ciclesonide Trial | 19 | 35 | 15 | 26 | 7.3% | 0.94 [0.60, 1.47] |
| Yu PRINCIPLE Trial | 272 | 787 | 341 | 1069 | 86.4% | 1.08 [0.95, 1.23] |
| **Total (95% CI)** | | **1019** | | **1298** | **100.0%** | **1.07 [0.95, 1.20]** |
| Total events | 319 | | 385 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%

Test for overall effect: Z = 1.05 (P = 0.30)

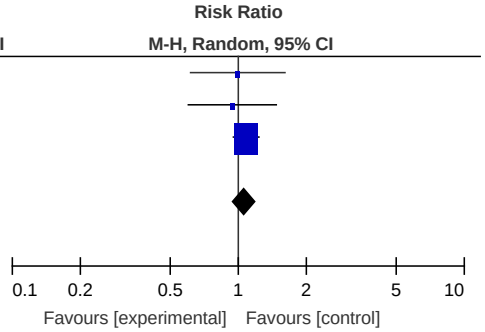


Figure 4a. Clinical Recovery/Clinical Improvement Day 7

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Song Ciclesonide Trial | 19 | 35 | 15 | 26 | 7.8% | 0.94 [0.60, 1.47] |
| Yu PRINCIPLE Trial | 272 | 787 | 341 | 1069 | 92.2% | 1.08 [0.95, 1.23] |
| **Total (95% CI)** | | **822** | | **1095** | **100.0%** | **1.07 [0.95, 1.21]** |
| Total events | 291 | | 356 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%

Test for overall effect: Z = 1.09 (P = 0.28)

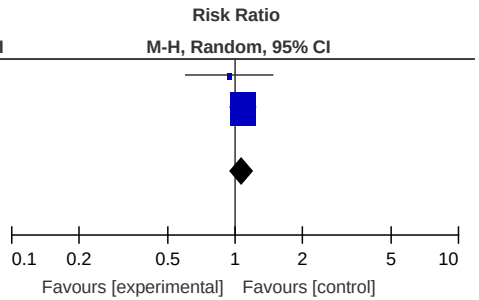


Figure 4b. Clinical Recovery/Clinical Improvement Day 7 (Sensitivity Analysis excluding preprint)

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Clemency Ciclesonide Trial | 28 | 197 | 29 | 203 | 6.8% | 0.99 [0.62, 1.61] |
| Yu PRINCIPLE Trial | 272 | 787 | 341 | 1069 | 93.2% | 1.08 [0.95, 1.23] |
| **Total (95% CI)** | | **984** | | **1272** | **100.0%** | **1.08 [0.95, 1.22]** |
| Total events | 300 | | 370 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

Test for overall effect: Z = 1.16 (P = 0.25)

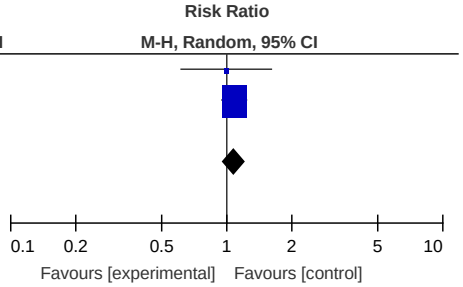


Figure 4c. Self-Reported Clinical Recovery Day 7

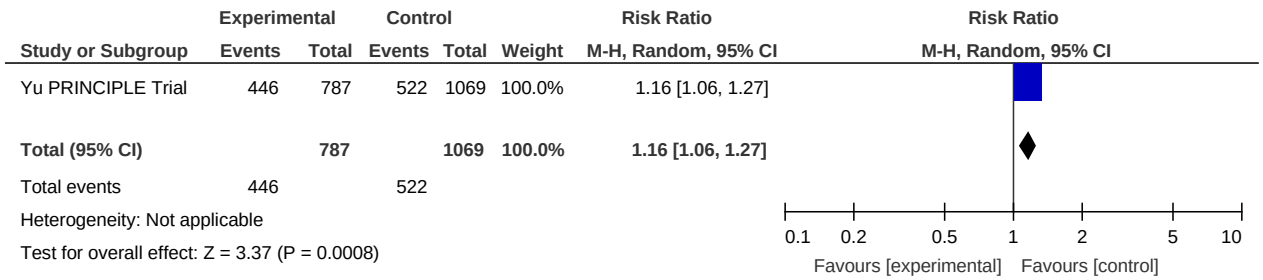


Figure 4d. Self-Reported Clinical Recovery D7 (Sensitivity Analysis)

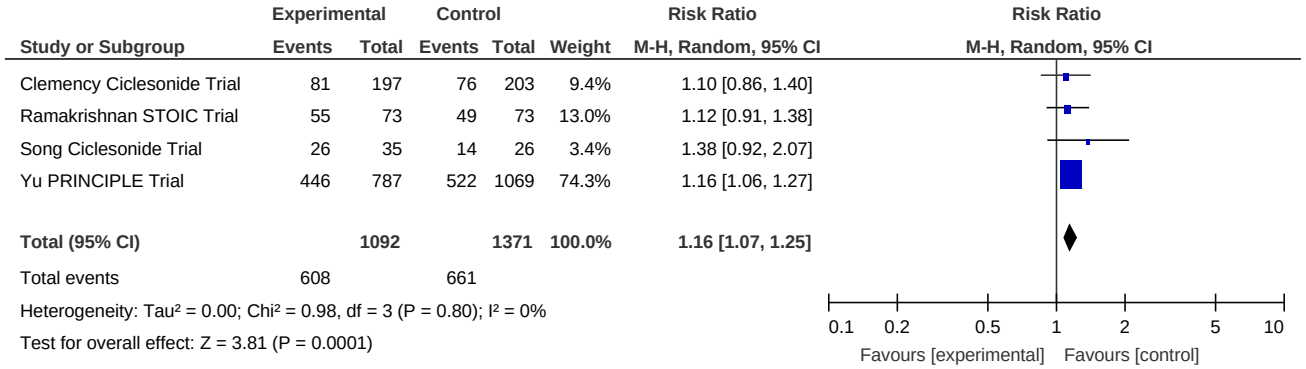


Figure 5a. Clinical Recovery/Clinical Improvement Day 14.

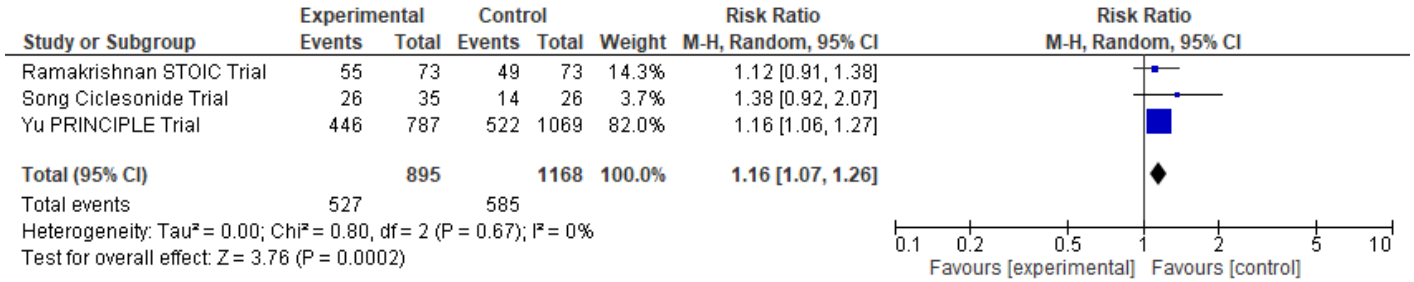


Figure 5b. Clinical Recovery/Improvement Day 14 (Sensitivity Analysis excluding preprint)

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Clemency Ciclesonide Trial | 81 | 197 | 76 | 203 | 9.7% | 1.10 [0.86, 1.40] |
| Ramakrishnan STOIC Trial | 446 | 787 | 522 | 1069 | 76.9% | 1.16 [1.06, 1.27] |
| Yu PRINCIPLE Trial | 55 | 73 | 49 | 73 | 13.4% | 1.12 [0.91, 1.38] |
| **Total (95% CI)** | | **1057** | | **1345** | **100.0%** | **1.15 [1.07, 1.24]** |
| Total events | 582 | | 647 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 2 (P = 0.89); I² = 0%

Test for overall effect: Z = 3.59 (P = 0.0003)

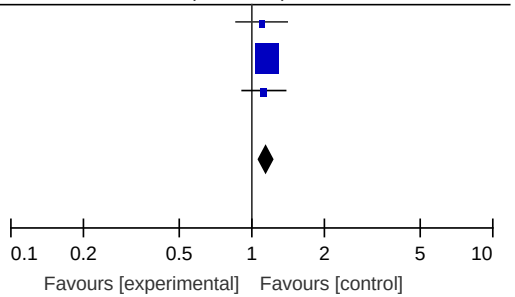


Figure 5c. Self-Reported Clinical Recovery Day 14

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ramakrishnan STOIC Trial | 55 | 73 | 49 | 73 | 14.8% | 1.12 [0.91, 1.38] |
| Yu PRINCIPLE Trial | 446 | 787 | 522 | 1069 | 85.2% | 1.16 [1.06, 1.27] |
| **Total (95% CI)** | | **860** | | **1142** | **100.0%** | **1.15 [1.07, 1.25]** |
| Total events | 501 | | 571 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%

Test for overall effect: Z = 3.53 (P = 0.0004)

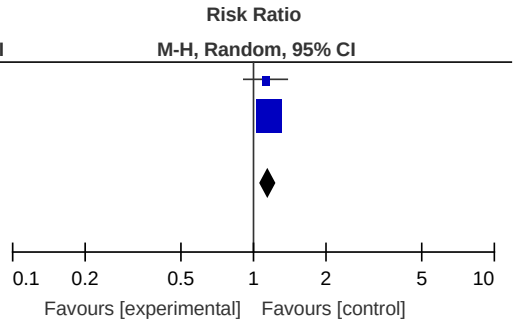


Figure 5d. Self-Reported Clinical Recovery D14 (Sensitivity Analysis)

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Clemency Ciclesonide Trial | 139 | 197 | 129 | 203 | 15.2% | 1.11 [0.97, 1.27] |
| Song Ciclesonide Trial | 34 | 35 | 21 | 26 | 7.5% | 1.20 [0.99, 1.46] |
| Yu PRINCIPLE Trial | 566 | 787 | 710 | 1069 | 77.3% | 1.08 [1.02, 1.15] |
| **Total (95% CI)** | | **1019** | | **1298** | **100.0%** | **1.10 [1.04, 1.16]** |
| Total events | 739 | | 860 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%

Test for overall effect: Z = 3.33 (P = 0.0009)

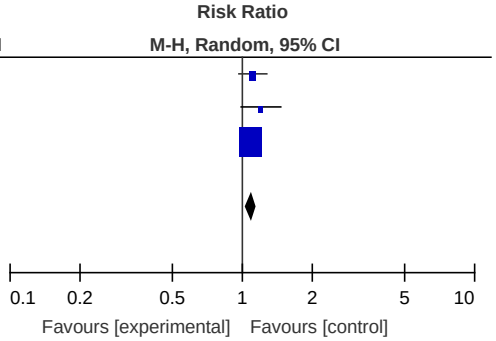


Figure 6a. Clinical Recovery/Clinical Improvement Day 28/Day 30

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Song Ciclesonide Trial | 34 | 35 | 21 | 26 | 10.2% | 1.20 [0.99, 1.46] |
| Yu PRINCIPLE Trial | 566 | 787 | 710 | 1069 | 89.8% | 1.08 [1.02, 1.15] |
| **Total (95% CI)** | | **822** | | **1095** | **100.0%** | **1.09 [1.03, 1.17]** |
| Total events | 600 | | 731 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%

Test for overall effect: Z = 2.80 (P = 0.005)

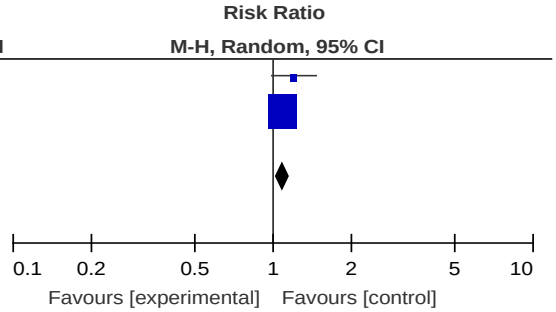


Figure 6b. Clinical Recovery/Clinical Improvement Day 28/30 (Sensitivity Analysis excluding preprint)

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| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Clemency Ciclesonide Trial | 139 | 197 | 129 | 203 | 16.4% | 1.11 [0.97, 1.27] |
| Yu PRINCIPLE Trial | 566 | 787 | 710 | 1069 | 83.6% | 1.08 [1.02, 1.15] |
| **Total (95% CI)** | | **984** | | **1272** | **100.0%** | **1.09 [1.03, 1.15]** |
| Total events | 705 | | 839 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

Test for overall effect: Z = 2.94 (P = 0.003)

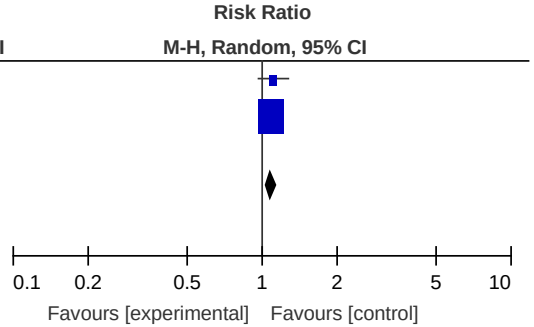


Figure 6c. Self-Reported Clinical Recovery Day 28/30

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Yu PRINCIPLE Trial | 566 | 787 | 710 | 1069 | 100.0% | 1.08 [1.02, 1.15] |
| **Total (95% CI)** | | **787** | | **1069** | **100.0%** | **1.08 [1.02, 1.15]** |
| Total events | 566 | | 710 | | | |

Heterogeneity: Not applicable

Test for overall effect: Z = 2.56 (P = 0.01)

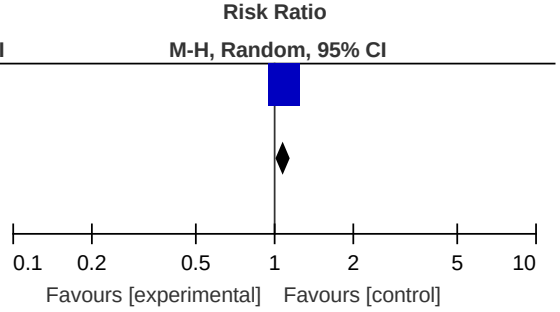


Figure 6d. Self-Reported Clinical Recovery D28/D30 (Sensitivity Analysis)

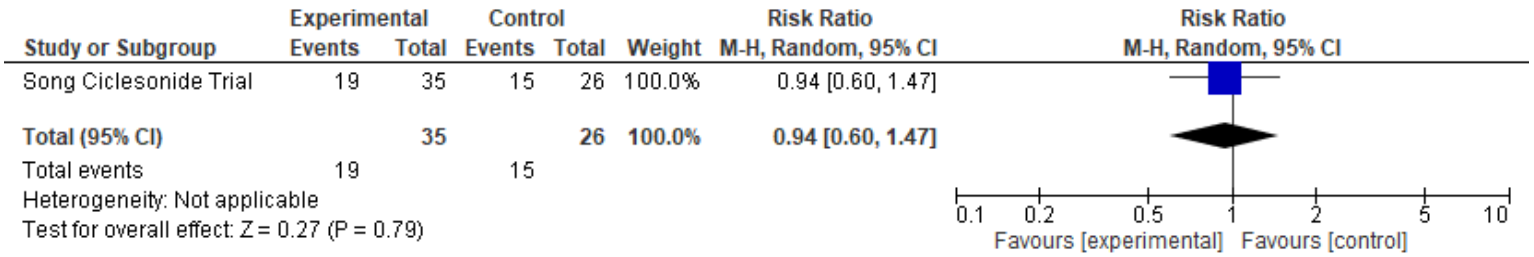


Figure 7. Clinical Improvement D7

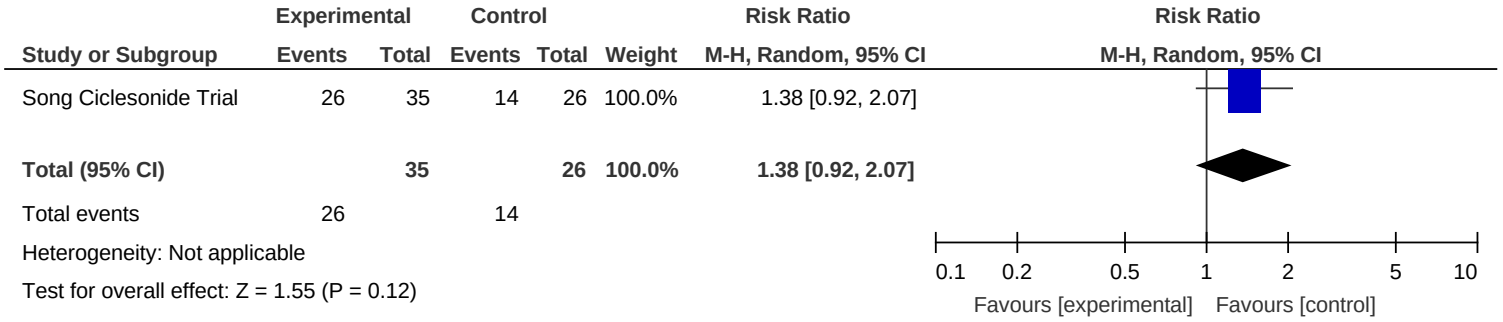


Figure 8. Clinical Improvement D14

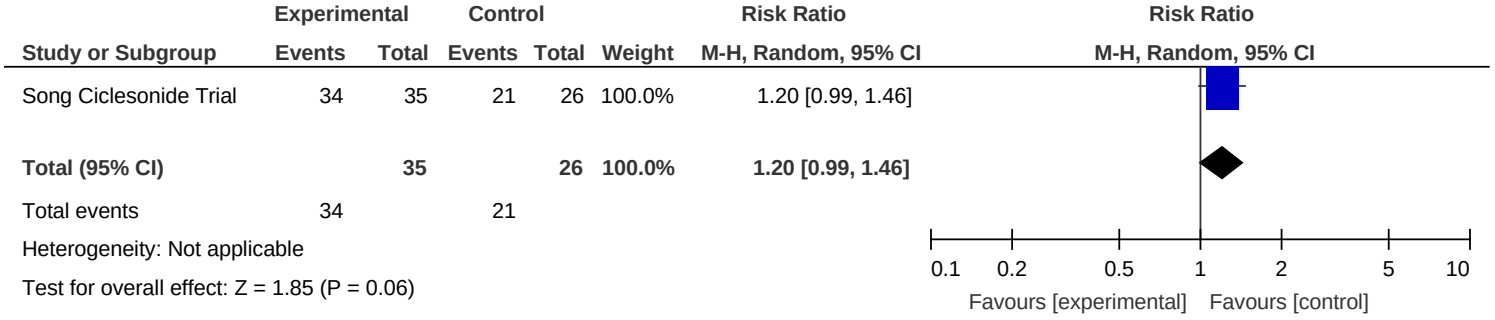


Figure 9. Clinical Improvement D28/D30

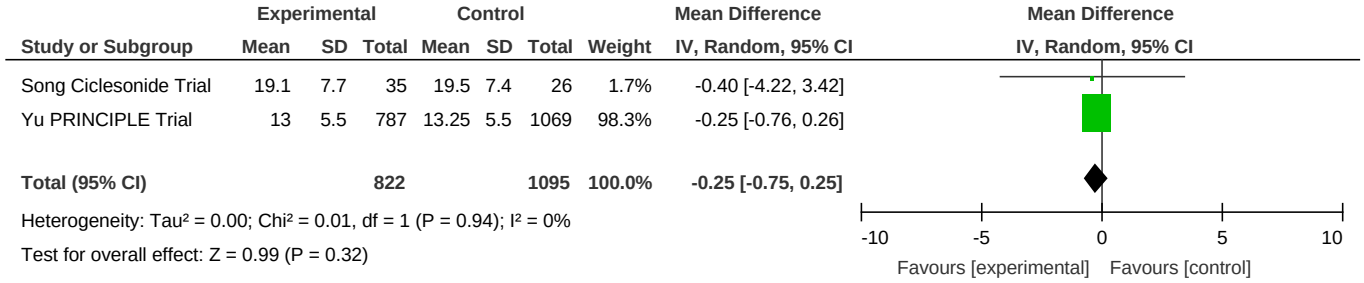


Figure 10. Duration of Hospitalization

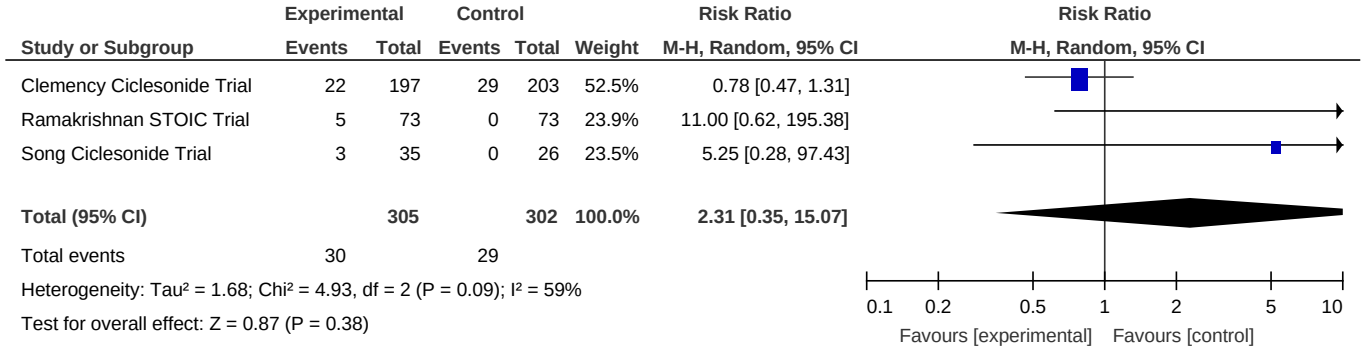


Figure 11a. Adverse Events

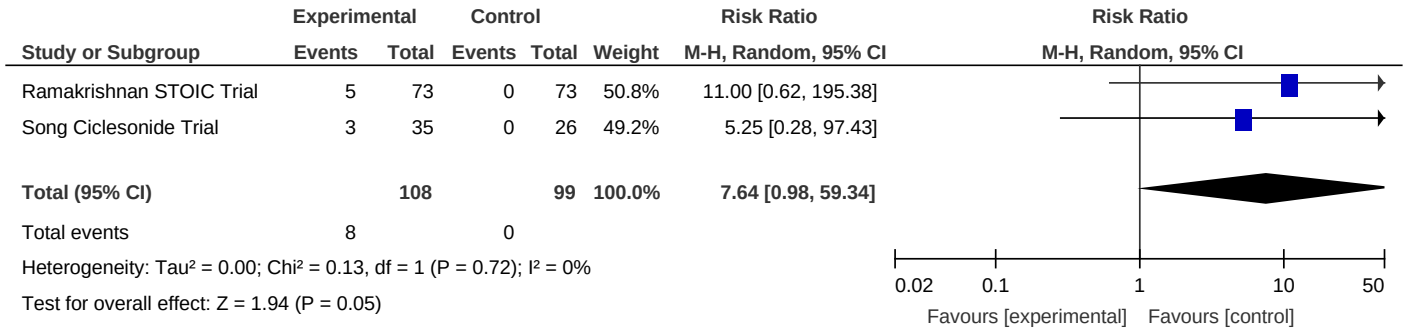


Figure 11b. Adverse Events (Sensitivity Analysis excluding preprint)

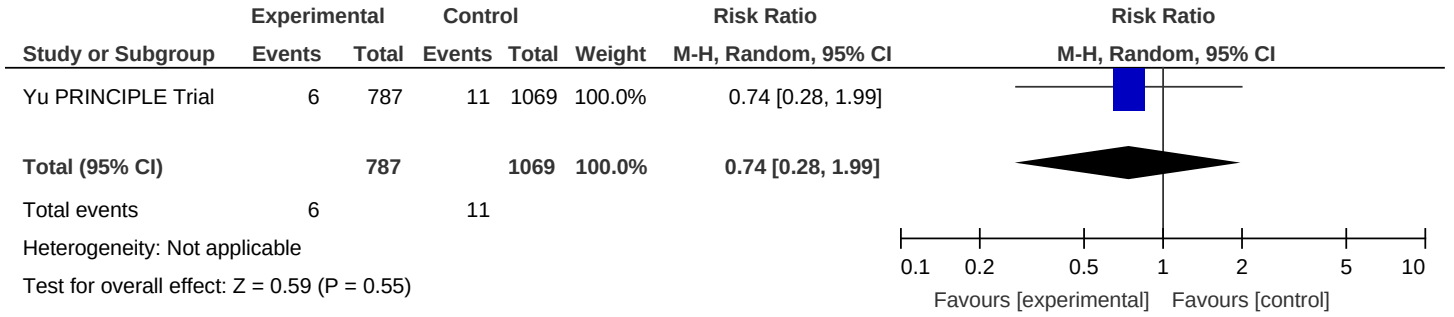


Figure 12. Mortality

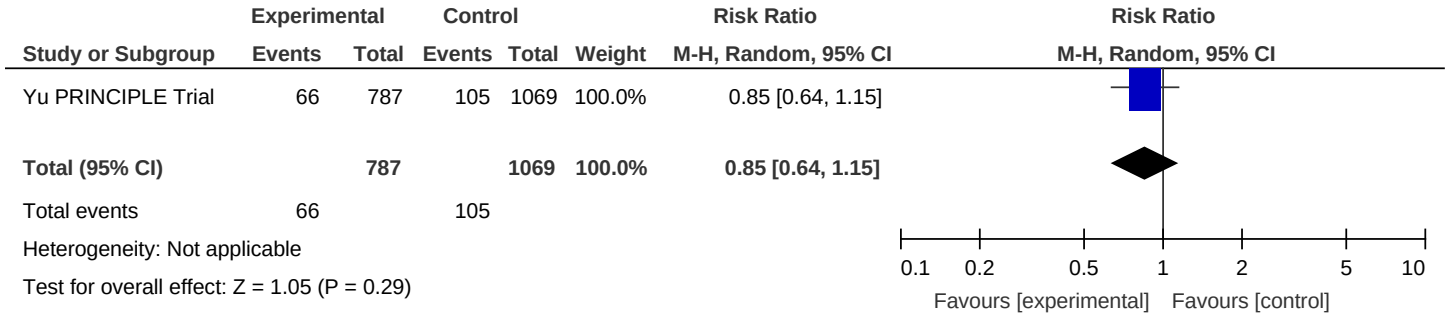


Figure 13. Hospitalization

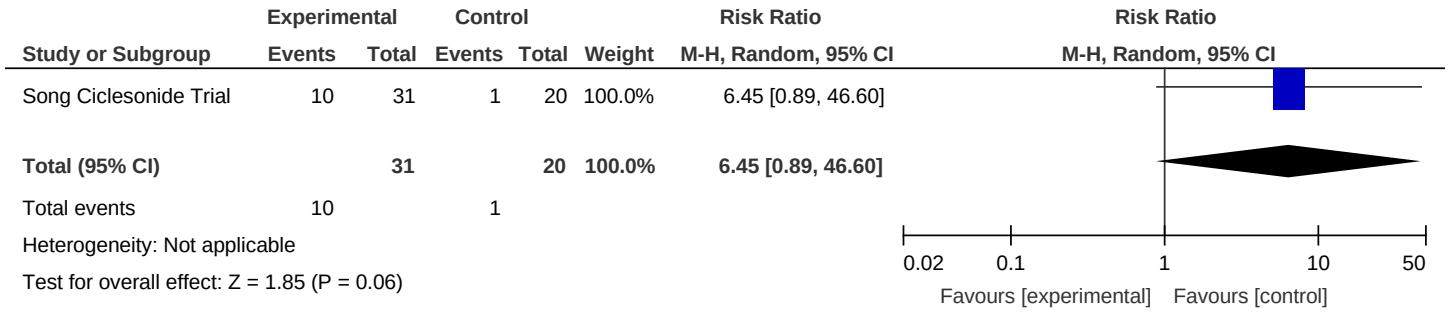


Figure 14. Viral Eradication Day 14

# Appendix 7. Characteristics of Ongoing Studies

| | Title | Population | Interventions | Characteristics | Outcome Measures |
|---|---|---|---|---|---|
| 1 | Arformoterol/Budesonide for COVID-19<br><br>NCT05055414 | 19 years and older (Adult, Older Adult) | UI030 | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Triple (Participant, Care Provider, Investigator)<br>Primary Purpose: Treatment | Time to Clinical Improvement on World Health Organization (WHO) Ordinal Scale<br>World Health Organization (WHO) Ordinal Scale for Clinical Improvement<br>World Health Organization (WHO) Ordinal Scale change<br>Clinical cure rate |
| 2 | Fluticasone in Covid Treatment (FLOT)<br><br>NCT05054322 | 18 years and older (Adult, Older Adult) | Fluticasone Propionate | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: None (Open Label)<br>Primary Purpose: Treatment | Incidence of adverse outcomes<br>Duration of isolation based on WHO's criteria<br>The incidence of patients with oxygen saturation by pulse oximetry (SpO2) < 94%;<br>Self-reported recovery rate |
| 3 | Efficacy of Nebulized Lidocaine, Salbutamol and Beclomethasone Plus Salbutamol in the COVID-19 Patient with ARDS on Non-Invasive Ventilation: Randomized Controlled Trial<br><br>NCT04979923 | 18 to 70 years old (Adult, Older Adult) | Lidocaine, Salbutamol, Beclomethasone | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Double (Participant, Care Provider)<br>Primary Purpose: Supportive Care | Cough suppression<br>Correction of hypoxia |
| 4 | Efficacy of Inhaled Therapies in the Treatment of Acute Symptoms Associated with COVID-19<br><br>NCT04937543 | 18 years and older (Adult, Older Adult) | Inhaled beclometasone, inhaled beclomethasone / formoterol / glycopyrronium | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: None (Open Label)<br>Primary Purpose: Treatment | Proportion of patients in preventing the use of health resources in patients<br>Airway obstruction<br>Small airway obstruction |
| 5 | Early Treatment of Vulnerable Individuals with Non-Severe SARS COV 2 Infection<br><br>NCT04920838 | 18 years and older (Adult, Older Adult) | Nitazoxanide and Ciclésonide<br>Telmisartan 20mg oral tablet<br>Paracetamol | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: None (Open Label)<br>Primary Purpose: Treatment | SpO2 >/= 93% within 14 days<br>Death within 14 days<br>Death within 28 days<br>Occurrence of at least one grade 3 or 4 clinical or biological adverse event within 14 days<br>Number of hospitalizations due to severe progression |
| 6 | ACTIV-6: COVID-19 Study of Repurposed Medications<br><br>NCT04885530 | 30 years and older (Adult, Older Adult) | Ivermectin<br>Fluvoxamine<br>Fluticasone<br>Placebo | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Double (Participant, Care Provider)<br>Primary Purpose: Treatment | Number of hospitalizations as measured by patient reports.<br>Number of deaths as measured by patient reports<br>Number of symptoms as measured by patient reports<br>Change in COVID Clinical Progression Scale<br>Number of hospitalizations as measured by patient reports<br>Number of Symptom Resolutions as measured by patient reports<br>Change in Quality of Life (QOL) as measured by the PROMIS-29<br>Composite score of hospitalizations, urgent care visits, and emergency room visits as measured by patient reports |
| 7 | Inhaled Ciclesonide for Patients with COVID-19<br><br>NCT04435795 | 18 years and older (Adult, Older Adult) | Normal Saline intranasal and placebo inhaler<br>Ciclesonide<br>Ciclesonide nasal | Allocation: Randomized<br>Intervention Model: Factorial Assignment<br>Masking: Triple (Participant, Care Provider, Investigator)<br>Primary Purpose: Treatment | Proportion of participants with no symptoms of cough, fever or dyspnea<br>Overall feeling<br>Improvement in dyspnea<br>Visual Analog scale for Cough<br>Hospitalization for SARS-CoV-2<br>Changes in Promis dyspnea characteristics scale<br>Change in dyspnea severity Promis scale<br>Incidence of new oxygen use<br>Mortality<br>Anxiety<br>Sleep Disturbance |
| 8 | Inhalation of Ciclesonide for Patients with COVID-19: A Randomized Open | 18 years and older (Adult, Older Adult) | Ciclesonide Inhalation Aerosol | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: None (Open Label) | Duration of received supplemental oxygen therapy<br>Treatment with systemic corticosteroids<br>Invasive mechanical ventilation or all-cause death (key secondary outcome) |

| | | | | | |
|---|---|---|---|---|---|
| | Treatment Study (HALT COVID-19)<br><br>NCT04381364 | | | Primary Purpose: Treatment | All-cause death<br>Invasive mechanical ventilation<br>Remaining dyspnea symptoms<br>Time from inclusion to initiation of treatment with systemic corticosteroids |
| 9 | A Study of the Safety and Efficacy of Ciclesonide in the Treatment of Non-Hospitalized COVID-19 Patients<br><br>NCT04377711 | 12 to 100 years old (Child, Adult, Older Adult) | Ciclesonide<br>Placebo | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Double (Participant, Investigator)<br>Primary Purpose: Treatment | Time to alleviation of COVID-19- related symptoms by Day 30<br>Percentage of patients with hospital admission or death by day 30<br>All-cause mortality by day 30<br>COVID-19-related mortality by day 30<br>Percentage of patients with subsequent emergency department visit or hospital admission for reasons attributable to COVID-19 by day 30<br>Percentage of patients with alleviation of COVID-19-related symptoms defined as symptom-free for a continuous period of more than 24 hours (ie, later than 3 AM/PM assessments) by day 7, by day 14, and by day 30<br>Time to hospital admission or death<br>Change from baseline in oxygen saturation levels<br>Change from baseline in COVID-19 viral load in nasopharyngeal sample at day 30 |
| 10 | Trial of COVID-19 Outpatient Treatment in Individuals with Risk Factors for Aggravation<br><br>NCT04356495 | 50 years and older (Adult, Older Adult) | Dietary Supplement: Vitamins<br>Telmisartan<br>Ciclesonide<br>Interferon #-1b | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: None (Open Label)<br>Primary Purpose: Treatment | Pilot Phase: Proportion of participants who had a Grade 3 or 4 adverse event<br>Efficacy phase: Death<br>Efficacy phase: oxygen therapy<br>Efficacy phase: hospitalization<br>Proportion of hospitalizations, overall and by cause, in each group<br>Death and causes of death<br>Proportion of intensive care hospitalizations, overall and by cause, in each group<br>Proportion of participants with negative SARS-CoV-2 RT-PCR<br>Hematological markers evolution<br>Inflammatory markers evolution and 6 more |
| 11 | Inhaled Corticosteroid Treatment of COVID 19 Patients with Pneumonia<br><br>NCT04355637 | 18 to 79 years old (Adult, Older Adult) | Inhaled budesonide | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: None (Open Label)<br>Primary Purpose: Treatment | Proportion of patients in both arms fulfilling the criteria for treatment failure<br>ICU admission<br>ICU refusal<br>Occurrence of complications<br>Lactate dehydrogenase (LDH)<br>C-Reactive Protein (CRP)<br>Ferritin<br>D-dimer<br>Leukocyte counts |
| 12 | Evaluation of Efficacy of Levamisole and Formoterol+Budesonide in the Treatment of COVID-19<br><br>NCT04331470 | 15 to 100 years old (Child, Adult, Older Adult) | Levamisole Pill + Budesonide+Formoterol inhaler<br>Lopinavir/Ritonavir + hydoxychloroquine | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: Double (Participant, Outcomes Assessor)<br>Primary Purpose: Treatment | Clear chest CT-scan<br>PCR test<br>Physical statues of patient |
| 13 | Protective Role of Inhaled Steroids for COVID-19 Infection<br><br>NCT04331054 | 18 to 75 years old (Adult, Older Adult) | Usual practice + Symbicort Rapihaler<br>Usual practice | Allocation: Randomized<br>Intervention Model: Parallel Assignment<br>Masking: None (Open Label)<br>Primary Purpose: Treatment | Time (in days) to clinical improvement within 30 days after randomization<br>Mortality rate at D30<br>Time (in days) from randomization to death<br>Number of days alive outside ICU within 30 days<br>Number of days alive free of invasive or non-invasive ventilation within 30 days<br>Number of days alive with oxygen therapy within 30 days<br>Maximal oxygen rate within 30 days<br>Difference between PaO2/FiO2 ratio at randomization and at Day 7 (or at the time of stopping oxygen therapy or discharge if occurs before Day 7)<br>Number of days alive outside hospital within 30 days<br>Use of antibiotics for respiratory (proved or suspected) infection within 30 days<br>Difference between CRP levels at randomization and at Day 7 (or at the time of discharge if occurs before Day 7)<br>Safety outcomes included events that occurred during treatment, serious adverse events, and premature discontinuation of treatment. |